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Yong-Ku Kim *Editor*

Major Depressive Disorder

Rethinking and Understanding Recent
Discoveries



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Preface

Depression has affected mankind for thousands of years. Melancholia, another word for depression, refers to the idea of “black bile” in ancient Greece and was first used by Hippocrates in 400 B.C. Most of the known symptoms of depression have been reported since ancient times, from which we have learned that depression is due to internal and external factors. Also, ancient people recognized that depression often was accompanied by anxiety or excessive alcohol consumption, both of which have been well-documented. It is impressive that understanding of depression is very similar between ancient and modern people. However, starting only in the mid-twentieth century has it been possible to study the brain for an understanding of the pathogenesis of depression.

Depression is a brain disease with various causes. Depression can be a complex genetic disorder involving multiple genes, and mutations in various genes can cause depression even among related individuals. Non-genetic factors also are important causes of depression. Depression can be caused by interactions of external stresses, such as divorce, bereavement, or negative childhood experiences in individuals with genetic vulnerabilities to stress, and internal stresses, such as viruses, stroke, and autoimmune diseases. Thus, a model that combines these stresses is more likely to properly explain the complexity of depression than a simplified model of only psychosocial or biological factors. This concept is supported by primate studies that emphasize the importance of environmental effects such as maternal deprivation on neurobiological development and by recent studies identifying complex interactions between the environment and the brain, as well as the environment and genetics. For example, people who have been physically or sexually abused in childhood or have experienced early life parental loss are likely to develop depression in adulthood due to association with negative experiences in critical periods of human development. Thus, a genetic predisposition to form a biologically vulnerable phenotype can reduce the threshold for future stress and development of depression.

Depression is a highly prevalent, chronic, relapsing-remitting disorder with a tremendous socioeconomic burden. Depression is a very common condition, affecting one of every six people. Despite this, there is lack of data on the causes, progress, pathology, and proper treatment of the disease. The current system of diagnosis

of depression, Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5), is based on clinical symptoms and does not adequately consider heterogeneous causes and pathophysiologies. To compensate for this, the National Institute of Mental Health (NIMH) defines depression as a brain circuit disorder and seeks a biological classification based on cause and pathogenesis through Research Domain Criteria. However, these criteria also can be ineffective in clinical use.

Though research has aimed to identify biological markers that predict diagnosis and treatment responses associated with depression, few biological indicators are known for clinical practice. Recently, interest in epigenetics has increased, suggesting the potential for biological indicators of diagnosis and treatment of depression based on associations with DNA methylation, histone modeling, and micro RNA. Furthermore, epigenetics can use environmental factors to explain mechanisms of depression.

Recent developments in network neuroscience have confirmed that depression is a network disorder of the brain, and neuroimaging, including resting state functional MRI, is expected to occupy an important position for diagnosis and treatment outcomes. Because of this, biological therapy for depression is moving away from conventional drugs. Of the drugs used, ketamine, an antagonist to NMDA receptors, is providing a new turning point in drug therapy for depression as it is effective at a much earlier stage than monoamine drugs and is effective in patients with treatment-resistant depression. New treatments for depression related to NMDA receptors are expected to continue to be developed and should be of interest.

Through study of neurotransmitter metabolism in the complex pathology and heterogeneity of depression, neuroinflammation, neuroleptic metabolism, and neuropeptide metabolism have emerged as important biological factors. Whether these are causes of depression, are related to pathogenesis, are a result of depression, or are an intermediate stage needs to be investigated to discover new treatments for depression. With recent emergence of precision psychiatry and customized treatment, new attempts have been made to develop a treatment model based on patient biosignature. Given that depression is a heterogeneous disease consisting of various causes, and that it presents various symptoms due to involvement of various parts of the brain, there is need to establish a diagnostic system within a homogeneous group and develop specialized treatments by identifying the causes and pathology of the disease.

This book reviews important aspects of depression, such as brain network, neurobiology, diagnostic and clinical issues, and present and potential treatments. This book is divided into four parts, the first of which explains depression from a network science perspective, including task MRI-based functional network, phenotype network, white matter-based structural network, resting state functional MRI, and neuroimaging-based biomarkers. The second part discusses current diagnostic and neurobiological issues of depression, with particular focus on current diagnostic challenges and future proposals, the role of epigenetics, glia-neuron communication and the gut-brain axis, potential biological markers, and pharmacogenomic testing for diagnosis and treatment. The third part considers current treatments for depression with emphasis on biofeedback, neurofeedback, cognitive behavioral therapy,

acceptance commitment therapy, neuromodulation therapy, complementary and alternative medicine, and current psychopharmacology algorithms. The concluding part considers promising treatments for depression, including a novel psychopharmacological approach, person-oriented narrative psychopharmacology, induced pluripotent stem cells technology, immunotherapy, psychedelic medicines, and biomarker-guided tailored therapy.

This book, written by leading global experts, will provide new insight on clinical-neurobiological underpinnings and development of treatments for depression and will be an excellent source of information for both researchers and practitioners in the field.

Ansan, Republic of Korea

Yong-Ku Kim

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Part I
Re-thinking Depression from a Network
Perspective

Chapter 1

Phenotype Network and Brain Structural Covariance Network of Major Depression



Je-Yeon Yun and Yong-Ku Kim

Abstract Phenotype networks enable clinicians to elucidate the patterns of coexistence and interactions among the clinical symptoms, negative cognitive styles, neurocognitive performance, and environmental factors in major depressive disorder (MDD). Results of phenotype network approach could be used in finding the target symptoms as these are tightly connected or associated with many other phenomena within the phenotype network of MDD specifically when comorbid psychiatric disorder(s) is/are present. Further, by comparing the differential patterns of phenotype networks before and after the treatment, changing or enduring patterns of associations among the clinical phenomena in MDD have been deciphered.

Brain structural covariance networks describe the inter-regional co-varying patterns of brain morphologies, and overlapping findings have been reported between the brain structural covariance network and coordinated trajectories of brain development and maturation. Intra-individual brain structural covariance illustrates the degrees of similarities among the different brain regions for how much the values of brain morphological features are deviated from those of healthy controls. Inter-individual brain structural covariance reflects the degrees of concordance among the different brain regions for the inter-individual distribution of brain morphologic values. Estimation of the graph metrics for these brain structural covariance networks uncovers the organizational profile of brain morphological variations in the whole brain and the regional distribution of brain hubs.

Keywords Brain structural covariance network · Graph theory · Magnetic resonance imaging · Major depressive disorder · Phenotype network

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1.1 Phenotype Network in the Major Depressive Disorder (MDD)

1.1.1 *Phenotype Networks Reflect the Interacting Patterns of Clinical Phenomena in MDD*

From the perspective of phenotype network, coexisting and interacting dynamics among the psychiatric symptoms and psychopathologies might constitute a clinical syndrome or psychiatric disorder [2–4]. Even activating or de-activating cascades of psychiatric symptoms could hypothetically propagate beyond the boundaries among different mental disorders [5]. For instance, irritability and mood lability bridge the two opposite poles of mood—depressive versus manic—in adolescents who experienced at least sub-syndromal depressive or (hypo)manic mood symptoms, even though fatigue and depressive mood are the central mood symptoms most densely connected to other mood symptoms [6]. Of note, comorbid psychiatric disorders could be conceptualized as intertwined connections of phenotype sub-networks segregated for each psychiatric disorder [7], especially in patients who suffer from comorbid depressive symptom and other primarily diagnosed psychiatric disorders such as obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), or eating disorder, among others.

The Gaussian graphical model (GGM) depicts conditional independence relationships or the partial correlations (= network edges) among the selected components or network nodes [8]. For better controlling the false positive associations between the nodes, the GGM is often further regularized using the graphical LASSO by applying the least absolute shrinkage and selection operator [9]. Also, estimation of phenotype networks as directed acyclic graphs (DAG; modeled by bootstrapping the Bayesian hill-climbing function) [10] could uncover the associations-segregating patterns among psychiatric symptoms.

1.1.2 *Comorbid Presence of MDD and Other Psychopathology in Phenotype Network*

1.1.2.1 Comorbid Presence of MDD and Anxiety Disorders

When comorbid psychiatric disorders including major depressive disorder (MDD) coexist, interacting patterns or dynamics among the diverse psychopathologies have to be elucidated for planning more effective treatment strategy, and also for targeting the principal symptoms that are densely connected or tightly associated with other coexisting symptoms. In teenagers previously exposed to earthquake about 6.5 years ago [11], regularized partial correlations among the diverse psychiatric symptoms uncovered the importance of MDD symptoms, as they connect and mediate several internal–external psychopathologies—measured by way of the PTSD

checklist for *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5; for symptoms of posttraumatic stress disorder) [12], the Revised Children's Anxiety and Depression Scale (for symptoms of MDD, generalized anxiety disorder, social phobia, panic disorder, social anxiety disorder, and obsessive-compulsive disorder) [13], and the Youth Self-Report (for aggressive behavior problem and rule-breaking behavior problem) [14]. Also, in cases of social phobia comorbid with MDD, sufferings from loss of self-confidence, suicidal idea, and distress of meeting and talking to new people could be reported [15]. For patients with comorbid diagnosis of MDD and social phobia, additional symptoms of anhedonia and "felt not good as others most days" were shown as mediators among the various mood and anxiety symptoms [15]. On the other hand, in terms of the differential diagnosis, strength of associations between suicidal thoughts and loss of self-confidence might be higher in patients with primary diagnosis of MDD compared to social phobia patients [15].

1.1.2.2 Comorbid Presence of MDD and Obsessive-Compulsive Disorder

For obsessive-compulsive disorder (OCD), lifetime comorbid rates of depression and OCD have been reported as 67.2% in natural clinical studies [16]. For teenaged OCD patients, comorbid depressive symptoms (measured using the Quick Inventory of Depressive Symptomatology—Self-Report version [17]) start from "sadness" and are principally influenced by directional effects from the obsessive-compulsive symptoms including "amount of time for obsessive thoughts" (to depressive symptom of "concentration impairment") and "hardship of controlling obsessive thoughts" (to depressive symptom of "guilt") [18]. In adults diagnosed with OCD, comorbid depressive symptoms are triggered by directed influence from the obsessive-compulsive symptom of "distress of obsessive thoughts" as that influences a depressive symptom of "sadness"; from activation of "sadness," propagation of depressive symptomatology such as guilt and suicidality would occur [19]. On the contrary, depressive symptoms related to the "difficulties in sleeping" and "appetite-weight changes" form two separated islands in the directed acyclic network and are not apparently affected by obsessive-compulsive symptoms [19]. These study results indicate the potential targets of symptom alleviation and follow-up for more effective treatment approach.

1.1.2.3 Comorbid Presence of MDD and Posttraumatic Stress Disorder

Previous studies have reported approximately 50% rates of comorbidity of depression in patients with a diagnosis of posttraumatic stress disorder (PTSD) [20]. Phenotype networks estimated using the fused graphical lasso (which enables jointed estimation of multiple Gaussian graphical models) [21] for combat veterans diagnosed with PTSD uncover the emergence of comorbid depressive symptoms (items of the Montgomery-Asberg Depression Rating Scale [22]) as distinctive

symptoms segregated from the PTSD symptoms (items of the Clinician-Administered PTSD Scale for DSM-IV: CAPS-IV [23]). On the other hand, these two clusters of comorbid depression and PTSD are also bridged by symptoms with higher one-step expected influences [24] including “reported sadness and inner tension” and “getting emotionally upset by trauma reminders”; additional estimation of completed partially directed acyclic network [25] reveals that most of the directional connectedness among these two symptom clusters flow from the PTSD symptoms to comorbid depressive symptoms [26].

1.1.2.4 Comorbid Presence of MDD and Eating or Body Dysmorphic Disorders

Patients with psychiatric disorders associated with distorted body images also often suffer from comorbid mood or anxiety symptoms [27]. Firstly, phenotype networks estimated using the self-reports of inpatients diagnosed with eating disorder reveal the bridged associations among the depressive mood (items of the Quick Inventory of Depressive Symptomatology [17]), anxiety (items of the State-Trait Anxiety Inventory [28]), and eating disorder-related symptoms (items of the Eating Disorders Examination Questionnaire [29]). In other words, in patients diagnosed with eating disorder, direct associations between restlessness and exercise/wanting to empty stomach, between feeling overwhelmed and fear of losing control over eating, as well as between the self-esteem and over-evaluation of shape/weight are shown [30]. Secondly, in patients diagnosed with body dysmorphic disorder, “feelings of worthlessness” and “loss of pleasure” are tightly associated with other comorbid depressive symptoms; however, relatedness between the comorbid depressive symptoms and body dysmorphic-related symptoms including the “interference in functioning due to compulsions” is not prominent [5].

1.1.3 Associations Among the Sub-component Symptoms of MDD in Phenotype Network

1.1.3.1 Negative Cognitive Style, Neurocognition, and Depressive Symptoms

Negative cognitive style attributes the reason of negative events to one’s own enduring characteristics that are regarded as negative or worthless in general and presumes that recent negative event(s) would lead to further adverse events [31]. Accordingly, people predominantly experiencing these negative cognitive styles might be at greater risk of suffering from the depressive mood episode(s) [1]. In adults who have been suffering from recurrent major depressive episode, a negative

cognitive style of “hopelessness” mediates the influences of “decreased self-confidence” and “psychomotor changes” with other depressive symptoms; another negative cognitive style of “helplessness” mainly bridges between the negative cognitive styles and anxiety symptoms [32]. Also, phenotype network of community-dwelling teenagers for the negative cognitive styles (items comprising the Adolescent Cognitive Style Questionnaire-Modified [33]) and mood symptoms (items of the Children’s Depression Inventory [34]) showed associations between the negative cognitive style of “negative self-worth” and “depressive mood,” which in turn affects the negative cognitive styles mainly by way of the influences toward “attribution of negative events to internal or self-related features” (Fig. 1.1) [31].

Additionally, a phenotype network estimated using the Ising model (which reflects conditional dependences among the binary variables) [35] for recurrent MDD revealed interactions among the mood symptoms versus negative cognitive styles and anxiety–irritability symptoms, mediated by way of the neurocognitive symptom of “concentration difficulty” [32]. As a matter of fact, phenotype networks calculated by way of the Spearman rho correlation coefficients between the sub-domains of the Montreal Cognitive Assessment (executive function, visuospatial ability, memory, attention, verbal fluency, and orientation) [36], calculated for unipolar depression and bipolar depression separately, show importance of executive function as a core influencer in the middle of neurocognitive performance both for unipolar and bipolar depression [37].

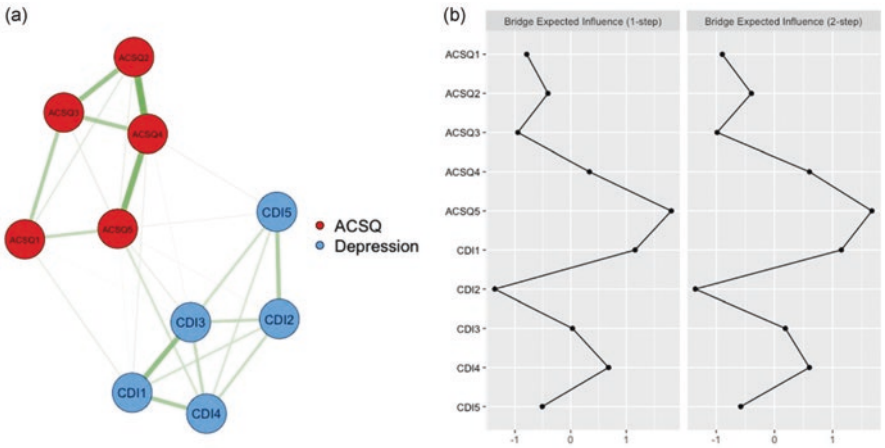


Fig. 1.1 Graphical LASSO comprising contemporaneous measures of cognitive style and depression. (a) Edges depict regularized partial correlations. The thickness of edges reflects the relative strength of association. Maximum edge strength = 0.64. Communities highlighted in unique colors. (b) Indices of centrality considering only the relation between a given node and nodes in the other community. Higher values indicate greater influence. ACSQ Adolescent Cognitive Style Questionnaire-Modified, CDI Children’s Depression Inventory, LASSO least absolute shrinkage and selection operator [31]

1.1.3.2 Differential Patterns of Phenotype Network in the Context of Environmental Factors

Phenotype network uncovers distinctive profile of inter-connectedness among the depressive symptoms in relevance to the associated stressors such as verbal abuse [38] or cancer [39], and raises the possible needs of more customized treatment approach accordingly (Fig. 1.2). Phenotype networks of the Questionnaire 9-item Depression Module [40] estimated for the cancer patients or healthy controls (HC) separately demonstrate a central role of “energy loss” symptom over depressive mood as an influencer in the middle of various depressive symptoms for cancer patients [39]. Of note, in cancer patients, associations between the suicidality and energy loss are increased compared to healthy controls; on the contrary, relatedness between the suicidality and psychomotor changes is reduced in cancer patients compared to healthy controls [39].

1.1.3.3 Differential Patterns of Phenotype Network in the Contexts of Treatment Response and Prognosis

Phenotype network that represents conditional dependence relations among depressive symptoms might be changed after pharmacotherapy, such as selective serotonin reuptake inhibitors (SSRIs), and reduction in depressive symptom severity. In a



Fig. 1.2 Directed acyclic network comprised of perceived, verbal abuse severity; psychopathology; and social interaction patterns. Perceived, verbal abuse severity components of parents (VAPa_total), peers (VAPeer_total), and supervisors (VAPro_total) are shown, as are six further components directly connected to these components (red arrows) including: (1) fidgeting when sitting for a long time (AD_05), (2) problems remembering appointments or obligations (AD_03), (3) fear of assertiveness (LSAS1_AST), (4) low levels of interest and/or pleasure (PHQ_01), (5) psychomotor change (PHQ_08), and (6) irritability (GAD_06); all are rimmed with yellow circles [38]

recent study that integrated two randomized placebo-controlled trials that examined treatment effect of SSRI named Paroxetine for MDD, 8 weeks of pharmacotherapy with Paroxetine resulted in the improvement in depressive symptom severity in addition to the increased inter-connectedness among the diverse depressive symptoms [41].

Phenotype network could be also used to find prognostic factors of MDD. Of note, an association between the “difficulty of falling asleep” and later first-onset of MDD was found in a recent “network outcome analysis (NOA)” that estimated a mixed graphical model or conditional dependencies among the nonclinical depressive complaints (measured using the Inventory of Depressive Symptomatology [42]) at baseline and first-onset MDD at 6-year follow-up in community-dwelling adults [43]. When we want to decipher more detailed profile of sleep difficulty in major depression, phenotype network also might be helpful. In other words, differential dynamics of sleep stage transitions (estimated from the sleep epoch types retrieved from the polysomnography data) in moderate MDD compared to nondepressive controls [44] was examined using the Gaussian graphical model (which reflects regularized partial correlations) with the gLASSO algorithm (which eliminates spurious associations) [45], directed relative importance regression, and estimation of the transition probabilities between each sleep states using a Markov algorithm [44]. The results show impaired homeostatic sleep regulation in moderate MDD compared to HC, as reflected in stronger associations between the sleep stage N1 (closest to wake) and stage N3 as well as between the stage N1 and wake stage, and higher probabilities of sleep stage transition from rapid eye movement (REM) to stage N2 as well as from stages N2 to N3 [44].

1.1.4 Summary and Future Directions

Phenotype networks estimated by way of the Gaussian graphical model [31], Ising network [35], Bayesian directed acyclic network [26], or intra-individual covariance network [46] enable clinicians to elucidate the patterns of coexistence and interactions among the clinical symptoms [7], negative cognitive styles [1], neurocognitive performance [37], and environmental factors [47, 48] (among others) in MDD beyond the traditional border of DSM-based diagnostic category [49]. The results of phenotype network approach could be helpful in finding the target symptoms to be monitored and treated first (as these are tightly connected or associated with many other phenomena within the phenotype network of MDD) [43]. Further, by comparing the differential patterns of phenotype networks before and after the treatment approach such as pharmacotherapy [41], changing or enduring patterns of associations among the clinical phenomena in MDD have been deciphered. Further studies either including the variable of interest such as treatment response or later prevalence of MDD at follow-up within the phenotype network [50] or comparing the patterns of phenotype networks between the subgroups of MDD segregated according to the differential outcome of interest such as disease prognosis [51] are required.

1.2 Brain Structural Covariance Network of MDD

1.2.1 *What Is Brain Structural Covariance Network?*

Brain structural covariance networks describe the inter-regional co-varying patterns of brain morphologies such as regional brain volume [52], gray matter density [53], cortical surface area [54], cortical thickness [55], cortical gyrification [56], among others. Intra-individual brain structural covariance illustrates the degrees of similarities among the different brain regions for how much the values of brain morphological features are deviated from those of healthy controls [57]. Inter-individual brain structural covariance reflects the degrees of concordance among the different brain regions for the inter-individual distribution of brain morphologic values, calculated using the Pearson's correlation or partial correlation coefficients (region by region) [58] or estimated by way of the independent component analyses (which find clusters or sub-networks with similar patterns of brain morphological features) [53]. Additional estimation of the graph metrics [59] for these brain structural covariance networks uncovers not only the organizational profile of brain morphological variations within the whole brain (by way of the global network metrics) but also the regional distribution of brain hubs (identified using the regional centrality metrics), which are more tightly associated with other brain regions in terms of the patterns of brain morphological variations (Fig. 1.3) [57]. In consideration of the overlapping patterns between the brain structural covariance network and coordinated trajectories of brain development and maturation (Fig. 1.4) [58, 60, 61], use of framework of brain structural covariance in examining the brain imaging data (specifically cross-sectional) acquired from MDD patients might be beneficial for extracting more detailed information of MDD pathophysiology reflected in the brain morphology.

1.2.2 *Characteristics of Brain Structural Covariance Network in MDD*

1.2.2.1 **Overlapping Patterns Between Brain Structural Covariance and Functional Connectome in MDD**

Patterns of structural covariance (or associations of the brain morphologic features between different brain regions) in the brain networks of emotional processing [62] and emotional regulation [63] as well as among the brain regions comprising the default mode (related to the self-referential information processing [64]) and salience networks (related to the novelty detection regarding the shifting of attentional focus [65]) [66] are changed in MDD compared to healthy controls. Specifically, degree of concordance in terms of the inter-individual distribution (calculated using the Pearson's correlation coefficients) between the cortical thickness of left dorsolateral prefrontal cortex versus the cortical thickness of right

Step 2: Graph Theory Approach for the Individualized Cortical-Subcortical Structural Covariance Networks [per dataset ($N = 37$)]

A Global network characteristics

Small-worldness measure of *balance* between the degree of *network segregation* versus *network integration*

Global efficiency

average of the inverse *shortest path-lengths* (= minimal number of edges that must be traversed to travel from one node to another) in a network

Network integration



Normalized clustering coefficient

connection probability among the nearest neighbor nodes in a network, normalized using the same value derived from the 1,000 random networks

Network segregation

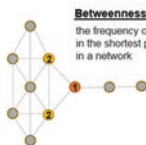
Modularity

the degree to which the network may be subdivided into more clearly delineated *Communities* (= densely connected subgroups of nodes in a network)

B Regional network characteristics

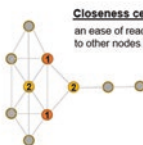
Betweenness centrality

the frequency of a node being located in the shortest path for two other nodes in a network



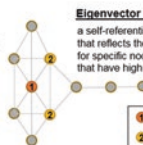
Closeness centrality

an ease of reach from specific node to other nodes in a network with shortcut



Eigenvector centrality

a self-referential measure of centrality that reflects the presence of connectedness for specific node to other nodes that have high eigenvector centrality

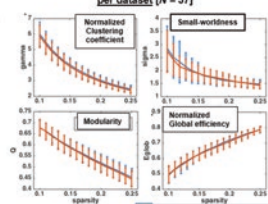


① 1st ranked node(s)
② 2nd ranked node(s)

Step 3: Meta-analytic Integration of Graph Theory Metrics for 37 Datasets

A Global network characteristics

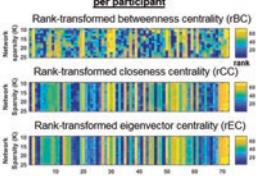
per dataset ($N = 37$)



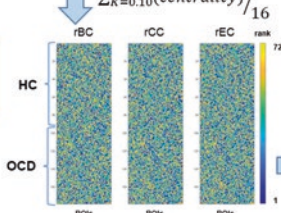
Meta-analysis of 37 datasets for bias-corrected standardized mean difference (SMD = Hedges' g) between HC vs. OCD

B Regional network characteristics

per participant



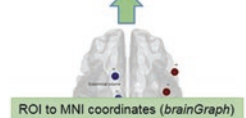
$$\sum k=0.25 (centrality) / 16$$



"Driver region(s) for the differential patterns of coordinated brain morphological changes with given contrast"

if valid for ≥ 2 centralities at given contrast

Coordinate-based Activation Likelihood Estimation
Meta-analysis of 37 datasets
(cluster-level inference of $P < .05$ (FWE); cluster-forming inference at voxel level of $P < .001$)



ROI to MNI coordinates (brainGraph)

if $P < 0.05$

per dataset ($N = 37$)

- HC vs. OCD
- Unmedicated- vs. medicated OCD
- Correlation with OCD illness duration

Fig. 1.3 Schematic diagram of graph metrics. (a) Calculation of graph theory metrics from the intra-individual brain structural covariance networks at single-subject level and (b) meta-analytic integration of graph theory metrics. HC healthy controls, ROI region of interest [57]

dorsolateral prefrontal cortex and the volume of left amygdala is different between groups of medication-naïve MDD patients and healthy controls [62]. Also, strengths of structural covariance between the volumes of amygdala and ipsilateral inferior parietal lobule and between the volumes of orbitofrontal cortex and right middle-inferior temporal cortices are increased in MDD compared to healthy controls; on the other hand, structural covariance of regional brain volumes among the brain regions comprising the default mode network (between right inferior parietal lobule and posterior cingulate cortex) and salience network (between dorsal anterior cingulate cortex and vermis of cerebellum) is decreased in MDD compared to healthy controls [63, 66].

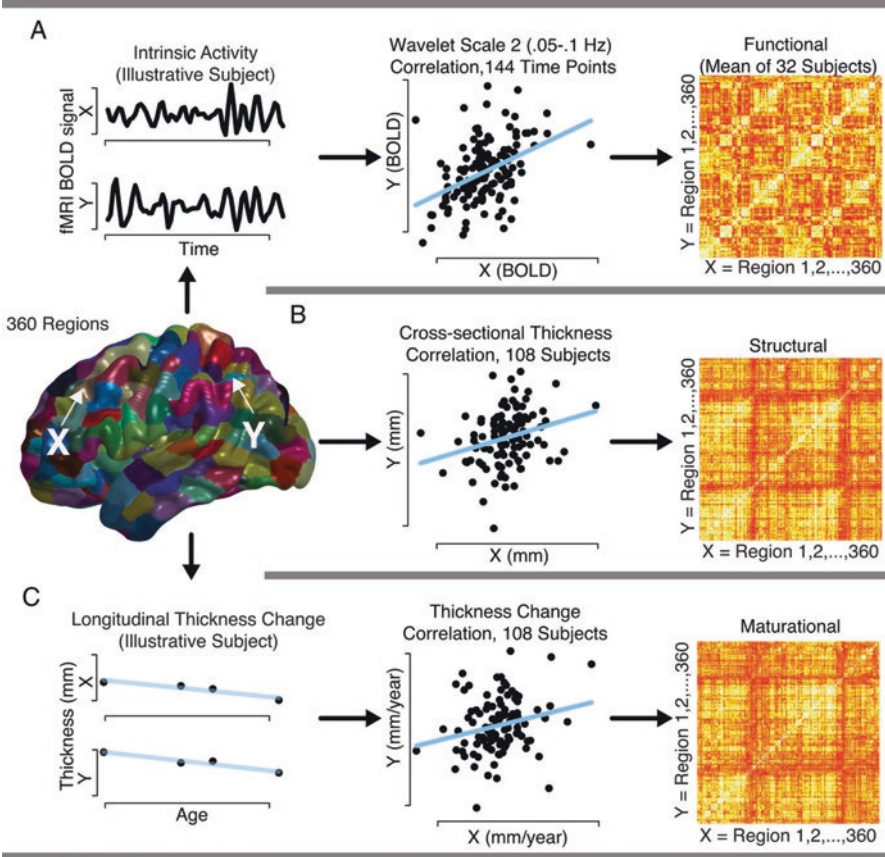


Fig. 1.4 Schematic illustration of the estimation of the three types of brain connectivity, between the same 360 cortical regions: functional connectivity, structural covariance, and synchronized maturational change. (a) For functional connectivity, wavelet correlations of intrinsic activity at 0.05–0.1 Hz were calculated between every pair of regions and averaged across the subjects. (b) For structural covariance, each region’s cortical thickness was estimated using the median scan in terms of age of acquisition for each subject, and pairwise correlations across subjects were calculated after regressing out linear effects of age and gender. (c) For synchronized maturational change, each region’s slope of maturation with age was calculated via linear regression for each subject, using all scans acquired in the age range of 9–22, and pairwise correlations in the rate of maturation were calculated across subjects [61]. (Copyright [2013] Society for Neuroscience)

1.2.2.2 Graph Theory Approach to Decipher the Organization of Brain Structural Covariance in MDD

In addition, graph theory approach helped to uncover the organizational characteristics of brain structural covariance in MDD compared to healthy controls. In general, strengths of similarities between different brain regions for the inter-individual distributions of cortical thickness are more dispersed across the whole brain

(measured using the global network metric of “clustering coefficient” [59]) in MDD compared to healthy controls [67]. Specifically, concordance of inter-individual distribution for cortical thickness at right insula, left middle temporal gyrus, and right transverse temporal gyrus with other brain regions (measured using the local network metrics of “degree centrality” [59] and “betweenness centrality” [59]) is decreased in MDD compared to healthy controls; on the contrary, degree of concordance for inter-individual distribution of cortical thickness between the left isthmus of cingulate and other regions is significantly increased in MDD compared to healthy controls [67]. Further, degrees of concordance for inter-individual distribution of cortical thickness between cingulate-parieto-orbitofrontal regions and other brain regions change in relevance to the severity of depressive symptoms [67].

1.2.2.3 Trials for Estimating the Directional Influences in the Brain Structural Covariance of MDD

Further, by assuming the illness duration for MDD patients as a “pseudo-time series” for the cross-sectional brain magnetic resonance imaging (MRI) data, Li et al. [68] estimated the causal network of group-wise structural covariance by way of the Granger causal analyses [69, 70] from the high-resolution T₁-weighted magnetic resonance images. The study results showed the possible occurrence of hippocampal volume reduction prior to the gray matter volume changes in amygdala and brain regions comprising the default mode network (precuneus, postcentral cortex, left middle temporal and bilateral inferior parietal cortices) in medication-naïve patients in their first major depressive episode [68].

1.2.3 Potential Use of Brain Structural Covariance in Predicting the MDD Prognosis

1.2.3.1 Differential Patterns of Brain Structural Covariance in the Context of Treatment Response

Patterns of the brain structural covariance network could be used to predict the treatment response for brain stimulation therapy such as repetitive transcranial magnetic stimulation (rTMS). For instance, compared to nonremitters, subgroup of treatment-resistant MDD patients who later resulted in symptom remission after the session of rTMS over the left dorsolateral prefrontal cortex showed stronger concordance for the inter-individual distribution of brain gray matter densities among the regions comprising the central executive network (including dorsolateral prefrontal cortex and posterior parietal cortex [71]) [72].

1.2.3.2 Potential Role of Brain Structural Covariance in Predicting the MDD Among the High-Risk Group

Future brain structural covariance studies for high-risk groups for MDD [73] combined with follow-up assessments to examine the clinical outcome [74] would be helpful for finding the potential brain-based markers of vulnerability for MDD prevalence. In cases of bipolar disorder, even in the premorbid time-point, brain structural covariance patterns of adolescents or young adults who had first or second degree relative with bipolar I disorder and later developed mood episode themselves within the next 5-year period showed increased strengths of structural covariance (or more concordant patterns of inter-individual distribution of the gray matter densities) in terms of the inter-network connectedness between the salience network (with a central region of frontoinsula cortex) [75] and inferior parietal-temporal-thalamic regions as well as between the executive control network (anchored in the dorsolateral prefrontal cortex) [76] and inferior frontal cortex [77].

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Chapter 2

Task MRI-Based Functional Brain Network of Major Depression



Chien-Han Lai

Abstract This chapter will focus on task magnetic resonance imaging (MRI) to understand the biological mechanisms and pathophysiology of brain in major depressive disorder (MDD), which would have minor alterations in the brain function. Therefore, the functional study, such as task MRI functional connectivity, would play a crucial role to explore the brain function in MDD. Different kinds of tasks would determine the alterations in functional connectivity in task MRI studies of MDD. The emotion-related tasks are linked with alterations in anterior cingulate cortex, insula, and default mode network. The emotional memory task is linked with amygdala-hippocampus alterations. The reward-related task would be related to the reward circuit alterations, such as fronto-striatal. The cognitive-related tasks would be associated with frontal-related functional connectivity alterations, such as the dorsolateral prefrontal cortex, anterior cingulate cortex, and other frontal regions. The visuo-sensory characteristics of tasks might be associated with the parieto-occipital alterations. The frontolimbic regions might be major components of task MRI-based functional connectivity in MDD. However, different scenarios and tasks would influence the representations of results.

Keywords Task MRI-based · Limbic · Frontal · Functional connectivity · Anterior cingulate cortex (ACC) · Dorsolateral prefrontal cortex (DLPFC)

2.1 Depression and Task MRI

Depression usually causes significant impairments in cognitive, social, and occupational function. It is classified as a major illness impacting the human health according to the World Health Organization report. Therefore, it is important for clinicians and scientists to understand the mechanisms and origins of depression. In this chapter, I will focus on major depressive disorder (MDD) and the perspectives of task

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magnetic resonance imaging (MRI)-related brain network to understand the underlying pathophysiology. The hypothesis of MDD is originated from the “limbic-cortical-striatal-pallidal-thalamic tract” model [1]. The limbic regions, such as the hippocampus and amygdala, have intense and wide connections with cortical-striatal-pallidal-thalamic regions. In recent years, the “limbic-cortical-striatal-pallidal-thalamic tract” model [1] has been condensed as the frontolimbic model, which also includes frontal regions, hippocampus, amygdala, thalamus, and caudate nucleus.

In addition to the frontolimbic model, the default mode network of brain might also be a part of pathophysiology model in MDD. The default mode network, such as the ventromedial prefrontal cortex, anterior cingulate cortex (ACC), and lateral parietal cortex, is related to the self-referential thoughts and negative ruminations [2]. The frontolimbic model might be the representative modern model to explain the pathophysiology of MDD. However, the other regions revealed by the default mode network, such as parietal regions, might also play a significant role in the pathophysiology of depression.

The top-down and bottom-up mechanisms are important for emotion regulation, which are also crucial for the pathophysiology of MDD. The major components of this theory include the dorsolateral prefrontal cortex (DLPFC), ACC, and amygdala. Bottom-up appraisal of negative stimuli would lead to a greater amygdala response and stronger functional interaction between amygdala and both dorsal ACC and DLPFC when compared with positive stimuli. The amygdala-related negative emotion responses would be regulated by the heightened activities of ACC and connectivity of ACC with DLPFC and amygdala, which can resolve the emotion conflicts. Then the attentional control from the DLPFC would produce the highest top-down regulation toward the ACC with increased connectivity between DLPFC and ACC, which would subsequently downregulate the exaggerated emotional responses from amygdala [3].

Before the starting of task MRI-related brain network in MDD, a new concept should be introduced. In current stage, a single model or region would not be specific for one kind of mental illness or physical illness. A possible share of a model or regions might exist in different kinds of mental illnesses. Therefore, even the current studies mostly support the frontolimbic model in the MDD pathophysiology. The frontolimbic model still would be related to other mental illnesses. The more advanced analysis, such as pattern recognition, should be used in the future to identify the cumulative severities and spreading regions of MDD when compared to other mental illnesses. The more sophisticated calculation would be more precise to identify what kind of network pattern would be more specific to MDD [4].

For the following sections, I will classify the task MRI into emotion-related, cognition-related, reward-related, and other categories according to the methods of tasks used in the study. Since different kinds of tasks will activate different kinds of regions, therefore the task MRI would be dependent on the methods of tasks. This is the major difference between task MRI and resting-state functional MRI. The task MRI will be significantly influenced by task categories and underlying mechanisms of different tasks.

2.2 Emotion-Related Task MRI Brain Network in MDD

The emotion-related tasks include many kinds of categories, such as emotional face-matching task, facial expression processing task, emotion regulation task, emotional conflict task, emotion processing task, emotional word evaluation task, emotion identification/recognition task, emotional discrimination and memory task, and emotion expectancy task.

MDD patients had more co-activation of subgenual cingulate with amygdala while processing the emotional face-matching tasks, which suggested the more negative self-referential evaluation while perceiving the emotional faces. In addition, less co-activation of supragenual cingulate with amygdala suggested the less cognitive control ability for emotional faces. The decreased co-activation between amygdala and supragenual cingulate might indicate a lack of ability to co-activate a cognitive control network during emotion processing [5]. The MDD patients also had less connectivity between orbitofrontal cortex and dorsal ACC, precuneus, and cerebellum during face-matching task. In addition, increased connectivity between orbitofrontal cortex and DLPFC and right inferior frontal operculum was observed, which suggested that orbitofrontal cortex might be a crucial area for processing bias in MDD [6]. The high-risk first-degree relatives of MDD also showed similar alterations in orbitofrontal cortex and DLPFC during emotional face-matching task. In addition, the DLPFC hypoactivation during negative stimuli would be the common pattern and orbitofrontal cortex connectivity would be associated with familial risk [7]. The face- and shape-matching task showed an altered prefrontal–amygdala effective connectivity while perceiving negative emotion faces in MDD [8]. Another face- and shape-matching task in MDD demonstrated that cholinergic basal forebrain moderated increased amygdala-PFC and amygdala-hippocampus connectivity, which were associated with attention, arousal, and memory, during processing the biologically salient stimuli [9]. Functional disconnection between limbic regions and frontal regions, especially the amygdala and ACC, during face-matching task might also be associated with emotion processing bias. It might suggest that the frontolimbic network alterations would be related to emotion processing of MDD [10]. In the serotonin depletion model study using facial emotion identification task, the impaired prefrontal–amygdala network might suggest the impairments in the aversive amplification circuit, which can explain the shared negative affective bias and frontolimbic model in mood and anxiety disorders [11]. The amygdala-prefrontal cortex connectivity deficits have also been replicated in adolescents with non-suicidal self-injury, which might also be implicated by underlying depression [12]. The risk for MDD has been associated with decreases in amygdala-frontoparietal functional connectivity during emotion face-matching task. The resilience in MDD would be associated with increased amygdala-ACC connectivity. It emphasized the importance of frontolimbic model again.

The reduction in amygdala-prefrontal connectivity during the facial expression processing task has been found in the MDD patients with monoamine oxidase A gene risk alleles, which might be associated with a longer and more severe disease

course [13]. In addition, the remitted MDD patients had opposite effects of face emotion processing tasks while compared to healthy controls. The bidirectional frontoamygdala connectivity during happy faces and unidirectional frontofusiform connectivity during sad faces were observed in remitted MDD, which also supported the trait pattern of frontolimbic model in MDD even after remission [14]. The inflammation model of depression also found an enhanced activity within the subgenual ACC during emotional face processing task, which would be associated with mood deteriorating effects of inflammation. In addition, the reductions in connectivity between subgenual ACC and amygdala, medial prefrontal cortex, superior temporal sulcus, and nucleus accumbens were modulated by the cytokine level [15]. The MDD patients also showed significant differences in the functional network during facial emotion processing task when compared to controls. The functional network included ventral medial prefrontal cortex, inferior frontal cortex, temporal cortex, and frontoparietal and occipital cortex. It seemed that facial emotion processing task would detect the alterations in frontolimbic areas and other sensory-related regions, such as the parietal and occipital cortex [16]. Another study using facial emotion processing task and attribution task demonstrated that lifetime MDD patients tended to attribute negative events to themselves and positive events to external circumstances. The positive event attribution would activate the precuneus. The negative event attribution would alter the parahippocampal gyrus. In addition, the downregulation of negative event attribution would need to recruit more cognitive efforts from frontal regions to regulate the negative emotions derived from the limbic regions, especially in more severe MDD patients. The internal dysfunctional attributional trait would be improved after receiving instructive attribution strategy, which suggested the effective control of negative emotions from psychotherapy in MDD [17]. The processing of fearful faces in MDD would be associated with neuro-functional alterations of dorsal striatal regions, which might be related to the interpersonal processing with increasing depression severity [18]. From these literatures, it is evident that most studies of facial emotion tasks supported the theory of frontolimbic model in MDD.

MDD patients with family history had greater activities of subcortical regions during shifting attention from the negative stimuli. MDD patients without family history had greater activities in the core limbic areas during the emotion processing task. It might suggest that MDD patients with genetic loading might lack the executive control ability during the attention from the negative facial emotion stimuli. The MDD patients without genetic loading might process the negative emotions via a more visceral way [19]. The fearful face recognition task demonstrated that MDD adolescents had significant alterations in subgenual ACC-based connectivity with amygdala, frontal regions, insula, and fusiform gyrus. The subgenual ACC dysregulation might lead to biased processing of negative stimuli and imbalanced intrinsic functional network of brain [20]. The negative effect stimuli would prominently shift the brain network with decreased global efficiency and increased local efficiency of frontolimbic model and occipitoparietal regions in MDD patients, which indicated the effective state-dependent changes in the network [21]. In addition, the study of high-risk MDD monozygotic twin during emotional face processing task

showed the alterations in the frontolimbic and occipitoparietal regions [22], which also corresponded to the frontolimbic model in the pathophysiology of MDD. Increased functional activations of default mode network and cognitive control network, which also include the frontolimbic regions, to happy faces were associated with greater decreases in self-reported depression severity [23]. In a study of sparse network classification of MDD patients using emotion event-related design and block-related design tasks, the most discriminative connections also included the frontolimbic connections [24]. The decreased activations in the ACC and increased activations in insula, middle frontal cortex, and parahippocampal gyrus of adolescent MDD during negative emotion task would predict better treatment response of antidepressant [25]. The late-life MDD with greater perceived loneliness would have aberrant networking in the subcortical areas during processing of negative stimuli [26]. Female elderly remitted MDD patients had greater functional connectivity between amygdala and hippocampus, which was positively correlated with attention facilitation for negative images [27]. However, the heterogeneity and overlapping features of brain activities should be reminded. The positive emotion processing task showed that more severe MDD patients would have hyperconnectivity of ventral affective areas. The heterogeneity of MDD would also influence the presentations of neuroimaging findings [28].

In the emotion regulation task, MDD patients exhibited diminished prefrontal activation and reduced prefrontolimbic coupling during active regulation. The reducing prefrontal activation should be related to the decreases in sustained-regulation effect in MDD [29]. The reducing activities of right ventral prefrontal cortex in the positive emotion regulation task during attempts to dampen the experience of positive emotions might be related to greater response in the anhedonia aspect of antidepressant treatment [30]. The MDD adolescents had greater responses of amygdala and less amygdala-medial prefrontal cortex connectivity during maintain phase of emotion regulation task, which might suggest heightened amygdala response and diminished reciprocal modulation ability from the frontal cortex [31]. The MDD with early life trauma failed to inhibit the medial prefrontal cortex–amygdala connectivity, which was an important circuit for emotion regulation. The early life trauma-type MDD seemed associated with more significant deficits in the emotion regulation function [32]. The impairments in amygdala activation and altered amygdala-prefrontal connectivity might represent the deficits in the stress buffering and resilience enhancement of MDD with early life trauma [33]. The emotion regulation task in MDD also supported the importance of ACC due to greater depression symptom severity, which seemed associated with less engagement of ACC [34]. The upregulation of positive emotion during emotion regulation task would exhibit the decreased functional connectivity between left middle frontal gyrus and right temporo-parietal regions, which would be associated with anhedonia symptoms in MDD. It also suggested that behavioral therapy would create better treatment effects on MDD patients with greater disturbances in brain reward network function and low motivation due to anhedonia [35].

MDD has excessive default mode network activation and connectivity with subgenual cingulate, which is usually associated with excessive ruminations and

preservations on negative self-referential thoughts [36]. The implicit emotion processing task in MDD also showed decreased functional connectivity between bilateral prefrontal cortices within the default mode network, which was negatively correlated with maladaptive severity in MDD [37]. Another study of implicit emotion processing task in late chronotype subjects, which were prone to have depression, showed a pattern of reduced amygdala-dorsal ACC functional connectivity. It also supported the dysregulation of emotion regulation areas, such as amygdala and ACC. The results also supported the potential importance of frontolimbic model in the pathogenesis of MDD [38]. The hyperactive rostral ACC might represent the deficient inhibitory control of negative self-referential process, which might in turn interfere with frontocingulate activation and cognitive control execution. The rostral ACC activities were also correlated with depression severity and might influence the frontocingulate connectivity in the self-referential and cognitive control abilities [39]. The MDD patients had deficits in the activations and connectivity between ventral ACC and amygdala in emotional conflict task, which also supported the concept of frontolimbic model. In addition, this model was shared by the generalized anxiety disorder patients. However, the MDD-specific pattern might be the concurrent compensating activations of anterior lateral prefrontal cortex, which was correlated with the successful implicit emotional regulation [40]. The MDD with high neuroticism character would be associated with increased activity and connectivity of insula with other brain regions during emotional conflict task. This type of personality dysfunction in MDD might be linked with the alterations in functional connectivity of right anterior insula [41].

The emotional word evaluation task in MDD showed decreased functional connectivity between frontolimbic model areas, such as the medial prefrontal cortex, ventrolateral prefrontal cortex, striatum, and fronto-opercular salience network. The frontolimbic decoupling phenomenon was also replicated [42]. The emotion identification task in adolescent MDD showed greater emotion-dependent connectivity between posterior cingulate cortex and ACC, which was associated with greater depression severity and earlier illness onset [43]. Another study of emotion recognition task and voluntary attention task in MDD showed that patients had hyperconnectivity between and within the default mode network and task positive network. In addition, MDD patients had altered amygdala-visual areas connectivity during processing of emotional pictures. The alterations in the perception from visual areas, recognition from ventral affective regions (also including ventral ACC), and attention allocation from dorsal attention (also including dorsal ACC) might be associated with the abnormal coupling in MDD patients [44]. For the emotional memory perspectives, the emotional discrimination task in late-life MDD showed that the impacts of basolateral amygdala on MDD symptoms would be mediated by the dentate gyrus and CA3 of hippocampus during discrimination and the amygdala-hippocampus connectivity would play a role in emotional episodic memory [45]. However, another study using emotion discrimination task for antidepressant treatment in MDD showed that deactivations of precuneus and posterior cingulate cortex predicted treatment response, and stronger suppression of default mode network would predict better response for antidepressant [46]. The emotion expectancy task

showed that MDD patients had decreased decoupling between medial frontal cortex, posterior cingulate cortex, and parieto-occipital cortex, which might interfere with the downregulation of intrinsic focus [47].

A review of pediatric MDD neuroimaging studies also mentioned that functional connectivity imaging might elucidate the importance of frontolimbic model, especially for the prefrontal, ACC, and limbic nodes [48]. The MDD is significantly impaired in the automatic regulation and voluntary regulation of emotion processing. The automatic regulation phase recruits the ACC, hippocampus, and parahippocampus. The voluntary regulation phase recruits the lateral prefrontal cortex. Dysfunctional automatic regulation might impair the successful voluntary regulation of emotion processing [49]. It is also compatible with frontolimbic concept. From the above literature of emotion-related tasks, the ACC, amygdala, hippocampus, and frontal regions are the major components of emotion tasks. For the emotion regulation and processing task, the ACC, amygdala, frontal regions, insula, and default mode network would be the altered regions of MDD patients. For the emotion memory task, the amygdala-hippocampus network would be responsible for alterations in emotional episodic memory.

2.3 Cognition-Related Task MRI Brain Network in MDD

The cognition-related tasks include many kinds of tasks, such as working memory tasks, Stroop task, cognitive activation task, visual attention task, response inhibition task (Go/No-Go task), cue-target task, and cognitive control task. The N-back working memory task caused more activations in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) of MDD patients, which suggested the possible crucial role of frontolimbic circuit in the pathophysiology, especially for working memory processing aspect [50]. The remitted MDD patients during working memory task showed most diminished deactivations in the anterior medial prefrontal cortex and the increased connectivity with DLPFC, which might be the key regions of antagonistic working memory network in MDD. The reduced default mode network suppression might be an important trait marker of MDD [51]. In the working memory task mixed with delayed visual recognition task, MDD patients revealed the lack of updating ability for working memory task and greater ruminations with depressive symptoms would be associated with more persistent activations to no-longer relevant task information. The disrupted working memory updating seemed associated with alterations in the connectivity between prefrontal cortex and visual association areas [52]. In addition, the MDD and bipolar depression patients showed the common feature of deactivation failure in the medial frontal cortex, which still confirmed the importance of frontal region in the working memory task, and that the default mode network dysfunction might be crucial for the depression etiology [53].

The Stroop Color-World task in MDD patients also found a decreasing connectivity between rostral and dorsal ACC. In addition, the lack of ability of DLPFC and

dorsal ACC to downregulate rostral ACC might form the backbone of frontocingulate dysfunction in MDD [54]. In addition, another study using Stroop task showed that MDD patients had significant alterations in the coupling between orbitofrontal cortex and DLPFC, which might suggest the existence of valuation biases in MDD [55]. The cognitive activation task revealed a dysconnectivity of dissociable prefrontal and cingulate regions in MDD, which demonstrated the increased connectivity of DLPFC during task-induced activation and the increased connectivity of ACC during task-induced deactivation [56]. The elderly MDD patients recruited more efforts in the frontosubcortical regions while performing the Go/No-Go task, which needed sustained attention and inhibitory control [57]. The response inhibition task in adolescent MDD showed inflexibility in the key node of ACC and medial frontal cortex in the central executive network, which suggested the alterations in the flexible network organization to enable better inhibition performance in the task. The dysfunctional self-regulation, represented by the altered local efficiency of ACC and medial frontal cortex, might also suggest the possible alterations in the maturation of ACC [58]. The functional connectivity of cognitive features in frontolimbic regions, such as the DLPFC, orbitofrontal cortex, and subcortical regions, during response inhibition task would be correlated with symptom improvements in MDD and predictive for antidepressant treatment responses [59].

MDD also alters the visuo-attentional system, which is related to the abnormal modulation of parietal lobe on visual cortex and the altered effective connectivity between parietal lobe and occipital lobe. It might contribute to the deficiency in the attentional filtering of information [60]. The cue-target task in remitted MDD patients demonstrated alterations in the functional connectivity of orbitofrontal cortex and hippocampus, which might suggest a possible pattern of deficient inhibition of return for emotional materials in MDD. This cognitive biomarker seemed significantly altered in MDD, which might be associated with orbitofrontohippocampus connectivity disturbances. This kind of frontolimbic pattern deficits in the inhibition of return might represent a trait marker for MDD [61]. The cognitive control task in MDD showed the importance of DLPFC and other frontal regions during the improvement after cognitive behavioral therapy [62]. From the above literature, the cognitive task would detect the alterations in the frontolimbic model, especially for the frontal regions such as the DLPFC, ACC, and orbitofrontal cortex.

2.4 Reward-Related Task MRI Brain Network in MDD

The reward-related tasks include monetary reward task, pleasant image reward task, computer probabilistic reward task, and incentive delay task. MDD patients had lower activation of right orbitofrontal cortex and subcallosal cortex during anticipating monetary reward task. However, the MDD patients had higher activations of right putamen while anticipating monetary reward task versus pleasant image reward task [63]. Another study of monetary task showed that MDD patients had decreased connectivity between caudate and dorsal ACC in response to monetary

gain. However, increased connectivity between caudate and rostral ACC was discovered in response to monetary penalties. This phenomenon had been restored to normal status after treatment in MDD patients, which suggested the importance of ACC and striatal regions in the reward system of MDD [64]. The MDD patients tended not to select previously rewarded stimuli, which might suggest a possible pattern of reward learning impairments. In addition, MDD patients had alterations in the connectivity between midcingulate cortex and nucleus accumbens during monetary incentive task [65]. The hyperactivation of reward network system during reward anticipation and hypoactivation of reward network system during reward outcome might suggest the double dissociation of reward system in remitted MDD patients, especially for the aberrant frontostriatal system. It was also within the major architecture of frontolimbic model [66]. For the treatment response of psychotherapy, the MDD patients with greater connectivity between paracingulate gyrus and left putamen during monetary incentive task would be associated with better treatment response. In addition, the greater attenuation of frontostriatal network during reward processing would be related to improved response [67]. MDD patients during the monetary instrumental learning task showed blunted reward learning and reward prediction error in the striatum. In addition, the overall reduced ventral tegmental area–striatum connectivity to the feedback and striatal blunted reward prediction error was associated with more MDD episodes. The impaired reward learning might be the endophenotype of MDD, and the ventral tegmental area–striatum connectivity alterations might represent the underlying mechanism for the reward learning deficits in MDD [68]. A recent trial of KCNQ channel opener ezogabine in MDD using computer probabilistic reward task showed that decreased functional connectivity of frontolimbic regions, such as the ventral caudate and midcingulate gyrus, would be associated with improvement in MDD symptoms and reward learning [69]. In addition, the psychological trauma would induce the ACC disconnection with decision-making and self-referential regions, which might reflect the aberrant regulation and resilience against negative emotions [70]. The role of ACC in reward learning has been replicated in the incentive delay task of subthreshold MDD, and the frontolimbic model might play another role in the social pain network [71]. From the above literature, the reward tasks in MDD would be associated with frontostriatal alterations, which also fall within the frontolimbic model with prominent alterations in the striatal regions.

2.5 Miscellaneous Task MRI Brain Network in MDD

Miscellaneous tasks in this chapter mean the tasks not typically classified in the emotion, cognition, and reward task categories. This category includes the pain anticipation task, visceral interoceptive sensation task, psychological stress task, the tower of London anxiety task, pleasure music task, and goal-directed task. MDD patients had greater activities in the right ventral anterior insula during high versus low pain anticipation. In addition, the increased insula–thalamus connectivity and

decreased frontoinsula connectivity were observed, which might suggest that overlapping response is not well regulated by the frontal system and subservient for the affective processing in the thalamus. It also supports the dysfunctional “top-down” and “bottom-up” processing of salient and unpleasant information in MDD [72]. The visceral interoceptive sensation task in MDD exhibited decreased activity in bilateral mid-insula cortex during interoceptive attention, which was negatively correlated with the severity of depression and somatic symptoms. The abnormal interoceptive attention in the insula might play a role in the pathophysiology of MDD [73]. The psychological stress task in remitted individuals of recurrent MDD showed increased caudate–amygdala and caudate–hippocampus connectivity and task-induced greater levels of cortisol and anxiety. It suggested that striatal hypersensitivity and hyperconnectivity with amygdala and hippocampus during psychological stress might be the trait marker of depression, which might represent the stress and reward dysfunction in MDD [74].

The tower of London anxiety task in MDD showed lower DLPFC activation and amygdala–DLPFC connectivity than controls during difficult condition of task. In addition, the MDD patients needed more help from DLPFC to regulate amygdala-related anxiety during easy condition of task [75]. When MDD patients perceived the pleasure music with positive emotion response, the ventrolateral prefrontal cortex had stronger connectivity with mesolimbic reward system when encountering pleasurable stimuli. The frontolimbic model has been confirmed in such a hedonic study design in MDD [76]. The goal-directed task in MDD also identified the affected interactions of several intrinsic networks, such as the dorsal attention network, executive network, and default mode network [77]. It also supported the concept of frontolimbic model in MDD. The miscellaneous tasks would have differences in the study results due to the different study characteristics. The interoceptive tasks in MDD would be more associated with insula alterations, and the stress or anxiety task would be related to frontolimbic alterations.

2.6 Task-General and Task-Specific Effects in MDD Network

In the meta-analysis of functional MRI studies in youth MDD, the task-general effects might be the hyperactivation in subgenual ACC and ventrolateral prefrontal cortex. The affective processing task-specific effects might be hyperactivation in thalamus and parahippocampal gyrus. The executive functioning task-specific effects might be hypoactivation in the dorsal ACC, dorsal anterior insula, and pre-cuneus. The positive valence task-specific effects might be hypoactivity in posterior insula. The negative valence task-specific effects might be hyperactivity in DLPFC and superior temporal cortex. The central hubs, subgenual ACC and thalamus, might be hypervigilant to emotional stimuli, which would be associated with MDD symptoms. In addition, the ineffective regulation of “top-down” mechanism from the DLPFC and ventrolateral prefrontal cortex toward the limbic systems during affective processing might lead to the MDD symptoms. The maladaptive

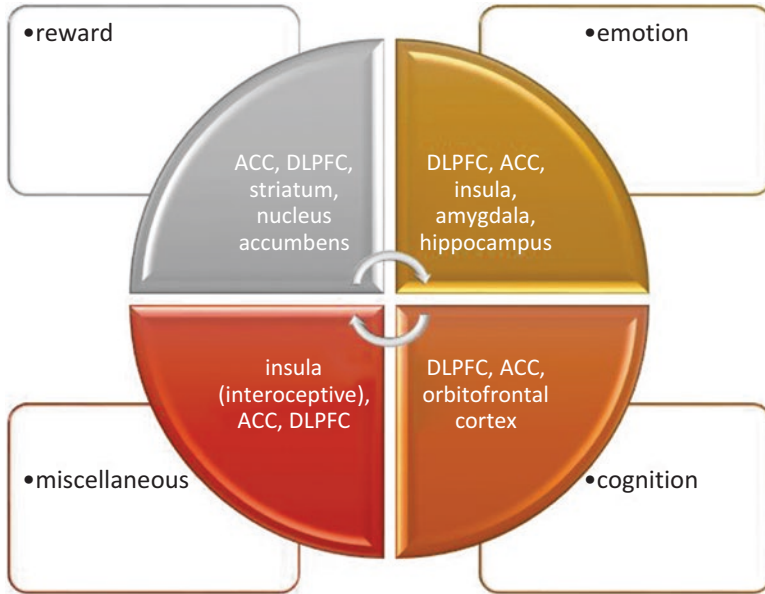


Fig. 2.1 Frontolimbic model and task MRI-based functional brain network alterations in MDD

ruminations and poor executive control might lead to difficulties in shifting from default mode network to task positive network during cognitive demanding task [78]. It confirmed the crucial role of frontolimbic model. I also summarized the task MRI-based functional network alterations in Fig. 2.1.

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Chapter 3

White Matter-Based Structural Brain Network of Major Depression



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Abstract Major depressive disorder (MDD) is frequently characterized as a disorder of the disconnection syndrome. Diffusion tensor imaging (DTI) has played a critical role in supporting this view, with much investigation providing a large amount of evidence of structural connectivity abnormalities in the disorder. Recent research on the human connectome combined neuroimaging techniques with graph theoretic methods to highlight the disrupted topological properties of large-scale structural brain networks under depression, involving global metrics (e.g., global and local efficiencies), and local nodal properties (e.g., degree and betweenness), as well as other related metrics, including a modular structure, assortativity, and (rich) hubs. Here, we review the studies of white matter networks in the case of MDD with the application of these techniques, focusing principally on the consistent findings and the clinical significance of DTI-based network research, while discussing the key methodological issues that frequently arise in the field. The already published literature shows that MDD is associated with a widespread structural connectivity deficit. Topological alteration of structural brain networks in the case of MDD points to decreased overall connectivity strength and reduced global efficiency as

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well as decreased small-worldness and network resilience. These structural connectivity disturbances entail potential functional consequences, although the relationship between the two is very sophisticated and requires further investigation. In summary, the present study comprehensively maps the structural connectomic disturbances in patients with MDD across the entire brain, which adds important weight to the view suggesting connectivity abnormalities of this disorder and highlights the potential of network properties as diagnostic biomarkers in the psychoradiology field. Several common methodological issues of the study of DTI-based networks are discussed, involving sample heterogeneity and fiber crossing problems and the tractography algorithms. Finally, suggestions for future perspectives, including imaging multimodality, a longitudinal study and computational connectomics, in the further study of white matter networks under depression are given. Surmounting these challenges and advancing the research methods will be required to surpass the simple mapping of connectivity changes to illuminate the underlying psychiatric pathological mechanism.

Keywords Connectivity · Connectome · Graph theory · Major depressive disorder · White matter · Diffusion tensor imaging · Psychoradiology · Biomarker

3.1 Introduction

Major depressive disorder (MDD) is one of the most prevalent and costly mental illnesses and is often defined by persistent general grief, worthlessness, guilt, and hopelessness, which can lead to serious negative psychosocial consequences, including suicide [1–3]. In addition to these core symptoms, MDD is frequently accompanied by somatic and other psychiatric symptoms, including anorexia, insomnia, anxiety, cognitive deficits, and psychomotor disturbances [4].

With the development of neuroimaging techniques, there is an emerging research field, that is, psychoradiology, resulting from integration between the fields of psychiatry and radiology [5]. As a new research subfield of radiology, psychoradiology plays important roles in the research and clinical practice of psychiatric disorders using traditional neuroimaging techniques, including magnetic resonance imaging (MRI) combined with new computational science [6]. The term psychoradiology was used to parallel that of the field of neuroradiology, and there are some main discrepancies between these two fields. Psychoradiology focuses on the emotion, behavior, and advanced cognitive function of subjects. Using traditional imaging methods, the abnormalities are usually invisible and need to be further analyzed with the help of computational science. Psychoradiology aims to investigate the association or causal relationship between cerebral alterations and changes in emotion, behavior, and advanced cognitive function.

A growing number of psychoradiology studies have revealed that these MDD-related disturbances are correlated with widespread brain abnormalities, as MDD is involved not only in many local brain regions [7, 8] and circuit connections [9, 10] but also in the whole brain network [3, 4]. Recent increasing imaging evidence strongly supports the dysconnectivity hypothesis for MDD. In theory, MDD is defined as a psychiatric disorder with “disconnection syndrome,” which results not from specific local regional alterations in the brain but rather from abnormal integration of the global neuroanatomical regions. Thus, brain network dysfunction is suggested as the best interpretation model for elaborating the biological mechanism of MDD.

The alteration of connectivity can be illustrated in maps of the brain structural connections in the newly developing field of the brain connectome. The graph theory network, one of the most common approaches in the field of brain connectome, is a novel and useful tool for the whole systems-level identification of the neurobiological basis that underlies depression. The graph theory network suggests the brain as a complex network and explores topological properties to characterize organizational patterns of these neural interactions between anatomical elements [11, 12]. In the last 10 years, graph network studies have demonstrated that MDD is accompanied by the disruption of the brain structural and functional network topological organization. In particular, structural network studies based on white matter imaging data have increased rapidly in the last 5 years. Their findings provide more evidence of whole brain connectivity, increasing our recognition of the neural anatomical basis of brain network disfunction in MDD. However, what consistent findings these white matter network studies obtained are not clear, and what theories and clinical significance these findings reveal are not known. In this chapter, we summarize the findings of recent white matter network studies and try to address the following questions: (1) What distinct stories can the white matter network and its properties tell us? (2) What consistent findings were found by previous white matter network research? (3) Will connectomics properties be helpful in MDD diagnostics or as a neuroimaging biomarker of depression severity? (4) What are the limitations and perspectives of white matter network research?

3.2 What Distinct Stories Can the White Matter Network and Its Properties Tell Us?

3.2.1 Cerebral White Matter

The human brain is known as the most complex and efficient organ in the human body. It governs specialized body functions as a “control system” and regulates all consciousness. The brain comprises a complex network of billions of nerve neurons. The cell bodies of neurons conglomerate into segregated subregions called gray matter areas, while the intricate wiring connects the cell bodies and other neurons by axons or tracts, which constitute the white matter. The cerebral white matter is a branching network of thread-like myelinated axons with a role in conducting

electrical impulses, which provides the capacity of coordinated information transform between the different gray matter regions of the human brain. Moreover, white matter has been shown not only to be passive tissue but also to play a pivotal role in brain functions, for example, affecting learning and modulating the distribution of action potentials in healthy individuals [13].

In the white matter of the human brain, the random microscopic motion of water molecules occurs more freely along the axonal tracts than across the tracts. Diffusion tensor imaging (DTI) has developed as a novel MRI technique to construct and virtually dissect white matter tracts by two typical measures: fractional anisotropy (FA) and the apparent diffusion coefficient (ADC). The ADC is used to characterize the magnitude of water molecules within cerebral tissue, as an increase in the ADC reflects that the white matter tracts are disorganized, while FA is the most widely used DTI characteristics and is used to measure the directionality of water diffusion, as a reduction in FA indicates abnormalities in the white matter tract integrity. Hence, the DTI approach provides a noninvasive way to explore the tissue microstructural organization and brain connectivity architecture in healthy and diseased populations.

3.2.2 *DTI-Based Structural Network*

As mentioned above, the human brain is characterized as a large and complex topological network of regions interconnected anatomically by white matter tracts. The term connectome was recently proposed to define a comprehensive topological network mapping extrinsic connection between structurally specialized brain regions [14]. Graph theory used a set of rigorous mathematical framework to describe the topological characteristics of a complex network map consisting of a set of nodes and the edges linking these nodes. An ideal network map involves both a list of connected nodes and the corresponding directionality and strength of each edge [15]. Hence, graph-based network analysis is a powerful approach for measuring the topological organization of brain structural connectivity and demonstrating the topological properties of brain networks.

Since diffusion MRI (dMRI) is used to quantify the diffusion of water molecules along different directions and DTI provides the most accurate reconstruction of white matter connectivity in vivo, a graph network based on DTI data is constructed to describe the anatomy of the connection across brain regions by the different tractography method. In a DTI-derived graph network, edges can be defined as the properties of white matter fibers across different brain regions, such as the fractional anisotropy, fiber number, and apparent diffusion coefficient in DTI data [16, 17]. The graph can be defined as a binary, weighted graph when the thresholds of weights on the edges are set as 0 (unconnected) and 1 (connected). Given the primary advantages of the ease of acquisition and analysis in dMRI, the DTI-derived connectome facilitates cross-sectional and longitudinal human research investigating the underlying structural connectivity layouts in the brain. Ultimately, the topological properties might be viable as potential markers of white matter network abnormalities across brain disorders.

3.2.3 *Properties of the Graph-Based Structural Network*

In graph theory, an optimized brain network has a small-world topological organization characterized by a balance between structurally integrative and segregated connectivity patterns and ensures efficiently parallel information communication at a low-level cost [18].

From a computational point of view, topological integration is defined by the ability to integrate distributed information in the network or the efficiency of global information communication, which is quantified in terms of the characteristic path length (L_p), normalized characteristic path length (λ), and global efficiency (E_{glob}). L_p is defined by averaging the minimum number of connections that link any paired nodes in the network, which measures the global efficiency and the ability of information integration [19]. λ , the normalized L_p and known as the connective strength, is defined by the mean L_p of 100 matched random networks that preserve the same number of nodes and edges as does the real network. E_{glob} is defined by the capacity of efficiency of the information transform at the global level [20].

In contrast, segregation is defined by the capacity of densely interconnected community of brain regions to conduct specialized processing and is quantified in terms of the characteristic clustering coefficient (C_p), normalized clustering coefficient (γ), local efficiency (E_{loc}), and modularity. C_p is measured by the fraction of a node's neighbors that are also neighbors of each other [19]. γ , the normalized C_p and known as transitivity, is measured by the mean clustering coefficient of the matched random networks that keep the same number of nodes and edges as does the real network. E_{loc} is measured by the capacity of the efficiency of information transform at the local level [20]. High E_{loc} reflects high levels of local connectedness of the brain network. Modularity is thought to be the degree at which a network is transformed into a community structure, which emerges from neurodevelopmental constraints and optimization. A module is defined as a set of nodes densely interconnected with any of them but with fewer interconnections with each other relative to the rest of the network [21].

According to the metrics mentioned above, a network can be classified by different types of networks, including random, regular, and small-world networks [19]. A regular network is defined by a higher γ but a lower λ , reflecting good local efficiency rather than poor global efficiency [20]. In contrast, a random network is defined by a lower γ but a higher λ , reflecting poor local efficiency rather than good global efficiency. In comparison, the small-world network (σ), a measure of the balance between integration and segregation, can be defined by both a relatively higher λ and γ , indicating better global efficiency than that of the regular network and better local efficiency than that of the random network. Specifically, σ can be calculated by the ratio between γ and λ . When $\sigma > 1$ and the conditions of $\gamma > 1$ and $\lambda \approx 1.43$ are fulfilled, a small-world network is defined and ensures the capability of preserving a relative degree of segregation while keeping a high-level integration [19].

Nodal metrics in a network can be described by several measurements, such as the degree, efficiency, betweenness, and other related metrics, including

assortativity and (rich) hubs. The nodal degree is defined as the total number of edges that link directly to it, which indicates the typical local index and the direct measurement of centrality. The efficiency of a node is calculated by taking the inverse of the averaged L_p between the node and each of the other nodes; this reflects the capacity of a node to propagate information to the other nodes within a network, and higher nodal efficiency indicates higher levels of information transfer efficiency [18]. The betweenness centrality of a node is measured by the shortest path length between any two nodes passing a node, reflecting the capacity of a node propagating information across all other nodes within the network [22]. Assortativity reflects the capacity of a node with similar level of connection with each other. An aberrant assortativity means a disturbance of interhub connections. Hubs are defined by a node connecting different local communities and are densely interconnected between them [23]. A rich hub is defined by a hub with more interconnection across other hub nodes than that of random effects within a network. Moreover, the connectivity of rich club is pivotal in the integration of information communication, and its alteration is thought as the source of dysfunction in psychiatric disorders [24]. In addition, network-based statistics (NBS) is a powerful approach in graph theoretical analysis. NBS is developed to describe the specific properties within a network with a relatively low level of control of multiple comparisons of the familywise error rate [25]. This technique is fit to identify weakened connections in some subnetworks.

3.2.4 *Patterns of Aberrant Small-World Network Properties*

Although graph theoretical networks have been widely used to characterize the topological properties of structural brain networks in healthy and disease people, connectome research has often revealed inconsistent interpretation of these. The unified criteria to define the altered small-world network metrics in terms of global topological index are required [26]. Thus, from the perspectives of integration (L_p , λ and E_{glob}) and segregation (C_p , γ and E_{loc}), four defined patterns of aberrant small-world metrics to determine the most consistently disrupted WM network characteristic in patients with MDD were proposed, including regularization, randomization, weaker small-worldization, and stronger small-worldization. A regularized network refers to a network tending to move towards a relatively regular network from a small-world one; a randomized network refers to a network tending to move towards a relatively random network from a small-world one; a network with weaker small-worldization refers to a network tending to move towards a relatively weaker small-world network from a small-world one; and a network with stronger small-worldization refers to a network tending to move towards a relatively stronger small-world network from a small-world one (Table 3.1 and Fig. 3.1).

Table 3.1 Four patterns of aberrant small-world network properties based on integration and segregation

Pattern	Integration				Segregation		
	L_p	λ	E_{glob}		C_p	γ	E_{loc}
Regularization	↑	↑	↓	and/or	↑	↑	↑
Randomization	↓	↓	↑	and/or	↓	↓	↓
Weaker small-worldization	↑	↑	↓	and	↓	↓	↓
Stronger small-worldization	↓	↓	↑	and	↑	↑	↑

C_p clustering coefficient, E_{glob} global efficiency, E local efficiency, L_p characteristic path length. γ = normalized clustering coefficient; λ = normalized characteristic path length

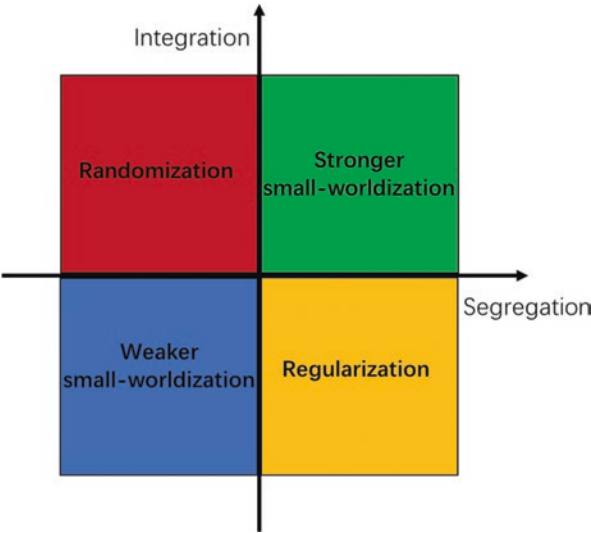


Fig. 3.1 Simple diagram of the four patterns of aberrant small-world network properties from the aspects of segregation and integration. Regularization is described as decreased integration and/or increased segregation. Randomization is described as increased integration and/or decreased segregation. Stronger small-worldization is described as increased integration and increased segregation. Weaker small-worldization is described as decreased integration and decreased segregation

3.3 What Consistent Findings Were Found by Previous White Matter Network Research on MDD?

3.3.1 Anomalous Overall Connectivity of the White Matter Network in MDD

A global decrease in the overall structural strength in MDD has been consistently demonstrated by several studies [27, 28]. For example, Bai and colleagues (2012)

combined diffusion tensor imaging with deterministic tractography method to build the WM networks of the patients with remitted geriatric depression (RGD). RGD patients showed reduced network strength, suggesting a disrupted organization of the structural network in these patients. These findings are in harmony with several previous graph-based WM network research on late-life depression (LLD) [28], which demonstrated lower connective average strength in the patients with LLD with memory deficits (LLD-MD) compared with LLD with intact memory (LLD-IM). These findings indicated the common WM network properties of elder patients with depression. The network overall strength is defined as the average of the overall weights across all of the nodes in the network. Reduced network overall strength is associated with sparse connectivity of the networks, directly reflecting a consequence of structural dysconnectivity in MDD. These findings suggest a reduced WM integrity of the structural network in MDD and support the view that MDD, especially the LLD, is a dysconnectivity syndrome (Table 3.2).

3.3.2 *The Altered Topological Integration Properties in MDD*

The topological integration properties include the characteristic path length (L_p), normalized characteristic path length (λ), and global efficiency (E_{glob}). Wang et al. (2019) employed graph-theory models to describe the topological features of WM networks in late-onset depression (LOD). They found LOD revealed a disrupted small-world architecture, for instance, increased path length and decreased global efficiency, indicating the abnormal topological organization of brain structural networks in LOD patients [29]. This is consistent with the findings of Bai and colleague (2012), as they found increased absolute path length and reduced global efficiency in the WM network in RGD patients [27]. In addition, Mai et al. (201) found LLD showed decreased global efficiency in the WM networks, consistent with the findings of the previous studies on MDD [30]. Caeyenberghs et al. (2019) also reported that treatment-resistant depression (TRD) had a shorter normalized path length, indicating the disability of rapidly combining specialized information from distributed brain regions [12]. These findings supported the view of LLD that core properties of the pathophysiology of this illness are related to an aberrant of the normal global integration in large-scale brain networks [39, 41].

However, the patient with first-episode and treatment-naïve depression (TD) showed the opposite pattern (decreased path lengths and increased global efficiency), where number of fibers thresholded by the sum of surfaces of ROIs were computed between 90 cortical and subcortical regions [31]. Yao et al. (2019) also added the evidence that reported that medication-free MDD patients showed increased normalized path length (λ), a measure reflecting the efficiency of information communication in the brain network [32]. These findings suggested that MDD showed the compensation mechanism for the WM disconnection [33].

The decreased characteristic or normalized path lengths and increased global efficiency are similar graph metrics suggesting that the network moves towards a

Table 3.2 Neuroimaging studies of graph-based white matter networks under depression

Study	Patients		Control subjects		MR scanner	Node definition	Node number	Edge definition	Network type
	n	Age	n	Age					
Bai et al. [27]	35	67.9 ± 4.5	30	71.3 ± 4.4	1.5 T GE	AAL	90	Deterministic	W
Ajilore et al. [44]	40	57.4 ± 11.9	43	61.3 ± 13.1	3.0 T Philips Achieva	FreeSurfer	87	Deterministic	NA
Charlton et al. [43]	28	65.29 ± 7.19	48	68.75 ± 5.77)	3.0 T Philips Achieva	FreeSurfer	87	Deterministic	NA
Korgaonkar et al. [66]	95	33.8 ± 13.1	102	33.9 ± 13.0	3.0 T GE Sigma	DKA	84	Probabilistic	W
Qin et al. [67]	29	38.97 ± 9.95	30	35.57 ± 11.73	1.5 T GE Sigma	AAL	396	Deterministic	W
Sacchet et al. [49]	14	36.6 ± 8.4	18	30.4 ± 10.2	3.0 T Discovery MR750	FreeSurfer	68	Probabilistic	B
Long et al. [31]	22	28.09 ± 9.91	19	24.37 ± 4.18	1.5 T	AAL	90	Deterministic	B
Sacchet et al. [50]	14	36.6 ± 8.4	18	30.4 ± 10.2	3.0 T GE Discovery MR750	DKA	68	Probabilistic	B
Chen et al. [39]	16	44.817 ± 2.2	30	45.037 ± 1.88	1.5 T GE Sigma	AAL	90	GQI	B
Chen et al. [39]	27	32.96 ± 8.84	40	31.43 ± 7.80	3.0 T Siemens Verio	AAL	90	Deterministic	W
Myung et al. [68]	25	55 (50, 60)	31	56 (51, 62)	3.0 T Philips Achieva	DKA	82	Deterministic	W
Li et al. [38]	24	69.67 ± 6.98	24	73.5 ± 8.58	3.0 T	AAL	90	Probabilistic	W
Lu et al. [41]	21	37.5 ± 11.57	25	31.4 ± 10.96	3.0 T Philips Achieva	AAL	90	Deterministic	W
Mai et al. [28]	24	66.21 ± 5.57	30	66.23 ± 4.95	3.0 T Philips Achieva	AAL	90	Probabilistic	W
Tymofiyeva et al. [7]	57	16.2 ± 1.3	41	16 ± 1.4	3.0 T GE 750	AAL	90	Deterministic	W
Liu et al. [69]	44	39.73 ± 8.94	37	35.35 ± 11.17	1.5 T GE Sigma	AAL	90	Deterministic	W
Caeyenberghs et al. [34]	46	41.6 ± 11.7	60	38.6 ± 12.5	3.0 T Siemens Trio	DKA	89	Deterministic	W
Jiang et al. [48]	35	44.400 ± 14.034	35	41.029 ± 12.871	3.0 T GE MR750	AAL	90	Deterministic	W
Liu et al. [51]	44	39.5 ± 13.0	28	34.1 ± 8.1	3.0 T Siemens Trio	AAL	90	NA	W
Wang et al. [29]	37	67.49 ± 4.15	30	71.03 ± 4.11	1.5 T GE Tesla	AAL	90	Deterministic	W
Wang et al. [29]	124	29.67 ± 8.04	209	28.91 ± 7.58	3.0 T GE Sigma	AAL	90	Deterministic	W
Yao et al. [35]	58	33.89 ± 12.14	71	34.84 ± 12.39	3.0 T Siemens Trio	AAL	90	Deterministic	W
Zheng et al. [36]	37	35.7 ± 11.0	38	32.2 ± 11.4	3.0 T GE 750	AAL	90	Deterministic	W

AAL Automated Anatomical Labeling, B binarized, DTI diffusion tensor imaging, NA not available, W weighted

random network. The increased characteristic or normalized path lengths and decreased global efficiency are similar metrics suggesting that the network moves away from a random network. Previous studies showed more evidence of a decreased normalized path length and decreased global efficiency [27, 29], and only one study consistently showed a decreased normalized path length and increased global efficiency in MDD [31]. However, the findings of the two metrics were derived from different studies. This variability in characteristic path length, normalized path length, and global efficiency suggests that the interpretation of topological integration properties is ambiguous. Meanwhile, more additional DTI studies employed FA as a connectivity index and reported no group differences in these global measures of the structural networks between MDD patients and healthy controls [34–36] (Table 3.2). These findings suggested that the brain structural network in MDD patients had decreased average global efficiency and decreased average strength of connectivity, implying aberrant network connectivity of some brain areas and an alteration of the global integration of the structural networks in MDD [37].

The decreased normalized path lengths and increased global efficiency are similar graph metrics suggesting that the network moves towards a random network. The increased normalized path lengths and decreased global efficiency are similar metrics reflecting that the network moves away from a random one. Previous studies showed more evidence of a decreased normalized path length and decreased global efficiency, and only one study consistently showed a decreased normalized path length and increased global efficiency in MDD; however, the findings of the two metrics were derived from different studies. This variability in characteristic path length, normalized path length, and global efficiency suggests that the interpretation of topological integration properties is ambiguous.

3.3.3 *The Altered Topological Segregation Properties in MDD*

The topological segregation properties include the characteristic clustering coefficient (C_p), normalized clustering coefficient (γ), local efficiency (E_{loc}), and modularity. Decreased C_p in WN network was observed in three previous studies [29, 30, 38], and only one study found an increase in C_p in MDD [39], although multiple studies did not find group differences between MDD and control subjects [35, 36]. Clustering coefficient is measured by the number of edges that link with a node's adjacent structures. The previous findings suggested MDD showed a trend towards decreased local segregation in structural network.

Yao and colleague (2019) demonstrated that MDD patients show decreased local efficiency in WM network. This finding is consistent with the other two structural network studies on remitted LOD (rLOD) patients [29] and MDD [30]. However, an increase in E_{loc} was reported in the other WM studies on TD with a decrease in γ [31], and MDD [39], and more studies found no difference of E_{loc} in WM network between MDD and control subjects. This is in line with the finding of Caeyenberghs et al. (2019) that MDD showed comparable modules in WM networks compared to

those in control subject [34] (Table 3.2). However, it is still unclear from these previous studies whether networks under MDD become more regular or random.

The E_{loc} measures the capacity to perform specialized processing within the short-range connections between neighboring regions. These findings indicated MDD, especially long-term depression in patients, was associated with disrupted local microstructural in WM network. This subtle change in WM network could be interpreted by atrophy and transneuronal degeneration [40]. Previous convergent evidences demonstrated that MDD was coupled with aberrant global network organization indexed by aberrant local efficiency, which indicated the generation of some symptoms of MDD patients. Of note, the findings about the altered topological segregation properties of the structural networks in MDD were inconclusive. All of these findings require confirmation by further studies with larger samples.

3.3.4 *The Patterns of Aberrant Small-World Network Properties in MDD*

Most previous studies demonstrated that the WM networks of both MDD and control subjects existed the small-world property. However, two studies reported a decrease in the small-world value in the case of MDD, indicating a different topology patterns from a normal network. According to the subtype criteria of small-world properties, four previous studies showed a shift towards regularization [27, 28, 39, 41]. For example, Bai et al. (2012) found decreased integration (decreased E_{glob} and increased L_p), Chen et al. (2016) found an increase in C_p and E_{loc} with increasing L_p . Lu et al. (2017) reported a decrease in σ . Mai et al. (2017) reported a decrease in L_p and E_{glob} . In contrast, three previous studies revealed a trend going towards randomized network with decreased segregation described by a decrease in C_p [38] and increased integration characterized by a decrease in λ [34]. In addition, Chen et al. (2016) reported a decrease in C_p and E_{loc} along with a decrease in E_{glob} [30].

Moreover, two previous studies revealed MDD network goes towards weaker small-worldization with decreased integration and decreased segregation [29, 35]. For example, Yao et al. (2019) revealed a decrease in E_{loc} and increase in λ ; Wang et al. (2019) found a decrease in C_p and E_{loc} along with an increase in L_p and a decrease in E_{glob} (Table 3.2). However, only one study reported that MDD structural network goes towards stronger small-worldization with increased integration (increased E_{glob} and decreased L_p and λ) and increased segregation (increased E_{loc}) [31].

To sum up, MDD patients did not show consistent aberrant in small-world properties. There is no substantial number of aberrant global organization defined as one of the four patterns. This finding might be contributed to the heterogeneity of the included patient samples (e.g., age and comorbidity). Of note, an exploratory subgroup analysis showed that more studies on the WM network in MDD seems to

reflect a trend towards regularization [27, 28, 39, 41]; this is consistent with the previous study [26].

3.3.5 *Aberrant Hub Properties in MDD*

Recently growing documents demonstrated that some hubs in WM network of MDD tend to become “rich club” with dense interconnection [42]. Three studies explicitly reported the spatial patterns of hubs in MDD, with one study finding increased hub metrics under MDD [43] and two studies finding decreased hub metrics [28, 43]. For example, Charlton et al. (2015) demonstrated stronger hubs in right temporal regions among healthy subjects and robust hubs in frontal regions in individuals with LLD. This conclusion is consistent with the hypothesized LLD-impacted regions (frontal regions) demonstrated by previous studies in the investigation of intercorrelations between gray matter volumes [44]. Caeyenberghs et al. (2019) used the nodal betweenness centrality to conduct a qualitative analysis of the hub distribution and found that both the healthy and TRD groups showed seven hubs, such as the left thalamus, bilateral superior frontal gyri, right superior parietal gyrus, and bilateral precuneus. Mai et al. (2017) showed decreased assortativity in the cognitive control network and corticostriatal circuits in patients with LLD [28]. Moreover, Caeyenberghs et al. (2019) found that patients with TRD revealed a decreased assortativity of the structural networks, indicating damaged club connectivity in MDD [34]. Notably, Mai et al. (2017) also showed aberrant rich-club property, as decreased mean value of connective strength was observed in patients with LLD compared with healthy subjects, indicating the damaged connectivity organization among hubs in MDD structural network.

The previous evidence showed that hubs in the WM networks tend to be selectively vulnerable in MDD. Three recent studies further investigated network vulnerability measured by specifically or randomly removing a hub node or a hub connection influencing other network features [29, 35, 43]. For instance, Yao et al. (2019) reported that the WM network showed more vulnerability to targeted or random node removal compared with the functional network in the case of MDD. Wang et al. (2019) found that the DTI networks in the rLOD group tended to be more vulnerable under the condition of targeted attacks than those in the healthy controls. Charlton et al. (2015) found that there are significant group differences in vulnerability in the right PFC and temporal regions, as the healthy group showed higher vulnerability in the right temporal region, whereas the LLD group showed higher vulnerability in the right PFC (Table 3.2). When a random or specific node was cut, both MDD and control networks might be influenced with a similar pattern. However, MDD networks decreased in size faster than the control networks when hubs were removed, indicating that the topology organization of MDD structural networks is more vulnerable to potential attacks. These findings suggest that for healthy subjects, the temporal regions are critical to the global efficiency of the

network, whereas for the LLD group, the frontal regions are more important to the global efficiency of the network.

3.4 Will Connectomics Properties Be Useful in MDD Diagnostics or as a Biomarker of Depression Severity?

A growing body of evidence suggests that the connectivity properties derived from neuroimaging has quite potential to be used to diagnose MDD and as a biomarker of depression severity. A biomarker is characterized by a quantitative indicator of the basic biological and pathogenic mechanism or clinical response to a treatment or an intervention, which should be reliable, reproducible and practical to use, as well as showing good sensitivity, specificity, and predictiveness. Generally, a biomarker is developed for different categories of criteria, including 6 category definitions [45] and 3 category definitions [46], while the category definitions developed for the main purposes, including prognostic, diagnostic, and theranostic purposes, have the advantage of neuroimaging evidence in depression [47]. Specifically, a prognosis biomarker is a measurable index that can be used to make predictions regarding who will develop a disease, assessing or predicting the likely course of a disorder and playing a role in the identification of those at high risk. A diagnosis biomarker is a measurable indicator that can be used to classify one as having a disease, which reflects some basic and clinical (severity) pathophysiological processes and has the potential to determine the presence or absence and subtyping of a disorder with both high sensitivity and specificity. A theranostic biomarker is a measurable characteristic used to predict an individual response to a particular therapy; it predicts and monitors a patient's biological and clinical response to a therapeutic intervention.

Connectomics has been shown to be useful as an important and complementary biomarker which not only helps increase our understanding of pathological mechanisms but also monitor the development and severity of mental diseases, as well as treatment effects. Measurements of global and local topological properties have been associated with disease severity, as scored by the Hamilton Depression Scale (HAMD). For example, Ajilore et al. (2014) found that normalized global efficiency declines with significantly increasing depression severity in patients with depression [44]. Interesting, Jiang et al. (2019) found that the functional–structural coupling of intrahemispheric connections increased with the HAMD scores of patients with MDD [48]. These findings suggested that the aberrant of the global network metrics in structural network has the potential to be a diagnostic biomarker for the patients with MDD.

Regarding the local network metrics, Qin et al. [67] found hippocampal structural disturbances with increasing severity of depressive symptoms. Moreover, the nodal efficiency in the right superior frontal gyrus and the centrality in the right inferior frontal gyrus were both positively associated with severity of depression.

And Yao et al. (2019) found that nodal efficiency in the left MOG, left PCUN, and left HES and altered edges in the NBS decreased with increasing HAM-D scores in patients with MDD, and the eigenvector centrality in the right gyrus rectus and the right middle frontal gyrus (MFG) were negatively associated with the duration of depression severity. And Long et al. (2015) found that altered orbitofrontal connectivity was associated with the manifestation of symptoms in patients with TD. In addition, Chen et al. (2016) found that the integrity of major fiber bundles of the corpus callosum decreased with increasing severity of current depressive symptom. Meanwhile, Zheng et al. (2019) found that the number of fiber tracts of the anterior cingulum and fiber number-based structural connections between the left MTG and left ITG showed higher depression scores in the case of MDD (Table 3.2). The aforementioned evidence suggested that the alteration of the local network metrics in structural network might be potential to be the diagnostic biomarker for MDD though more further studies are required to confirm and duplicate these findings.

The potential of graph properties was investigated for the diagnosis of MDD. Previous studies explored the diagnostic potential of graph properties and reported high classification accuracies [49–51]. For example, Sacchet et al. (2014) reported that the small-worldness, a metrics reflecting the balance between local specialization and global integration, differentiated patients with MDD from the health control individuals with highest accuracy, and these classifications were contributed by the heightened connectivity at the subcallosal cingulate gyrus (SCG) in patients with MDD [49]. Sacchet et al. (2015) found that small-worldness was the most powerful indicator for the classification of depression in the MDD study using graph-based WM network method [50]. Recently, Liu et al. (2019) classified the MDD patients into two subtypes with relative high specificity and sensitivity by insular-anchored connectivity, which serves as a biomarker for depression under the definition of traditional Chinese medicine (TCM) [51]. There is great significance in the potential of the small-world property and other graph network properties as diagnostic biomarkers, since the problems of curse and a reduction in dimensionality might not be so obvious, which is helpful in the improvement of the generalizability. Even so, the generalizability of these classifiers needs to be investigated through more research in the future.

3.5 What Are the Limitations and Perspectives of White Matter Network Research?

3.5.1 Limitations to the Present White Matter Network Studies

The application of graph theory to explore the alteration of white matter network in MDD is still at the early stages; thus, many important issues and questions remain. First, diffusion MRI reflects indirectly the nature of connectivity which might lose the directional information [52]. Thus, the aberrant structural connectivity measures

must be explained with caution, since their biological process is varied and hard to be separated with dMRI [53]. These are common limitations for all DTI studies, and these issues will be addressed by the higher accuracy of tract reconstruction obtained from the development of new acquisition sequences and advanced tractography algorithms.

Second, DTI has the “fiber crossing” problem, resulting in a loss of existing fibers when deterministic tractography is used to build the structural brain networks. These problems of crossing and long-range fiber tracking may substantially influence the interpretations of graph theoretical approaches. Due to the limitations of DTI analysis in resolving sharp angulations and crossing fibers of tracts, the loss or inaccuracies of fiber crossing eventually lead to the false-positive description of interregional anatomical connectivity, particularly within regions of the interhemispheric side, which belong to long-distance tracts but are calculated as close to each other [54]. Further studies are encouraged to examine the potential of different tractography methods, such as newly developed tractography methods. To address these issues, one of the proposals has suggested using probabilistic tractography in defining network edges [16, 55]. Another method to resolve this issue is anatomical validations, although the human data are insufficient at present.

Third, most of the previous structural network organization in mental disorders has employed a single tensor-based model or index, such as FA or mean diffusivity, to measure the orientation and magnitude of diffusion of water molecular within each voxel of an image. The myelinated axonal fibers can constrain the free diffusion of water, as FA or mean diffusivity can be used to illustrate the aberrant WM organization. However, they are not satisfactory in addressing the nature of the disorganization. Aberrant single tensor index might reflect abnormal changes in several metrics, for instance, the orientation or myelination of axonal fibers, number or density of fibers, their combination and other possible interpretations. To resolve the issue more precisely, diffusion weighted imaging (DWI), which offers greater clarity regarding the cellular substrates, is suggested for further study of the correction or prevention of anatomical dysconnectivity in psychiatric disorders. There are another broad range of recently reported factors significantly impacting the DTI-based structural connectome organization, such as MRI acquisition approaches, the number of diffusion encoding directions, tractography algorithms, structural connectome building strategies, node definition, and edge weighting methods [56].

3.5.2 *Future Perspectives*

First, a higher spatial resolution of the acquired diffusion imaging data is important to reveal detailed fiber pathways not visible on in vivo images. Recently, some researchers tried to obtain even higher resolutions in postmortem samples [57, 58], carrying out direct validation with the histology of tractography reconstructions [59]. The method of high-angular resolution diffusion imaging (HARDI) tractography is suggested to resolve axonal pathways across different neuronal elements in

the brain, which can advance the understanding of cerebellar neural circuitry and structural connectivity in both cortical gray matter and white matter.

Longitudinal work is another future perspective for the research of brain networks in MDD. By increasing longitudinal studies, we can better understand the generative mechanisms of connectomic disturbances in MDD. Specifically, the investigation of these mechanisms needs to be elaborated on the basis of the following three questions: (1) Are the brain network disturbances in MDD just a global phenomenon or a repercussion of a localized dysfunction broadcasting the entire network? (2) Is interregional disconnectivity a cause or consequence of intraregional dysfunction? (3) Are functional network abnormalities caused by anatomical network deficits or vice versa? From the clinical point of view, a longitudinal investigation will prove particularly valuable in the search for potential biomarkers, such as prognosis and theranostic biomarkers. A theranostic biomarker can be used to predict an individual response to a particular therapy, and a prognosis biomarker can be used to predict who will develop a disease. The determination of the two types of biomarkers requires much evidence from longitudinal studies.

Third, graph analyses with different neuroimaging modalities are required and important to supply a more comprehensive view of the topological alterations of brain networks in patients. Specifically, structural–functional coupling analysis is a helpful way to address these issues. The combination of structural and functional networks allows for an examination of the structural–functional coupling. This kind of coupling is an important research topic in the field of network neuroscience [18], as it is a clinically meaningful indicator for exploring brain diseases [18–20]. In a recent study, Jiang et al. (2019) reported that the structural–functional coupling of intrahemispheric connectivity was significantly decreased in individuals with MDD compared with healthy individuals. Moreover, the structural–functional coupling in the number of overlapping intrahemispheric connections in MDD was found to be positively associated with the HAMD scores of the patients, indicating that higher depression severity is accompanied by stronger structural–functional couplings for patients with MDD. The counterintuitive relationships between brain network metrics and behavioral measurements may indicate compensatory reorganization of the brains of patients with MDD in response to atypical conditions. In addition, the positive correlations in their study suggested that the structural–functional couplings of brain networks were altered by the depressive symptoms in the patients with MDD. These findings also indicate the potential of structural–functional network coupling as a promising imaging biomarker for detecting the disease development of MDD.

Fourth, the emergence of computational connectomics is important for understanding the mechanism and development of MDD. Computational modeling can generate hypotheses for further empirical investigations by setting the explicit formulation of processes. For example, the whole-brain computational modeling is newly developed as a computational model constructed by a set of stochastic equations for global and individual coupling according to the connectivity matrix based on the combination of structural connectivity data (derived from DTI tractography) and functional connectivity data [derived from blood oxygenation level-dependent

(BOLD) or MEG signal] [60]. This model can yield important new information to understand the dynamic correlations and entrainment between different local brain region formed by the underlying structural connectivity, by means of constraining and coupling the functional local dynamics between brain areas depending on the underlying structural connectivity of the brain obtained empirically from the DTI data [61]. The whole-brain computational modeling eventually yields the information for mapping the dynamical interactions and consequences of large-scale brain networks over many timescales in neuroimaging studies on neuropsychiatric disorders [62]. Computational connectomics in psychoradiology seeks to model the whole or a partial breakdown of the spontaneous dynamics of rest- and task-related brain connectivity networks in healthy and diseased individuals. Moreover, these computational neuropsychiatry models could provide computer models and generate rational ways to carry out effective treatments or brain interventions to rebalance the dynamics of these networks. Of note, there is a neuroinformatics platform, namely the Virtual Brain (<http://www.thevirtualbrain.org>), which allows the researchers to perform customized simulations, analyze the results, and compare them with other neuroimaging results [63]. Computational connectomics is already developing as a way to understand the structural basis of dynamic changes and disease progression [64, 65].

3.6 Conclusions

In summary, for the investigation of complex mental disorders such as MDD, the study of large-scale brain networks is consistently thought to be increasingly important. In particular, graph-based imaging connectomics provides a broadly conceptual and analytical framework for the comprehensive mapping of brain network abnormalities in cases of MDD. Recent research on the human connectome combines neuroimaging techniques with graph theoretic methods to highlight the aberrant topological properties of structural brain networks in depression, involving global metrics (e.g., global and local efficiencies) and local nodal properties (e.g., degree the betweenness), as well as other related metrics, including a modular structure, assortativity, and (rich) hubs. The previous literature demonstrates that MDD is associated with a widespread structural connectivity deficit. Topological disruption of structural brain networks in MDD points to decreased overall connectivity strength and reduced global efficiency, as well as decreased small-worldness and network resilience. Topological disturbances of structural brain networks in MDD are characterized as decreased overall connectivity strength and reduced global efficiency, as well as decreased small-worldness and network resilience. These structural connectivity disturbances entail potential functional consequences, although the relationship between them is very sophisticated and requires further investigation. In summary, the present study comprehensively mapped the structural connectomic disturbances in patients with MDD across the entire brain, which added important weight to the view suggesting connectivity abnormalities of this disorder

and highlighted the potential of network properties as diagnostic biomarkers in the psychoradiology field. Although graph measurements can measure and interpret different aspects of brain connectivity, several common methodological issues of DTI-based network studies should be considered, for instance, those factors involving sample heterogeneity and fiber crossing problems and the tractography algorithms. Moreover, several important future perspectives have been suggested as conclusions, including imaging multimodality, a longitudinal study and computational connectomics. In particular, multimodal research is suggested for further research to better understand the structural–functional coupling of the brain. By unifying different imaging modalities, a new spatiotemporal perspective on connectomic pathophysiological mechanisms can be provided to keep our understanding of neural basis and pathological mechanism in depression.

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Chapter 4

The Application of a Machine Learning-Based Brain Magnetic Resonance Imaging Approach in Major Depression



Kyoung-Sae Na and Yong-Ku Kim

Summary Major depressive disorder (MDD) shows a high prevalence and is associated with increased disability. While traditional studies aimed to investigate global characteristic neurobiological substrates of MDD, machine learning-based approaches focus on individual people rather than a group. Therefore, machine learning has been increasingly conducted and applied to clinical practice. Several previous neuroimaging studies used machine learning for stratifying MDD patients from healthy controls as well as in differentially diagnosing MDD apart from other psychiatric disorders. Also, machine learning has been used to predict treatment response using magnetic resonance imaging (MRI) results. Despite the recent accomplishments of machine learning-based MRI studies, small sample sizes and the heterogeneity of the depression group limit the generalizability of a machine learning-based predictive model. Future neuroimaging studies should integrate various materials such as genetic, peripheral, and clinical phenotypes for more accurate predictability of diagnosis and treatment response.

Keywords Machine learning · Neuroimaging · Depression · MRI

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4.1 Background

Traditional research methodologies have mainly focused on the identification of risk factors using group-level analysis; however, machine learning utilizes individual-level analysis [1]. Further, machine learning-based research has produced results that can be applied to real-world clinical practice [2].

In the field of psychiatry, neuroimaging techniques such as magnetic resonance imaging (MRI) can elucidate the neural substrates of the essential symptoms and signs of major psychiatric disorders. Because most psychiatric symptoms and behaviors result from the activity of neural systems, neuroimaging findings have been considered very proximal to understanding these characteristics. Particularly, structural and functional MRI studies have been widely conducted owing to their safety and high structural resolution relative to positron emission tomography and single-photon emission computed tomography. Hence, a number of researchers have used MRI data as major materials for machine learning for psychiatric disorders [3].

Among psychiatric disorders, major depressive disorder (MDD) has received significant attention due to its high prevalence and associated disability. Worldwide, MDD has become one of the most prevalent individual psychiatric disorders. Each year, depression causes 50 million person-years of disability worldwide, which is the largest socioeconomic burden among major diseases [4]. From 2003 to 2018, the prevalence of MDD among adults increased from 6.6% to 10.4% (at 12 months) and from 16.2% to 20.6% (lifetime) [5].

The substantial burden of MDD at both the socioeconomic and individual levels has created the need for the early detection and optimized treatment of MDD. Currently, operationally defined criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) is used for the diagnosis of psychiatric disorders [6]. MDD is characterized by vegetative symptoms such as sleep and appetite problems, cognitive symptoms such as attentional disturbances and amnesia, physical symptoms such as fatigue, and two essential symptoms such as depressed mood and loss of interest. Although the DSM-5 defined characteristic features and the minimum number of clinical symptoms to be met for diagnosis, there remain arguments that a diagnostic system based on neurobiological markers should be introduced [7].

4.2 Neuroimaging for the Diagnosis of MDD

To date, many individual studies and meta-analyses have revealed characteristic neuroimaging findings among patients with MDD [8–12]. The common structural neuroimaging features of MDD are decreased volumes in the hippocampal, prefrontal, and limbic area [13–15] and decreased fractional anisotropy in the corpus callosum, right inferior temporal gyrus, and right superior frontal gyrus [16]. However,

such traditional MRI studies have fundamental shortcomings. First, most studies compared major structural and functional findings by a group-level analysis. For example, when comparing MRI findings in MDD patients and healthy controls, hippocampal volume is decreased in the former. This reduced hippocampal volume has important implications for understanding the pathophysiology of MDD in relation to stress, glucocorticoid receptors, and inflammatory activities [17]. If a researcher aimed to identify neuroanatomical structures in MDD, the above approach will yield satisfactory results. However, if clinicians want to utilize MRI findings for differential diagnosis or to guide the selection of therapeutic modalities, such results from group-level analysis cannot provide the necessary data. Clinicians typically are not interested in the mean reduction in hippocampal volume in MDD patients relative to healthy controls. Instead, they generally want to know if the patient sitting in front of them is likely to have MDD or not given the MRI findings. This gap between existing research findings and clinical utility has caused fundamental suspicion about the necessity of neuroimaging methodology in clinical practice.

The rise of machine learning-based approaches has brought about new opportunities for MRI results to be used in clinical practice. A recent review summarized structural and functional MRI studies that classified depression by machine learning technique [18]. Most of these MRI studies aimed to differentiate depressed patients from healthy controls, and the most frequently used algorithm was the support vector machine. The number of participants in each group ranged from 9 to 158, including individuals mostly between 15 and 40. The overall accuracy ranged from 62.0% to 99.0%. Elsewhere, one study predicted the future onset of depression among children and adolescents within 3 to 4 years [19]. This model showed high predictability (accuracy, 96%; sensitivity, 100%; specificity, 93%).

4.3 Differentiating MDD from Other Psychiatric Disorders

Generally, differentiating depression from other psychiatric disorders is much more difficult than differentiating patients with depression from healthy controls because psychiatric disorders partly share similar neurobiological risk factors and clinical features. Indeed, one study group examined differences in the gray matter and white matter between MDD and panic disorder patients, respectively. In the group-level analysis, MDD patients had a smaller right medial frontal cortex and right temporal gyrus as compared to those with panic disorder [20]. In addition, white matter connectivity in the left anterior thalamic radiation, left uncinate fasciculus, left inferior fronto-occipital fasciculus, and bilateral corpus callosum was reduced relative to panic disorder [21]. Another study developed a machine learning algorithm that predicted panic disorder with and without comorbid depressive disorder [22]. This algorithm classified patients with comorbid depression with an accuracy of 73%, sensitivity of 77%, and specificity of 70%.

One study investigated cortical thickness among MDD and generalized anxiety disorder (GAD) patients [23]. Patients with MDD and GAD or MDD had greater

bilateral middle frontal, left medial frontal, and left frontal pole cortical thinning as compared with healthy controls. Additionally, patients with MDD and GAD had cortical thinning in the right medial orbitofrontal cortex, fusiform gyri, left temporal pole, and lateral occipital cortex. Another study examined differences in the functional state between GAD and MDD [24]. In this study, only patients with GAD (i.e., the anxiety-only and comorbid groups) failed to implicitly regulate emotional conflict. Elsewhere, researchers applied a machine learning algorithm (support vector machine) for classifying GAD ($n = 19$), MDD ($n = 14$), and healthy controls ($n = 24$) [25]. This study employed a multimodal approach. Cortisol level measurement and clinical questionnaires were also included as predictive variables. The overall classifying accuracy was 67.5%.

4.4 Insufficient Treatment Response in MDD

Early optimized treatment is usually necessary for patients with moderate to severe MDD [26]. For decades, most randomized controlled trials have shown that the efficacy of antidepressants is superior to that of placebos [27]. However, contrary to the success of clinical trials sponsored by the pharmaceutical industry, real-world pharmacological treatment of MDD has achieved much lower rates of efficacy. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the seminal real-world psychopharmacological trial, showed that initial remission rates were less than 30% [28, 29]. In the STAR*D study, the remission rates for four different antidepressants were 67%. The stark contrast between the efficacy of controlled clinical trials and that of this real-world trial suggests that the efficacy of antidepressants might be overinflated. Indeed, for 252 placebo-controlled randomized controlled trials performed during the last 25 years, the pooled response rate for the placebo was approximately 37% (95% confidential interval: 36–39%) [30]. This is a very high rate considering that all of the participants of the clinical trials were diagnosed with MDD rather than just temporary depressive feelings.

4.5 Limited Availability of the Current Antidepressants

A variety of factors such as drug adherence, personality traits, severity, and subtypes of symptoms as well as comorbid psychiatric and physical conditions influence the insufficient therapeutic effects of antidepressants. For example, in the case of drug adherence, less than half of outpatients with MDD were still taking their antidepressants after 6 months [31]. A recent study reported that many people with MDD do not receive minimal treatment in 21 high-income countries and that only 16.5% of people with MDD receive the minimally required treatment [32].

Despite the above factors, inadequate treatment response is fundamentally a result of the limited pharmacological mechanism of action of current

antidepressants. From tricyclic antidepressants to selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants such as desvenlafaxine, vortioxetine, and agomelatine, enhancing serotonergic and noradrenergic neurotransmission has been the main conceptual mechanism of action [33]. Although ketamine and other novel glutamate receptor-related drugs have received much attention, ethical problems and side effects hinder ketamine from being used more widely in the clinical setting [34]. Hence, clinicians face a growing need to improve the treatment response rather than waiting for the development of a “magic bullet” antidepressant.

4.6 Need for Optimizing Treatment Strategy

Given the limited pool of available antidepressants, how can clinicians raise the treatment response rate?

Systematic and rigorous clinical practice, such as measurement-based care, may be one possible solution [35]. However, due to a variety of factors such as the health insurance system, not all clinicians can perform measurement-based care in their everyday practice. A more automated and convenient frame is needed. If clinicians can know in advance how their patients will respond to treatment, the initial stage of treatment will likely be much more effective.

This sort of approach has become a possibility due to the development of machine learning, big data, and precision medicine [36, 37]. Broadly, the machine learning-based approach for the treatment response to antidepressants can be divided into three categories: symptoms, genetics, and neuroimaging. Before describing neuroimaging, we henceforth briefly discuss current updates related to symptoms and genetics.

Machine learning algorithms have enabled better predictions of treatment response by using old datasets. By analyzing nine clinical trials, including the STAR*D [28] and Combining Medications to Enhance Depression Outcomes [38] studies, Chekroud et al. (2016) showed that different antidepressants address different clusters of MDD symptoms [39]. For example, a high dose of duloxetine showed better efficacy than escitalopram in addressing core emotional symptoms. Separately, there was no significant difference in the change in core emotional symptoms during 8 weeks between escitalopram and placebo. Such an approach can be practical for clinical psychiatrists because the information needed to build the predictive algorithms can be easily obtained.

On the other hand, pharmacogenomic approaches have been widely incorporated within clinical practice. There are several diagnosing kits available that determine the genotypes of cytochrome P450 enzymes (CYP450) of patients with MDD [40]. Pharmacokinetics and pharmacodynamics are largely determined by metabolism. Individual antidepressants have different profiles of influence on CYP450 and metabolism by CYP450. Hence, clinicians can consider the patient’s CYP450

genotype when selecting and/or dosing antidepressants [41–43]. The pharmacogenomic approach is more cost-effective relative to usual care [43].

4.7 Fruits of Group-Level Neuroimaging Studies for Treatment Response

To date, neuroimaging studies have aimed to stratify the neural substrate for depression as compared to healthy populations [9, 11] and other psychiatric disorders [44]. The approach has contributed substantially to our understanding of the neuroanatomical and functional mechanisms underlying depression. However, there has been increasing criticism of the neuroimaging approach because the results cannot be directly translated to clinical practice [45]. Unlike the pharmacogenomics approach, which has mainly focused on the analysis of CYP450 genotypes [42], the neuroimaging-based approach has focused on vulnerability to treatment response, rather than the optimization of specific antidepressants.

Neuroanatomical substrates (i.e., gray matter, cortical thickness, and white matter integrity) and neural function (i.e., resting-state BOLD and functional connectivity) are essential pathophysiologic correlates of MDD. Although neuroimaging is unlikely to help clinicians determine the optimal antidepressant, it can help predict the treatment response by electroconvulsive therapy (ECT). A meta-analysis reported that functional neuroimaging markers vary according to the type of treatment [46]: anterior insular activity decreased after SSRI treatment, whereas DMN activity decreased after ECT. Many group-level studies have reported a close relationship between neuroimaging findings and treatment response in MDD. Elsewhere, a different meta-analysis showed that increased frontolimbic functional connectivity is associated with treatment response to antidepressants in resting-state functional MRI (fMRI) [47]; here, subcallosal cortical connectivity influenced the treatment response to repetitive transcranial magnetic stimulation (TMS). However, while such studies greatly contribute to our understanding of the neural substrates of depression, they cannot be applied to clinical practice.

4.8 Machine Learning-Based Neuroimaging Studies for Predicting Treatment Response

About a decade ago, machine learning-based predictive models were introduced to predict the treatment response in MDD [48]. Table 4.1 selectively summarizes results from eight neuroimaging studies that predicted the treatment response among patients with MDD. Of note, the included studies show several commonalities. First, the studies had small sample sizes. The study with the smallest sample size included 24 participants (11 responders and 13 nonresponders) [49] who underwent fMRI to determine the treatment response to antidepressants. The median

Table 4.1 Major findings of machine learning-based MRI studies for predicting treatment response in MDD

Author-year	Sample size	Modality	Intervention	Outcome	Definition	Performance
Leaver 2018 [52]	Responders 20; nonresponders 26	fMRI	ECT + antidepressants	Responders vs. nonresponders	More than 50% reduction in the mean scores of HRSD, MADRS, QIDS	Accuracy 58%–68% Sensitivity 54%–64% Specificity 55%–74%
Hu 2018 [57]	Early responders 25; nonresponders 13	sMRI (hippocampus)	Antidepressants	Early responders vs. nonresponders	More than 50% reduction in HRSD after 6 weeks (early response)	AUC 0.717–0.831 Sensitivity 53.8%–76.9% Specificity 80.0%
Cao 2018 [58]	Remitters 20; nonremitters 20	sMRI (hippocampus)	ECT	Remitters vs. nonremitters	HRSD ≤ 7	AUC 0.90 Accuracy 83.3% Sensitivity 91.7% Specificity 75%
Wade 2016 [55]	Responders 20; nonresponders 14	sMRI	ECT	Responders vs. nonresponders	More than 50% reduction in the combined scores of HRSD, MADRS, QIDS	AUC 0.90 Accuracy 89%
Redlich 2016 [56]	Responders 26; nonresponders 15	sMRI	ECT	Responders vs. nonresponders	More than 50% reduction in HRSD	Accuracy 73.9%–78.3% Specificity 40%–50% Sensitivity 100%

(continued)

Table 4.1 (continued)

Author-year	Sample size	Modality	Intervention	Outcome	Definition	Performance
van Waarde 2015 [53]	Remitters 20; nonremitters 20	fMRI	ECT	Remitters vs. nonremitters	MADRS $\leq$ 10 after ECT	Sensitivity 80%–84% Specificity 80%–85% Positive predictive value 80%–88%
Patel 2015 [49]	Responders 11; nonresponders 13	fMRI	Antidepressants	Responders vs. nonresponders	HRSD <10	Accuracy 89.5% Specificity 90.0% Sensitivity 88.9%
Korgaonkar 2015 [54]	Remitters 54; nonremitters 103	sMRI	Antidepressants (escitalopram, venlafaxine extended-release, sertraline)	Remitters vs. nonremitters	HRSD $\leq$ 7	Accuracy 84%–85%

QIDS The 16-item quick inventory of depressive symptomatology

sample size of the 8 studies was only 39.5 patients. Recent systematic reviews and narrative reviews similarly suggest that sample size has been a dilemma [50] given that accuracy increases as the sample size increases and vice versa. A large sample size may enhance the heterogeneity of a group with a psychiatric disorder. In the case of MDD, various combinations of symptoms can arise according to the DSM-5 [51]. Second, all eight studies used MRI, including three studies that used fMRI [49, 52, 53] and five that used structural MRI [54–58]. Other neuroimaging modalities have been applied in specific subgroups. For example, ^{18}F -FDG-PET was used in one study examining patients with geriatric depression [59], where changes in glucose metabolism after antidepressant treatment were correlated with changes in the clinical symptoms of depression. However, these findings could not be used in clinical practice because the correlations were obtained after treatment rather than before initiating treatment.

The performance of predictive models does not appear to depend upon the mode of MRI (functional or structural). Four studies have predicted the response to ECT monotherapy [53, 55, 56, 58]. One study considered the treatment response to ECT augmented with antidepressants [52]. Three studies built predictive models for the response to antidepressants [49, 54, 57]. Among the four studies that included antidepressants as a treatment option, only one noted the type of antidepressant [54]. In that study, escitalopram, venlafaxine extended-release, and sertraline were compared. As summarized in Table 4.1, recent neuroimaging studies that have aimed to predict treatment response are limited in several ways.

4.9 Limitations

A machine learning predictive model can be developed and elaborated based on numerous examples and features of the topic in question. When there are large numbers of examples as well as features, the machine can learn statistical patterns more accurately. This is why machine learning is referred to as a data-driven technique. However, most of the machine learning-based MRI studies only recruited 20 to 30 participants in each group. Such a small number of examples substantially limit the generalization and clinical utility of the predictive model. Further, although many of the models showed a superior level of predictive accuracy under testing, they still must be applied in real-world clinical practice. The problem in this case goes beyond the sample size of participants; for example, there could be large heterogeneity in the clinical features of depression. The MDD as defined in the DSM-5 does not guarantee that the samples might have homogenous clinical features with other patients in different sociocultural and geographic regions. Even in the same society, there can be substantial differences in the clinical features of depression according to the melancholic, atypical, and anxious/distressed types. On the other hand, differences in the manufacturer, type of model, strength of the magnetic field, and detailed settings of parameters can all result in variations among images. Solving the above issues would make it easier to apply findings from the neuroimaging studies to clinical practice.

4.10 Future Directions

Future neuroimaging studies are expected to measure neuroimaging from the perspective that complex structures interact with each other and jointly contribute to the onset and course of depression. In short, there is no possibility that the therapeutic response to depression can be solely predicted by neuroimaging materials. Although neuroimaging results reflect various demographic (e.g., age and sex), past history (e.g., early life adversity and suicide attempt), substance (e.g., alcohol and illegal drugs), and psychopathology (e.g., depression and anxiety) factors, each component should have its own position within a predictive model. The reason that a unimodal approach (e.g., neuroimaging, genetic, symptomatic) is often used is that the tools and sample size required to analyze high-dimensional data and build a predictive algorithm are limited. Similar to the progress of technology related to artificial neural network theory, which was first proposed decades ago, the integration of clinical, genetic, and neuroimaging information is poised to rapidly advance. Indeed, a recent study revealed that a predictive model built on neuroimaging data alone could not outperform a model built on the combined data of neuroimaging and clinical variables [60].

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Chapter 5

“Common Currency” Between Experience and Brain: Spatiotemporal Psychopathology of the Resting State in Depression



Georg Northoff

“Neither the ‘brainless’ psychiatry of the middle of the 20th century, nor the ‘mindless’ variety of the past 30 years should be taken to represent the most we can achieve. The future should yield a synthesis” ([24], 17)

Abstract The aim of this contribution is to introduce Spatiotemporal Psychopathology and the way it may complement and extend Phenomenological Psychopathology by bridging the methodological gap between the brain and experience. In the first part, I will provide examples for spatiotemporal correspondence between neuronal and psychopathological features. Specifically, I will discuss how spatial changes in the brain’s spontaneous activity translate into abnormal experience of the self in major depressive disorder (MDD). Finally, I will briefly discuss the method of such Spatiotemporal Psychopathology and distinguish it from the methods relied on in other forms of Psychopathology with a special focus on showing the continuity between Spatiotemporal and Phenomenological Psychopathology.

Keywords Phenomenological Psychopathology · Spatiotemporal Psychopathology · Experience · World · Brain and resting state activity · Spatiotemporal features

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5.1 Introduction

5.1.1 *Methodological Gap Between Experience and Brain*

Psychopathology concerns the empirical and theoretical framework in which symptoms, behavior, and experiences in psychiatric patients can be described, categorized, and classified [25, 27–30]. Different empirical and theoretical frameworks have been suggested in past and present approaches to psychopathology, including Cognitive Psychopathology [4, 8], Affective Psychopathology [24], Phenomenological Psychopathology [6, 7, 19, 25, 27–30], clinical psychopathology (current classification systems like DSM-5 and ICD-10), and the recent Research Domain Operational Classification (RDoC) that entails behavioral and computational psychopathology [3].

Despite their virtues for single functions (like affective, cognitive, etc.), all these approaches suffer from a methodological gap between the brain, on the one hand, and experience and symptoms on the other. Neither approach show why and how the symptoms and their experience are related to and based on the brain. This is not a problem specific to psychiatry though but holds for current neuroscience in general. We currently do not know how and why the neuronal activity of the brain generates or yields mental features like self and consciousness. This lack of knowledge reverberates particularly in psychiatry where the various psychopathological symptoms are essentially mental symptoms.

The different psychopathological approaches take either side of the gap, that is, mental or neuronal, as starting point. For instance, Phenomenological Psychiatry takes experience or consciousness itself as starting point and focuses on exploring first-person experiences in detail [25, 26, 28, 29]. Specifically, the focus is on the first-person experience of time and space as well as body, self, and world. The brain, in contrast, nowhere surfaces in experience in particular and phenomenology in general, since it cannot be accessed in experience in first-person perspective but only in observation as in third-person perspective. The brain is thus excluded in experience of the own self, body, and world including time and space in particular and phenomenology in general. Such exclusion of the brain in experience or consciousness occurs by default, e.g., on methodological grounds, since the brain cannot be accessed in experience in first-person perspective.

The exclusion of the brain in experience raises the question for Phenomenological Psychopathology of how experience can be linked to the brain. This question becomes even more crucial given the fact that recent brain imaging shows the relationship of psychopathological symptoms to neural alterations in the brain. That leaves open though how the experience of those psychopathological symptoms and of self, world, and body including time and space can be related to the brain and its neural changes. In other words, Phenomenological Psychopathology needs to establish a bridge or link to the brain and thus from phenomenal to neural activity. How is that possible? One way is to search for a “common currency” that is shared by both experience and the brain and, at the same time, underlies our experience of

self, body, and world as well as our observation of neural activity changes in the brain. I suggest in this contribution that such “common currency” shared between experience and the brain consists in time and space. Alterations in time and space may then be manifest in both abnormal experience of self, body, and world and abnormal neural activity changes in the brain. Psychopathological symptoms may then ultimately be traced to alterations in time and space hence my suggestions of what I describe as “Spatiotemporal Psychopathology.” Considered in this way, Spatiotemporal Psychopathology can be considered an extension of Phenomenological Psychopathology from experience to the brain.

Very much like Phenomenological Psychopathology, Biological Psychiatry too is confronted with a gap which occurs from the opposite side though. Biological Psychiatry investigates the brain’s neuronal states in all their molecular, genetic, cellular, regional, and network levels as they can methodologically be approached in third-person perspective. This leaves out experience and its first-person perspective though. Experience is thus excluded on methodological grounds in Biological Psychiatry in the same way and as much as the brain is often (though not always) excluded in Phenomenological Psychiatry. The methodological gap between experience and the brain is thus mutual, being fostered from both sides, the brain and experience, e.g., Biological and Phenomenological Psychiatry.

How now can we bridge the gap from Biological Psychiatry to Phenomenological Psychopathology? For that we need to go back to what potentially underlies the observed neural activity changes in the brain which, as I will demonstrate below, can be found in the temporal and spatial organization of the brain’s neural activity. There is recent empirical evidence that such temporal and spatial changes do indeed feature psychiatric disorders like depression and schizophrenia (see below). These alterations in time and space underlying the observed brain’s neural activity may then provide the bridge to the abnormal experience of time and space that underlie the abnormal experience of self, body, and world as investigated in Phenomenological Psychopathology. Spatiotemporal Psychopathology can consecutively be considered an extension of Biological Psychiatry from the brain toward experience in more or less the same way (though reversed direction) as it is an extension of Phenomenological Psychopathology from experience to the brain. In the following, I shall specify the exact positioning and characterization of Spatiotemporal Psychopathology as extension of both Phenomenological Psychopathology and Biological Psychiatry in methodological regards which will be followed by illustrating such approach by specific examples.

5.1.2 “Common Currency” Between Experience and Brain

How can we close the [...]gap between experience and the brain? Closing this gap is central for psychiatry since we need to understand the processes that transform abnormal neuronal into phenomenal states which psychiatric patients experience in first-person perspective. How can we apprehend these transformative processes,

e.g., neuronal-phenomenal transformation? For that we may want to search for a shared overlap or “common currency” between neuronal and phenomenal states that drives the transformation of the former into the latter.

The shared overlap or common currency between neuronal and phenomenal states, e.g., the brain and experience, may consist in spatiotemporal features. On the side of the brain, it is the spontaneous activity (rather than its stimulus-induced or task-evoked activity) that may be central in providing or constituting such spatiotemporal structure (see below for details). The brain’s spontaneous activity shows certain spatiotemporal feature, a particular spatial and temporal structure in its neural activity that surfaces in and is transformed into phenomenal state, e.g., experience (see [16] for many examples). One would consequently expect a common, similar, or analogous spatiotemporal structure between the brain’s spontaneous activity and the phenomenal features of experience.

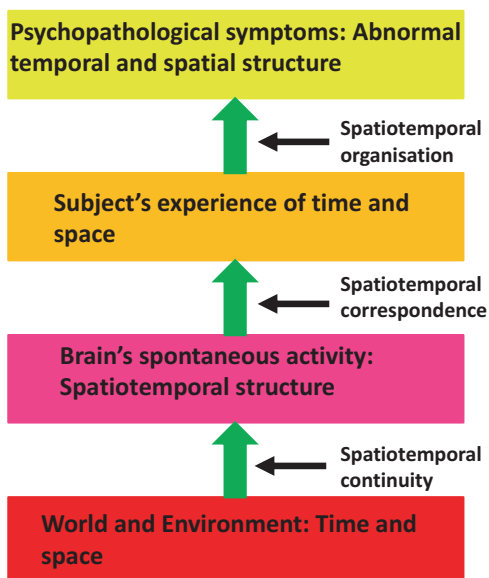
Such common, similar, or analogous spatiotemporal structure between the brain and experience amounts to what I describe as “spatiotemporal correspondence.” The concept of spatiotemporal correspondence means that the brain’s spontaneous activity and the phenomenal features of experience show corresponding or analogous spatial and temporal features: the spatial and temporal configuration or structure of the neural activity in the brain’s spontaneous activity surfaces in the spatial and temporal features within which the contents of experience (like specific objects or events including body, self, and world) are integrated and thus structured and organized. For instance, a recent study of ours demonstrated that private self-consciousness is directly related to the temporal patterns of spontaneous or resting state activity across different frequency ranges (as indexed by what is described as “power law”) [10]. This suggests that mental features like self may be rooted in spatiotemporal features of the brain’s spontaneous activity. The self as mental feature may then be characterized in spatiotemporal terms, that is, by specific spatiotemporal schemata or structure rather than by cognition of particular contents (see Fig. 5.1).

Unlike Biological Psychiatry that focuses on the brain itself independent of its respective ecological context, Phenomenological Psychiatry emphasizes the integration of experience including the subject of experience within the ecological context of the world. There is continuity between experience and world with such continuity often assumed to be mediated by the body, e.g., experience of the body as lived body (see, for instance, [22]). Such continuity between subject and world is deemed central for making experience including the first-person perspective itself first and foremost possible.

5.1.3 *Spatiotemporal Psychopathology*

What exactly is the “common currency” that allows for continuity between experience and the brain? The continuity between experience and the brain may ultimately be traced to the continuity between world and the brain. Let us give an

Fig. 5.1 Different levels in spatiotemporal psychopathology



empirical example. Duncan [5] recently demonstrated that early childhood traumatic experience is manifest in adulthood in the spatiotemporal patterns of the brain's spontaneous activity (as indexed by entropy) which, in turn, impacts subsequent stimulus-induced activity in relation to aversive stimuli. The continuity between experience and the brain can thus be traced to continuity between world and the brain as it is manifest in the spatiotemporal pattern of the latter's spontaneous activity. One may consequently want to speak of “spatiotemporal continuity” between world and the brain. The concept of “spatiotemporal continuity” refers to the fact that certain spatial and temporal features are continuous from world to the brain as, for instance, when certain temporal differences in the environment (as between specific stimuli) resurface in the temporal difference of the brain's spontaneous activity.

I postulate that the two features as introduced here, spatiotemporal correspondence and spatiotemporal continuity, are hallmark features of what can be described as “Spatiotemporal Psychopathology” [18–21]. The concept of “Spatiotemporal Psychopathology” refers to the fact that psychopathological symptoms are conceived primarily in spatiotemporal terms rather than in cognitive (as in Cognitive Psychopathology), phenomenological (as in Phenomenological Psychopathology), affective (as in Affective Psychopathology), or neuronal terms (as in Biological Psychopathology).

How does such Spatiotemporal Psychopathology stand in relation to the other forms of psychopathology? One central distinguishing feature concerns the contents of our experience. Biological Psychiatry, in contrast, focuses on contents in that it aims to reveal the neural underpinnings of the cognitive, affective, sensorimotor, and social contents. This is different in Spatiotemporal Psychopathology. Here the focus is not on contents at all but rather on how these contents can be

characterized in spatial and temporal terms including their respective spatiotemporal context which, phenomenologically, can be traced to the lifeworld, e.g., the world as experienced.

The focus is thus not on contents themselves but on the spatiotemporal structure within which the contents are organized. Psychopathological symptoms are consequently characterized by structure-based alterations of temporal and spatial structure rather than content-based changes. This puts Spatiotemporal Psychopathology in close relation to Phenomenological Psychopathology that also considers the contents of experience in the wider context of self, body, and world. However, Spatiotemporal Psychopathology is even more radical than Phenomenological Psychopathology in that the central phenomenological constituents like self, body, and world are also conceived in spatiotemporal terms and thus within the context of time and space.

The aim of this contribution is to introduce Spatiotemporal Psychopathology and the way it may complement and extend phenomenological psychopathology by bridging the methodological gap between the brain and experience. In the first part, I will provide examples for spatiotemporal correspondence between neuronal and psychopathological features. Specifically, I will discuss how spatial changes in the brain's spontaneous activity translate into abnormal experience of the self in major depressive disorder (MDD). This is followed by the second part where I will focus on spatiotemporal continuity. Specifically, the second part highlights the special relevance of temporal changes in spontaneous activity and its relation to the world and how that translates into hallucinations in schizophrenia. Finally, in a third part, I will briefly discuss the method of such Spatiotemporal Psychopathology and distinguish it from the methods relied on in other forms of Psychopathology with a special focus on showing the continuity between Spatiotemporal and Phenomenological Psychopathology.

5.2 “Spatiotemporal Correspondence”: From the Spontaneous Activity's Abnormal Spatial Structure to Abnormal Experience of Self in Major Depressive Disorder (MDD)

As an example of the approach of Spatiotemporal Psychopathology, we can examine major depressive disorder (MDD). In a recent meta-analysis, Alcaro (Antonio [1]) looked at the brain's resting state activity, that is, the neural activity that can be observed in different regions and networks during the absence of specific stimuli or tasks [14]. This yielded hyperactive regions in medial prefrontal cortex like perigenual anterior cingulate cortex (PACC) and ventromedial prefrontal cortex (VMPFC) (as well as subcortical midline regions as thalamic regions like the dorsomedial thalamus and the pulvinar, pallidum/putamen, and midbrain regions like ventral tegmental area (VTA), substantia nigra (SN), the tectum, and the

periaqueductal gray (PAG)). In contrast, resting state activity was hypoactive in lateral prefrontal cortex regions being reduced in the dorsolateral prefrontal cortex (DLPFC) (and other regions like the posterior cingulate cortex (PCC) and adjacent precuneus/cuneus [1] (see also [13] for similar results). Especially the medial prefrontal resting state hyperactivity changes in PACC and VMPFC seem to be somehow specific for depression since in schizophrenia there is rather hypoactivity (see [13, 31] (see Fig. 5.2).

The medial prefrontal regions like PACC and VMPFC are core regions of the default mode network (DMN), while lateral prefrontal regions like DLPFC are a part of the central executive network (CEN). A recent meta-analysis of resting state functional connectivity observed the following abnormal changes in these networks that seem to be (more or less) specific to MDD as distinguished from other psychiatric disorders [12]. The DMN shows functional hyperconnectivity among its regions and especially between anterior and posterior midline regions. In contrast to the regions within the DMN, regions within the CEN show functional hypoconnectivity and also less connected to parietal regions implicated in attention toward the external environment. This suggests spatial disbalance between the two networks with an abnormal spatial shift toward the DMN and away from the CEN with the former also enslaving the latter (as suggested by abnormally negative functional hyperconnectivity between DMN and CEN [12]. These findings are specific to MDD as in BD such a pattern cannot be observed [15], while in schizophrenia functional connectivity between DMN and CEN is positive (rather than abnormally negative as in MDD) [2].

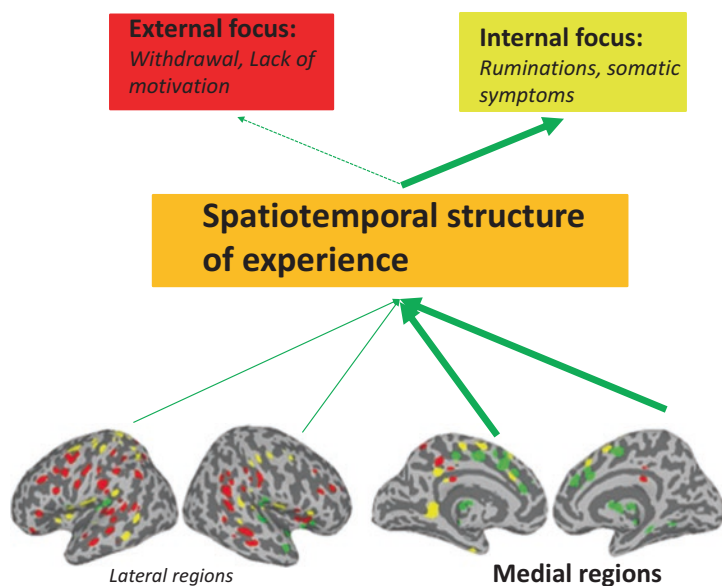


Fig. 5.2 Spatial correspondence in depression

In sum, the data provide evidence for abnormal resting state hyperactivity in medial prefrontal regions as part of the DMN in MDD, while there is resting state hypoactivity in lateral prefrontal regions as part of the CEN. This suggests the opposite, that is, reciprocal modulation between medial and lateral prefrontal cortex with resting state activity being abnormally increased in the former and decreased in the latter. Abnormal opposite or reciprocal modulation between medial and lateral prefrontal cortical resting state activity in MDD is further supported by analogous functional connectivity: increased functional connectivity in PACC-VMPFC and thus within DMN is accompanied by decreased functional connectivity in lateral prefrontal cortex and the CEN [9, 16, 23, 31]. One can thus speak of abnormal reciprocal modulation between medial/DMN and lateral/CEN prefrontal cortex with their spatial balance tilting abnormally toward the former at the expense of the latter.

How now is the abnormal spatial balance between medial and lateral prefrontal cortex related to the psychopathological symptoms in MDD? This spatial imbalance on the level of the brain's spontaneous activity is well reflected on the phenomenal level: MDD patients' experiences are characterized by an increased focus on the own internal contents as consisting in either thoughts, as in ruminations with increased self-focus and/or the body leading to the various unspecific somatic symptoms, e.g., increased body focus. In contrast, these patients' experience is no longer focused on the external environment at all, e.g., decreased environment focus, which psychopathologically is manifest in social withdrawal and lack of motivation. One can consequently say that the abnormal spatial structure in the brain's spontaneous activity translates and surfaces in the spatial structure of experience, e.g., the spatial organization of contents with regard to body, self, and environment, which in turn leads to the various kinds of psychopathological symptoms.

5.3 Spatiotemporal Psychopathology Versus Phenomenological Psychopathology

5.3.1 *Direct Link with “Common Currency” Between Brain and Experience*

How can we characterize the methodology of Spatiotemporal Psychopathology, and how does it compare to other forms of Psychopathology? First and foremost, Spatiotemporal Psychopathology views and approaches psychopathological symptoms in terms of spatial and temporal features rather than contents themselves: psychopathological symptoms are traced to abnormal spatial and temporal structuring of cognitive, affective, social, and sensorimotor contents. For instance, one may hypothesize that the internal thought contents are processed in depression in a spatial context that puts abnormal emphasis on them at the expense of external contents leading to ruminations and increased self-focus. The internal contents, e.g., the

thoughts, are thus structured and integrated spatially in an abnormal way. The same applies to schizophrenia where the spontaneous activity can no longer structure and organize its own temporal features, that is, its phase onsets, in order to align and link them to the auditory tones. Psychopathological symptoms are thus traced to abnormal spatial and temporal structuring of sensorimotor, cognitive, affective, and social contents in perceptions, emotions, and cognitions.

Such spatiotemporal approach distinguishes Spatiotemporal Psychopathology from other forms of Psychopathology that view psychopathological symptoms in either cognitive, affective, behavioral, or phenomenal ways (see Table 5.1).

Spatiotemporal Psychopathology aims to establish direct links between neuronal and phenomenal states by focusing on the spatiotemporal features as shared overlap or “common currency” between the brain’s spontaneous activity and experience. The spatiotemporal features allow to transform neuronal into phenomenal activity, thus establishing a direct link between the brain and experience; the temporal and spatial features as constructed by the brain’s spontaneous activity allow for extending and transforming neuronal into phenomenal activity. At the phenomenal level, those very same spatial and temporal features are experienced in first-person perspective as, for instance, described in the concept of “phenomenal time” [22] and the “stream of consciousness” [11]. The experience of time and space, in turn, underlies our experience of self, body, and world as main focus of Phenomenological Psychopathology. Spatiotemporal Psychopathology can therefore be considered as much as an extension of the brain/Biological Psychiatry to experience/ Phenomenological Psychopathology as it can be regarded as extension from the latter to the former. Metaphorically speaking, Spatiotemporal Psychopathology

Table 5.1 Comparison between different forms of Psychopathology

	Spatiotemporal Psycho-pathology	Affective Psycho-pathology	Cognitive Psycho-pathology	Phenomenological Psychopathology	Descriptive Psycho-pathology
Psychopathological symptoms	Spatiotemporal features	Affective features	Cognitive features	Phenomenal features	Operational features
Link neuronal and mental	Direct and spatiotemporal	Indirect through Affect	Indirect through Cognition	None	None
Neural activity	Spontaneous activity	Task-evoked activity	Task-evoked activity	None	None
Role of experience	Methodological starting point	Emotional feeling	none	Starting and end point	None
Self, body, and world	Secondary constructs	Body as basis of emotions	Cognitive constructs	Lived body as primary	Operational constructs
Time and Space	Primary pre-phenomenal constructions	No special role	Cognition of time and space	Phenomenal features: Inner time/space consciousness	No special role

provides the bridge between experience and brain, and like any bridge in reality, it allows for direct access from both sides, e.g., phenomenal and neural.

This is different in the other forms of Psychopathology where there is a rather indirect link between the brain and experience with regard to symptoms: the psychopathological symptoms are here conceived to be mediated by the cognitive, affective, or behavioral functions of the brain (or the phenomenal features of experience). Such indirect link ultimately opens a gap between the brain and symptoms as described above.

Spatiotemporal Psychopathology focuses mainly on the brain's spontaneous activity rather than the task-evoked or stimulus-induced activity. This is different in the other forms of Psychopathology that target cognitive, affective, and/or behavioral functions as related to stimulus-induced or task-evoked activity in the brain.

5.3.2 Spatiotemporal Psychopathology Versus Phenomenological Psychopathology

Spatiotemporal Psychopathology shares with Phenomenological Psychopathology the assumption of a central role of experience. Both take very seriously experience as the subjective account of what objectively is described as psychopathological symptoms. In that sense Spatiotemporal Psychopathology can be considered as phenomenological as Phenomenological Psychopathology. In other words, Spatiotemporal Psychopathology in this sense can be considered an extension of Phenomenological Psychopathology that shifts the focus from self, body, and world to their underlying temporal and spatial features in experience. Taken in this sense, Spatiotemporal Psychopathology may be considered a subset of Phenomenological Psychopathology with regard to the experience of specifically time and space and how that is related to the experience of self, body, and world.

However, unlike Phenomenological Psychopathology, Spatiotemporal Psychopathology does not remain within the boundaries of experience itself. It goes beyond experience in that it aims to link experience to the brain and its neural activity. That raises the question for the “common currency” between experience and the brain which, so Spatiotemporal Psychopathology, can be found in temporal and spatial features: both the brain's neural activity especially its spontaneous activity and experience share the spatial and temporal structuring and organizing of contents – spatiotemporal features are the “common currency” between experience and the brain.

Methodologically, this amounts to what can be described as “double access” in Spatiotemporal Psychopathology. The symptoms can be accessed in terms of the brain and its neural activity and, at the same time, in terms of their experience by the respective subject. Both the brain's neural activity and the subjects' experience are conceived in primarily spatiotemporal terms – the brain's neural activity changes may then be conceived in the spatiotemporal features of the subject's experience

and vice versa. One can, for instance, investigate whether the degree of shift between self- and environment focus, that is, the spatial shift between internal and external contents, corresponds to the spatial shift between medial/DMN and lateral/CEN prefrontal cortical regions (see above). Analogous so in the temporal domain. The degree of temporal detachment of the brain's phase onsets from the environment's tones may correspond to the degree to which the subject's experiences are determined by internal (rather than external) contents like delusions and hallucinations. In short, Spatiotemporal Psychopathology supposes spatiotemporal correspondence and continuity between neural and experiential activity.

The role of self, body, and world is different in Spatiotemporal Psychopathology. Phenomenological Psychopathology takes subjective experience of time and space as well as of self, body, and world as central and most basic features of Psychopathology. Spatiotemporal Psychopathology, in contrast, focuses mainly on time and space, e.g., the subjective experience of time and space, as the most basic and fundamental experiential dimensions as they underlie our experience of self, body, and world. Self, body, and world are not neglected but, unlike in Phenomenological Psychopathology, are no longer considered as independent constituents of experience. Instead, they are traced to spatial and temporal features. As mentioned above, a recent study shows that self-consciousness can be linked with the overall temporal structure of the spontaneous activity [10]. The same holds analogously for the body, that is, the lived body, that can be traced to the spatial structure of the brain's spontaneous activity [22]. These data lent support to the view that self, body, and world may by themselves be conceived in the spatiotemporal terms of the brain's spontaneous activity.

Why does Spatiotemporal Psychopathology conceive self, body, and world in spatiotemporal terms rather than as basic phenomenal constituents by themselves? This makes it possible for Spatiotemporal Psychopathology to transgress the boundaries of experience and to link it with the brain. Time and space are considered as the bridge or “common currency” between experience and the brain since, as I suggest, they allow for transforming merely neuronal activity (as we can observe it in the brain) into phenomenal features (as we can experience them). Spatiotemporal Psychopathology thus complements Phenomenological Psychopathology by extending it beyond its own phenomenal boundaries, that is, the border of experience, to the brain and its spontaneous activity. At the same time, Spatiotemporal Psychopathology extends the borders of neuroscience beyond the brain itself to experience. In the case of both transitions from experience to the brain and the brain to experience, spatiotemporal features serve as guiding thread and “common currency” underlying both our experience of self, body, and world as well as our observation of neural activity changes in the brain. Accordingly, as pointed out already above, Spatiotemporal Psychopathology can be regarded as extension of both Phenomenological Psychopathology and Biological Psychiatry though from reversed directions.

Finally, it shall be pointed out that, due to its functional role as bridge between experience and the brain, Spatiotemporal Psychopathology is somewhat intrinsically hybrid. It is phenomenal in that it relies and draws on experience of time and

space. At the same time, Spatiotemporal Psychopathology is neuronal in that it searches for how time and space are constructed and realized by the brain and its spontaneous activity. Taken in this sense, Spatiotemporal Psychopathology can be considered truly neuro-phenomenal (rather than being either purely neuronal or phenomenal) [16, 17].

Finally, taken in a more philosophical context, Spatiotemporal Psychopathology can be considered a methodological or epistemological framework for investigation of Psychopathology in particular and mental features like self and consciousness in general. Finally, Spatiotemporal Psychopathology also carries an ontological dimension in that it targets time and space, e.g., the construction of time and space by the brain in its relation to body and world, as they actually exist and are real in the world. The rather complex reality of psychiatric disorders as basic disturbances of self, body, and world as thematized so well in Phenomenological Psychopathology is thus well reflected in the hybrid nature of Spatiotemporal Psychopathology.

5.4 Conclusion

I here suggested a novel approach to psychopathology, namely, to conceive psychopathological symptoms in terms of their underlying spatiotemporal features. Spatiotemporal Psychopathology assumes correspondence and continuity between the spatial and temporal features of the brain's spontaneous activity on the one hand and the spatial and temporal structure underlying psychopathological symptoms. Such spatiotemporal correspondence was exemplified by ruminations in depression. Moreover, Spatiotemporal Psychopathology assumes continuity between the spatial and temporal features of the world and the ones of the brain entailing spatiotemporal continuity. Such spatiotemporal continuity is disrupted in, for instance, schizophrenia which may be central in constituting hallucinations and delusions.

Spatiotemporal Psychopathology aims to complement and extend Phenomenological Psychopathology beyond the phenomenal boundaries of experience reaching out to the brain. Specifically, spatial and temporal features shared by both experience and brain are sought to correspond with each other; the changes in the spatiotemporal structure of the brain's spontaneous activity are assumed to surface and translate into abnormal spatiotemporal structuring on the phenomenal level of experience resulting in the various kinds of psychopathological symptoms. Methodologically, this requires double access: the spatiotemporal psychopathologist needs access to subjects' experience like a phenomenological psychopathologist, while, at the same time, he requires access to the brain's spontaneous activity just as the spatiotemporal neuroscientist. This will ultimately enable Spatiotemporal Psychopathology to bridge the gap by providing time and space as "common currency" between experience and the brain, e.g., by their shared spatiotemporal features.

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Chapter 6

Development of Neuroimaging-Based Biomarkers in Major Depression



Kyu-Man Han, Byung-Joo Ham, and Yong-Ku Kim

Abstract A leading goal in the field of biological psychiatry for depression is to find a promising diagnostic biomarker and selection of specific psychiatric treatment mode that is most likely to benefit patients with depression. Recent neuroimaging studies have characterized the pathophysiology of major depressive disorder (MDD) with functional and structural alterations in the neural circuitry involved in emotion or reward processing. Particularly, structural and functional magnetic resonance imaging (MRI) studies have reported that the brain structures deeply involved in emotion regulation or reward processing including the amygdala, prefrontal cortex (PFC), anterior cingulate cortex (ACC), ventral striatum, and hippocampus are key regions that provide useful information about diagnosis and treatment outcome prediction in MDD. For example, it has been consistently reported that elevated activity of the ACC is associated with better antidepressant response in patients with MDD. This chapter will discuss a growing body of evidence that suggests that diagnosis or prediction of outcome for specific treatment can be assisted by a neuroimaging-based biomarker in MDD.

Keywords Major depressive disorder · Magnetic resonance imaging (MRI) · Neural circuit · Emotion regulation · Reward processing · Treatment outcome

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6.1 Introduction

Major depressive disorder (MDD) is a common psychiatric illness with a 1-year prevalence of about 6% and lifetime prevalence of about 16% [1]. MDD has a deleterious effect on social function in the workplace, school, and home [2, 3]. MDD also poses a great socioeconomic burden on the society. A study on the cost of illness has reported that the economic burden of MDD is approximately \$210 billion in the United States [4]. There has been cumulative research investigating the pathophysiology of MDD. It has been reported that alterations in monoaminergic neurotransmission (e.g., serotonin, norepinephrine, dopamine), disturbance in hypothalamic-pituitary-adrenal (HPA) axis, activated immune-inflammation processes, dysfunction in neuroplasticity, or neuro-endocrinologic alterations are associated with the neurobiology of MDD. Furthermore, heritability of MDD is estimated to be approximately 0.32–0.41 [5], and numerous genetic candidates including single nucleotide polymorphism or epigenetic markers (e.g., DNA methylation) are suggested to be involved in the neurobiology of MDD [6, 7]. A growing body of evidence from neuroimaging studies suggests that the abovementioned neurobiological or genetic factors may contribute to an individual's predisposition to MDD through functional and/or structural alterations in the neural circuits. With recent advances in analysis techniques, neuroimaging studies have provided deep insights into the changes in neural network involved in emotion, reward, or cognitive processes by in vivo approach with a systemic investigation of structure and function of the brain in patients with MDD and healthy people [8]. A cumulative knowledge of the changes in the brain in MDD derived from research using neuroimaging tools gives hope that biological indicators will benefit diagnosis, prognosis (including suicidality), and selection of treatment mode – what type of antidepressant, psychotherapy, or non-pharmacological treatment – and lead to the development of a neuroimaging-based biomarker for MDD [9]. A biomarker in medical science refers to an objectively measurable indicator reflecting a normal or pathogenic neurobiological process which can be used in diagnosis, staging of disease, prognosis, or response to a therapeutic intervention [10]. Neuroimaging-based biomarkers in MDD include biological indicators derived from structural or functional magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), near-infrared spectroscopy (NIRS), magnetic resonance spectroscopy (MRS) which can provide information about the morphologic changes in the brain, functional activity patterns within the brain networks, or neurochemical alterations in the depressive brain [11]. In the present chapter, we discuss recent studies that use neuroimaging-based biomarkers for the diagnosis and prediction of treatment outcomes for specific psychiatric treatment in patients with MDD. Among the various neuroimaging modes, this chapter will focus on neuroimaging studies using structural and functional MRI (fMRI) because a majority of neuroimaging studies in psychiatry have been performed using MRI. We also introduce neuroimaging-based neural models of

depression which provide a framework for linking neuroimaging findings and the pathophysiology of MDD.

6.2 Neuroimaging-Based Neural Model of Depression

In this section, we first briefly introduce neuroimaging-based neural model of depression which can yield a theoretical framework for understanding the pathophysiology of MDD from the perspective of structural and functional alterations of neural circuits, followed by a discussion about the recent efforts on development of neuroimaging-based biomarkers for MDD. Among several neural models of depression, we will introduce a neural model suggested by Phillips and colleagues [1, 8, 12, 13]. In this neural model of depression, dysfunction of neural circuits involved in the emotion regulation and reward processing can cause core depressive symptomatology such as persistent low mood, anxiety, or anhedonia. Brain structures such as the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), amygdala, ventral striatum, and hippocampus which consist of emotion or reward processing neural circuits play a pivotal role in it [8]. During emotion regulation, ventral ACC, ventromedial PFC (vmPFC), and medial orbitofrontal cortex (mOFC) are involved in recognizing emotionally salient stimuli generated by the amygdala and implicit or automatic regulation of emotions, while the lateral part of PFC including dlPFC, vlPFC, and dorsal ACC are involved in cognitive, voluntary, or effortful regulation of emotion (voluntary top-down control of emotion) [1, 14]. In their neural model, an abnormal pattern of emotion regulation neural circuit such as abnormally elevated amygdala (and ACC) activity and a decreased amygdala-mPFC functional connectivity to negative emotional stimuli plays a critical role in the pathophysiology of MDD [14]. Particularly, abnormality in the implicit emotion regulation circuitry may lead to a persistent low mood and anxiety in patients with MDD [8, 14]. In reward processing, the neural model highlights the role of the ventral striatum, mPFC including vmPFC, ACC, and vlPFC, suggested to be involved in anticipation or prediction of reward, reward-related decision-making, reward learning, or reward valuing [8]. Previous neuroimaging studies have reported abnormally increased activity in the rostral region of ACC to previous reward stimuli, decreased ventral striatal activity to rewarding or positive emotional stimuli, and increased habituation of ventral striatal activity to rewarding stimuli in MDD [8]. A dysfunctional reward circuitry may be associated with anhedonia or apathy in patients with MDD [8]. In addition to the neural model suggested by Phillips et al., a recent review by Williams (2016) discussed a neural circuitry-based taxonomy of core depression symptomatology such as rumination, anhedonia, negative bias, or cognitive dysfunction [15]. The neural model by Williams focused on the large-scale intrinsic and task-evoked neural circuits from previous neuroimaging studies on depression or anxiety disorders. These large-scale neural circuits include default mode network (DMN), salience network, negative and positive affect networks,

attention network, and cognitive control network [15]. This neural model made a linkage between the specific symptomatology of depression and dysfunction in the neural circuitry. For example, hyperactivation of DMN and increased functional connectivity between cortical regions that consist of DMN such as mPFC, posterior cingulate cortex (PCC), and angular gyrus are associated with rumination [15]. Positive affect circuit has a critical role in reward processing, and ventral striatal hypoactivation to rewarding or positive emotional stimuli, and greater activation of orbitofrontal cortex (OFC) as compensation for striatal hypoactivation which were associated with anhedonia [15]. The abovementioned neural models of depression integrating the findings from previous fMRI studies provide a more comprehensive view linking diverse core symptoms of MDD and dysfunction of relevant neural circuits.

6.3 Neuroimaging-Based Biomarker for Diagnosis of MDD

6.3.1 Structural MRI as a Diagnostic Biomarker

For two decades, numerous neuroimaging studies using MRI data have reported a difference in the brain structure between patients with MDD and healthy controls building a foundation for neuroimaging-based biomarker for diagnostic utility. Previous studies with structural MRI data focused on structural alterations of the brain with regard to the cortical gray matter volume, thickness, subcortical volume and shape, and microstructure (i.e., integrity) of the white matter tracts. In this section, we will review several meta-analytic studies on these structural MRI parameters.

Based on cortical and subcortical volumes, several meta-analyses on voxel-based morphometry (VBM) studies have reported distinct patterns of gray matter volume difference between patients and healthy controls. A meta-analysis by Wise et al. including 50 VBM data sets from 4101 individuals with MDD reported a volume reduction in the inferior and middle frontal gyri (which refer to vlPFC and dlPFC, respectively), vmPFC, PCC, dorsal ACC, insula, hippocampus, parahippocampal gyrus, and caudate nucleus, but an increased volume of superior occipital gyrus and cuneus in patients with MDD [16]. This is consistent with a previous meta-analysis by Bora et al. which reported a volume reduction in PFC, OFC, ACC, caudate nucleus, and putamen [17]. Another meta-analysis by ENIGMA-Major Depressive Disorder working group also focused on subcortical volume alterations in MDD. This study included 1728 patients with MDD and 7199 healthy controls from 15 data sets and found that the volume reduction in hippocampus was the only significant finding and showed the greatest effect size (Cohen's $d = -0.14$) [18]. They also reported a volume reduction of the amygdala, thalamus, caudate, accumbens, and pallidum and increased volume of lateral ventricle and putamen which was not statistically significant in patients with MDD [18]. Interestingly, the effect size of

hippocampal atrophy was mainly driven by patients with recurrent MDD, and no significant volume reduction was observed in first-episode patients [18]. A meta-analysis by Arnone et al. including 101 structural MRI studies and 4118 patients with unipolar depression found greater volume loss in the frontal cortex (total of gray and white matter), OFC (total and gray matter), hippocampus (total and gray matter), caudate, and putamen in patients than in healthy controls [19]. Based on aforementioned meta-analytical studies on cortical and/or subcortical volumes, greater volume reduction in the PFC, OFC, ACC, hippocampus, and caudate nucleus is a relatively consistent finding, and a volume loss in these brain regions may be a potential neuroimaging-based biomarker for the diagnosis of MDD.

A similar pattern of abnormalities has been reported with regard to cortical thickness change in patients with MDD. A recent meta-analysis by ENIGMA-Major Depressive Disorder working group including structural MRI data from 2148 patients with MDD and 7957 healthy controls with harmonized protocols at 20 sites around the world found cortical thinning of the medial and lateral OFC, rostral ACC, inferior temporal gyrus, fusiform gyrus, and insula in patients with MDD with the greatest effect size measured by Cohen's d [20]. They also reported cortical thinning of other prefrontal regions including the superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus (e.g., pars opercularis, pars orbitalis, and pars triangularis), PCC (including isthmus), entorhinal cortex, and parahippocampal gyrus [20]. The meta-analysis investigated the association between clinical characteristics of MDD and cortical thickness changes considering the age of onset, recurrence, or severity of the depressive symptoms. However, they could not find a significant difference in the cortical thickness during direct comparison between recurrent MDD and first-episode MDD and between adult age onset (i.e., ≥ 21 years) and adolescent age onset (i.e., < 21 years) [20]. There was also no significant correlation between the severity of depression and cortical thickness in adult patients with MDD [20]. A recent meta-analytic study by Li et al. using 15 structural MRI data of 529 medication-free patients with MDD and 586 healthy controls reported a different pattern of cortical abnormalities compared to the study by ENIGMA consortium [21]. They reported that medication-free patients with MDD showed cortical thickening in the PCC, vmPFC, and ACC, while there was cortical thinning in the gyrus rectus, orbital part of the superior frontal gyrus, and middle temporal gyrus [21]. Considering that a substantial portion of patients were taking antidepressants at the time of MRI scanning ($n = 951$) in the meta-analysis by ENIGMA-Major Depressive Disorder working group, antidepressant use may be a potential confounding factor in cortical thickness analysis in MDD [20]. Further studies, well-controlled for antidepressant use, are required to disentangle this issue.

Recently, studies on microstructural abnormalities on white matter tracts using diffusion tensor imaging (DTI) have come into the spotlight. These studies use DTI parameters (scalars) such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) which reflect axonal degeneration, demyelination, white matter maturation, and axonal packing density [22, 23]. Previous DTI studies on MDD have reported reduced integrity of white matter tracts connecting the prefrontal regions and subcortical structures, which support

dysfunction of emotion regulation neural circuits in MDD, abnormally increased amygdala activity, and reduced functional connectivity between the amygdala and mPFC [1, 8]. A recent meta-analysis by ENIGMA-Major Depressive Disorder working group using DTI data of 1305 MDD patients and 1602 healthy controls from 20 samples worldwide found that adult patients with MDD showed significantly lower FA in the entire corona radiata and its anterior part, entire corpus callosum and its genu and body parts, anterior limb of the internal capsule, superior fronto-occipital fasciculus, sagittal stratum, internal capsule, posterior corona radiata, superior corona radiata, fornix/stria terminalis, superior longitudinal fasciculus, and cingulate gyrus of the cingulum bundle with the greatest effect size (Cohen's $d = -0.253 \sim -0.165$) [24]. They also found that the reduction of white matter integrity was mainly driven by patients with recurrent MDD and those with adult age of onset [24]. Another meta-analysis that focused on first-episode, drug-naïve MDD patients has also provided similar results. A meta-analysis by Chen et al. using 14 DTI studies with 399 patients with first-episode, drug-naïve MDD and 396 healthy controls found reduced FA in the body of the corpus callosum, bilateral anterior limb of the internal capsule, right inferior temporal gyrus, and right superior frontal gyrus in patients with MDD [25]. They also found that the severity of depression and illness duration negatively correlated with FA values in the right anterior limb of the internal capsule and right superior frontal gyrus, respectively [25].

6.3.2 *Functional MRI as a Diagnostic Biomarker*

There have been efforts to elucidate the functional alterations of neural circuitry involved in emotion or reward processing in MDD. Previous fMRI studies on MDD have investigated the neural substrate of the disease using emotion, reward, and cognition-related tasks, and a majority of the studies focused on emotional tasks such as emotional face tasks. More recently, a growing body of studies have investigated the resting-state functional connectivity (rsFC) within and between neural networks in a task-free setting. In this section, we will discuss recent research on fMRI linking the functional activity patterns during the aforementioned tasks and resting state with the pathophysiology of MDD.

With regard to emotional task, neural models of emotion regulation have been centered around increased amygdala or ACC activity, decreased PFC activity, and altered functional connectivity between the amygdala and PFC in response to emotional stimuli in depressive patients [8]. A meta-analysis by Hamilton et al. using data from 24 fMRI studies found that patients with MDD showed greater activity in the amygdala, dorsal ACC, and superior temporal gyrus while decreased activity in the right dlPFC in response to negative stimuli [26]. A voxel-based meta-analysis by Delvecchio et al. using global activation likelihood estimation (ALE) analyses on studies using facial affective paradigms found that patients with MDD showed increased activation in the right parahippocampal gyrus which extends to the amygdala but decreased activation in the right putamen and left caudate [27]. A

comprehensive meta-analysis by Groenewold et al. using data of 44 fMRI studies (795 patients and 792 healthy controls) also found that patients with MDD showed greater activity in bilateral amygdala, parahippocampal gyrus, dorsal ACC, mid-cingulate cortex, right cerebellum, left putamen, and left fusiform gyrus but decreased activity in the left dlPFC in response to negative stimuli when compared to a neutral stimuli [28]. They also observed that in response to positive stimuli, patients showed lesser activity in the left cerebellum, left temporal/parietal regions, dorsal and pregenual ACC, fusiform gyrus, right insula, striatum, amygdala, hippocampus, and bilateral parahippocampal gyrus [28]. For functional connectivity during an emotional task, several studies have reported altered functional connectivity of neural circuits involved in emotion regulation. Kong et al. performed seed-based functional connectivity analysis with bilateral amygdala defined as a seed region of interest (ROI) in their sample of 28 patients with MDD and 30 healthy controls [29]. They observed decreased amygdala-left rostral PFC functional connectivity in the patient group during the fearful face condition [29]. There is another study linking functional connectivity within a neural circuit and integrity of white matter tracts. de Kwaasteniet found that patients with MDD showed increased functional connectivity between the subgenual ACC and medial temporal lobe (MTL, i.e., bilateral amygdala and right hippocampus) during a facial affective paradigm [30]. They also observed that the integrity of uncinate fasciculus – which connects MTL with the subgenual ACC or OFC – was negatively correlated with functional connectivity between the subgenual ACC and hippocampus [30]. This finding implicates that increased functional connectivity between the subgenual ACC and subcortical region (i.e., hippocampus) is associated with decreased structural connectivity of white matter tract connecting the two brain regions.

Considering reward processing abnormalities, patients with MDD showed altered ACC activity and decreased ventral striatal activity during reward-related tasks [8]. Several fMRI studies have reported that MDD patients showed significantly reduced ventral striatal activity during reward learning [31], consummatory phase of reward [32], reward prediction error [33], response to happy facial expression (i.e., positive emotional stimuli) [34], reward-based reversal learning [35], receipt of unexpected reward [36], and monetary reward task [37] compared to healthy controls. In addition to lesser activity of ventral striatum to reward, it has been reported that patients with post-partum depression showed increased habituation of ventral striatal activity in response to reward receipt [38]. Along with reduced ventral activity, it has also been reported that patients with MDD showed greater ACC and vmPFC activity in response to anticipation of reward [39] and positive emotional stimuli [40], respectively. A recent meta-analysis by Keren et al. using data of 38 fMRI studies analyzed the activation likelihood estimation (ALE) in reward anticipation and reward feedback [41]. In a meta-analysis that included only whole-brain analyses, they found that patients with MDD showed significantly decreased striatal activity in the right caudate body and head as well as the left caudate body during reward feedback phase, without any significant finding during the reward anticipation phase [41]. After inclusion of ROI studies in their meta-analysis, they found significantly decreased ventral striatal activity both during reward

anticipation and reward phases in patients with MDD [41]. Decreased ventral striatal activity in response to rewarding stimuli in MDD can be considered as a consistent finding in fMRI studies, and it indicates the potential utility of this neuroimaging finding as a diagnostic biomarker for MDD.

Recent studies have investigated rsFC in MDD, because “task-free” resting-state fMRI has the following potential advantages – decreased burden with regard to the design of experiment, compliance and training of participants, and attractive in a clinical population [8]. Furthermore, rsFC studies may provide a wider view of functional alterations of neural circuitry by investigating a “large-scale neural network” and hypothesis that abnormal communication within/between neural networks may be associated with specific depressive symptomatology [15]. For example, altered connectivity within the DMN or connectivity with other neural networks is associated with ruminative, self-referential thoughts in MDD [42, 43]. A growing body of evidence has suggested hyper- or hypoactivity within and/or between multiple distributed neural networks such as DMN, salience network, negative and positive affect networks, attention network, and cognitive control network [15]. A meta-analysis by Kaiser et al. including 25 seed-based voxel-wise rsFC studies (556 patients with MDD and 518 healthy controls) found that patients with MDD showed decreased connectivity within the frontoparietal network (FN), involved in top-down cognitive regulation of attention and emotion, and decreased connectivity between FN and parietal regions of dorsal attention network (DAN), involved in externally oriented attention [42]. They also found that patients with MDD showed increased connectivity within the DMN, between FN control systems, and in several brain regions of DMN [42]. This finding may be associated with a predisposition to ruminative thoughts with decreased attention to external world in MDD [42]. A decreased connectivity between affective network and mPFC in patients with MDD may be associated with impairment of up- or downregulation of emotions, while abnormal connectivity between ventral attention network and the brain regions of FN or DMN may reflect biased salience monitoring in MDD [42]. More recently, a meta-analysis by Tang et al. examined a previous “amygdalo-centric” model in MDD using 19 rsFC studies on the amygdala (665 patients with MDD and 546 healthy controls) [44]. They found that adult patients with MDD showed increased connectivity between the amygdala and right ventromedial OFC, and between amygdala and hippocampus/parahippocampal gyrus, but decreased connectivity of amygdala with bilateral insula, inferior frontal gyrus, superior temporal gyrus, and left caudate [44]. In the analysis, rsFC abnormalities of the amygdala were located in the affective network, which is involved in emotional and motivational regulation in MDD, and this finding may implicate an emotional dysregulation in MDD [44]. Despite the heterogeneous findings in rsFC studies in MDD, recent efforts to elucidate abnormalities in rsFS may provide a wider view and deeper insight into the neural circuitry-based pathophysiology of MDD.

6.4 Neuroimaging-Based Biomarker for Treatment Outcomes in MDD

A leading goal in the field of biological psychiatry is to develop a biomarker for selection of a particular psychiatric treatment most likely to be beneficial to individual patients. This goal is strongly connected with the recently developed concept of “precision psychiatry” [45]. A growing body of evidence has been gathered to predict treatment outcomes of specific psychiatric treatment (i.e., antidepressant, psychotherapy, or brain stimulation therapy) for MDD based on neuroimaging-based biomarker. In this section, we will briefly review recent advances in neuroimaging-based biomarker for the prediction of treatment outcomes in MDD.

Functional neuroimaging studies have yielded more consistent findings for the prediction of antidepressant response in MDD compared to structural MRI studies, and these fMRI studies highlight a pivotal role of ACC or mPFC activity [8]. It has been reported that hyperactivity of amygdala in response to negative stimuli and decreased activity in the lateral prefrontal region were normalized after antidepressant treatment [9]. This finding implicates that monoaminergic action of antidepressants, particularly serotonin, is deeply involved in the amelioration of dysfunction in emotion processing neural circuits [9]. Furthermore, the neural model of Phillips et al. also suggested that emotion regulation neural circuitry is specifically related with serotonergic neurotransmission [8]. After Mayberg et al. first identified ACC activity as a potential predictor for antidepressant response using PET data in MDD [46], numerous fMRI studies have focused on the relationship between pre-treatment ACC activity and response to antidepressants [9, 47]. Pizzagalli suggested rostral ACC resting activity as a potential biomarker for antidepressant response and performed meta-analysis including 23 studies using fMRI ($n = 4$), PET ($n = 7$), SPECT ($n = 8$), and EEG/MEG ($n = 4$) data [48]. The meta-analysis found that elevated rostral ACC activity before antidepressant treatment was associated with greater treatment response in patients with MDD [48]. Meanwhile, a meta-analysis by Fu et al. including 20 fMRI studies from 15 independent samples found that elevated pre-treatment activation of (pregenual and subgenual) ACC and mPFC was associated with a better clinical response, while increased activity in striatum and insula was associated with a poorer clinical response to antidepressant treatment or cognitive behavioral therapy (CBT) (antidepressant study, $n = 17$; CBT study, $n = 6$) [49]. With respect to functional connectivity, increased functional connectivity between PFC and limbic structures and decreased connectivity within the DMN have been reported to be an indicator of better response to antidepressant treatment in MDD [50, 51]. A systematic review of 21 resting-state fMRI studies by Dichter et al. has suggested that treatment response is associated with the following neuroimaging findings [50]: i) increased connectivity between the frontal and limbic brain regions is associated with better treatment response; ii) decreased amplitude of low-frequency fluctuations (ALFF) in the visual recognition circuit – lingual gyrus, middle occipital gyrus, fusiform gyrus, and cuneus – is associated with treatment resistance; iii) connectivity of the subcallosal (or subgenual) cingulate cortex was

associated with treatment response to transcranial magnetic stimulation (TMS); iv) increased connectivity of DMN and decreased connectivity of cognitive control network, composed of the dlPFC, ACC, and parts of the parietal lobe, were associated with a better antidepressant response. For structural MRI markers, it has been reported that the hippocampal volume is associated with antidepressant response in MDD – the greater the hippocampal volume at baseline, the better is the antidepressant response [52–55]. For example, Sämann et al. found that greater gray matter volume of the left hippocampus and bilateral PCC and lower gray matter volume of right temporolateral region were associated with better antidepressant response [55]. Fu et al. performed a meta-analysis on three studies on hippocampal volume and found that reduced right hippocampal volume was associated with poorer antidepressant response, while left hippocampal volume was not [49]. They also performed another meta-analysis on five whole-brain VBM studies and observed that reduced gray matter volume of the left dlPFC was associated with a poor antidepressant response [49]. A recent meta-analysis by Liu et al. including ten VBM studies found that responders to antidepressant treatment showed significantly greater gray matter volume in the bilateral ACC and right superior frontal gyrus compared to the non-responders [56].

There have been fewer studies on neuroimaging markers and psychotherapy compared to studies on the antidepressant response in MDD, and most of the studies have focused on functional neuroimaging and treatment response of CBT [57]. Siegle et al. found that lower subgenual ACC activity in response to negative words was associated with greater improvements in cognitive therapy of 16–20 sessions in a sample of 49 unmedicated patients with MDD [58]. On the other hand, Ritchey et al. found that greater baseline activity in the vmPFC and the valence effects (negative > positive affective stimuli) in the anterior temporal lobe and dlPFC were associated with greater improvement of depressive symptoms after CBT of 10–35 sessions [59]. Straub et al. found that greater baseline rsFC between the amygdala, dlPFC, and anterior insula was associated with greater symptom improvement after group CBT of five sessions in adolescents with MDD (13–18 years) [60]. Functional neuroimaging studies suggest that the ACC, PFC, amygdala, insula, and temporal lobe are key regions in the prediction of treatment outcomes of CBT [57].

Recently, a growing number of studies have investigated potential structural or functional neuroimaging marker for the prediction of treatment outcomes in brain stimulation therapy such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or deep brain stimulation (DBS) in MDD. A study by Ten Doesschate et al. found that greater amygdala volume was associated with a good response after ECT in a sample of 53 patients with MDD [61]. Joshi et al. observed that the volume of hippocampus and amygdala increased after ECT and suggested that a smaller hippocampal volume at baseline was associated with greater symptom improvement after ECT in 43 patients with MDD [62]. Another study by Lyden et al. reported that increased white matter integrity (i.e., FA values) in dorsal fronto-limbic circuits including the anterior cingulum, forceps minor, and left superior longitudinal fasciculus after ECT was associated with an improvement of depressive symptoms in a sample of 20 patients with MDD [63]. A recent

systematic review by Levy et al. suggested that a smaller volume of hippocampus and greater volume of amygdala and subgenual ACC were associated with a better response to ECT [64]. The review also suggested that connectivity between the posterior DMN and left dlPFC may be a potential predictor of the efficacy of ECT [64]. For rTMS, a prospective study found that the treatment response was associated with an increase in amygdala volume from baseline, while non-response to rTMS was associated with a reduction in the left hippocampus from the baseline [65]. The study also reported that a smaller right amygdala volume was associated with a good response to rTMS [65]. To date, there have been few studies on brain stimulation therapy and MRI markers, and there has been no meta-analysis on this topic. We hope that further studies are carried out to shed light on this issue.

6.5 Conclusion

In this chapter, we have discussed recent efforts in the development of a neuroimaging-based biomarker for the diagnosis and prediction of treatment outcomes in MDD. A growing body of evidence from structural and functional MRI studies on MDD has provided promising potential biomarkers for diagnostic utility and response to specific treatment for MDD. For the diagnosis of MDD, structural MRI studies have suggested that volume loss, cortical thinning, or decreased integrity of white matter tracts in the brain regions involved in emotion regulation such as the PFC, ACC, hippocampus, corpus callosum, and cingulum may be a useful diagnostic biomarker [16, 20, 24]. Functional neuroimaging studies have focused on the “amygdalo-centric” neural model of MDD, hyperactivity of amygdala in response to negative emotional stimuli and increased activity of ACC/vmPFC which is involved in automatic regulation of emotion, and decreased activity of lateral or dorsal part of PFC (i.e., dlPFC) which is involved in cognitive and voluntary top-down control of emotions [8]. In addition to emotion regulation processing, decreased activity of ventral striatum which has a pivotal role in reward processing to rewarding stimuli has been reported to be a prominent finding related to the pathophysiology of MDD, especially for anhedonia [8, 41]. Recently, cumulative fMRI studies on rsFC have suggested that dysfunction of large-scale neural network, an altered activity within and/or between neural networks involved in self-referential thought at rest, detecting salient changes, regulation of negative emotion (or threat), reward anticipation, or cognitive processing such as attention or working memory could be potential neuroimaging-based biomarker for MDD [15]. Particularly, altered activity within the DMN or altered connectivity of DMN with other neural networks has come into the spotlight with regard to their association with the core symptom of MDD – ruminative thinking [43]. For prediction of treatment outcomes, fMRI studies have consistently suggested that hyperactivity of ACC is associated with better antidepressant response in patients with MDD [9]. Furthermore, functional neuroimaging studies on functional connectivity have suggested that an increased connectivity between the frontal and limbic regions, which

may reflect overloading of emotion processing neural circuit, was associated with better antidepressant response [57]. Even though there have been a few studies investigating a neuroimaging-based biomarker for treatment outcomes in psychotherapy or brain stimulation compared to studies on antidepressants, a growing body of studies have reported structural and functional alterations of neural network as indicators of treatment response [57]. Considering the growing use of brain stimulation therapy in clinical practice of MDD, further studies are required. This review implies that neuroimaging findings will have a pivotal role in establishment of “precision psychiatry” based on neuroimaging-based biomarker-guided diagnosis, selection of specific treatment, and prediction of treatment response in MDD.

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Part II
Current Diagnostic and Neurobiological
Issues

Chapter 7

Challenges and Strategies for Current Classifications of Depressive Disorders: Proposal for Future Diagnostic Standards



Seon-Cheol Park and Yong-Ku Kim

Abstract The *Diagnostic and Statistical Manual of Mental Disorder*, Fourth Edition (DSM-IV) was revised based on a combination of a categorical and a dimensional approach such that in the DSM, Fifth Edition (DSM-5), depressive disorders have been separated as a distinctive disease entity from bipolar disorders, consistent with the deconstruction of Kraepelinian dualism. Additionally, the diagnostic thresholds of depressive disorders may be reduced due to the addition of “hopelessness” to the subjective descriptors of depressed mood and the removal of the “bereavement exclusion.” Manic/hypomanic, psychotic, and anxious symptoms in major depressive disorder (MDD) and other depressive disorders are described using the transdiagnostic specifiers of “with mixed features,” “with psychotic features,” and “with anxious distress,” respectively. Additionally, due to the polythetic and operational characteristics of the DSM-5 diagnostic criteria, the heterogeneity of MDD is inevitable. Thus, 227 different symptom combinations fulfill the DSM-5 diagnostic criteria for MDD. This heterogeneity of MDD is criticized in view of the Wittgensteinian analogy of language game. Depression subtypes determined by disturbances in monoamine levels and the severity of the disease have been identified in the literature. According to a review of the Gottesman and Gould criteria, neuroticism, morning cortisol, cortisol awakening response, asymmetry in frontal cortical activity on electroencephalography (EEG), and probabilistic reward learning, among other variables, are evidenced as endophenotypes for depressive disorders. Network analysis has been proposed as a potential method to compliment the limitations of current diagnostic criteria and to explore the pathways between depressive symptoms, as well as to identify novel and interesting relationships between depressive symptoms. Based on the literature on network analysis in this field, no differences in the centrality index of the DSM and non-DSM symptoms were

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repeatedly present among patients with MDD. Furthermore, MDD and other depressive syndromes include two of the Research Domain Criteria (RDoC), including the Loss construct within the Negative Valence Systems domains and various Reward constructs within the Positive Valence Systems domain.

Keywords Major depressive disorder (MDD) · Depressive disorders · *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) · Heterogeneity · Network analysis · Research Domain Criteria (RDoC)

7.1 Introduction

Although the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) task force aimed to construct a “radical paradigm shift in psychiatry” from a “symptom-based classification system” to an “etiology-based classification system,” the paradigm shift was strongly resisted by most researchers supporting disease essentialism (e.g., Allan Frances, the former chair of the DSM-IV task force) [1–7]. Thus, the aim of the DSM-5 task force was subtly changed to “bridging the gap between presumed etiologies-based symptomatology and identifiable pathophysiological etiologies” [8]. In order to combine the categorical and dimensional approaches, the transdiagnostic specifiers were deemed more sophisticated, and the severity scales were newly adapted in the diagnostic criteria of the DSM-5 [5–7].

7.2 Diagnostic Boundaries of Depressive Disorders

In the revised DSM-5, the psychiatric taxonomy of the diagnostic construct of depressive disorders was changed as follows [9, 10]. First, mood disorders have been dichotomized into bipolar disorders and depressive disorders; this is consistent with Kraepelinian dualism, which consists of two disease entities, namely, dementia praecox (chronic psychosis) and manic depressive insanity (recurrent mood illness with psychosis). Thus, in the DSM-5, based on the psychiatric taxonomy, depressive disorders are regarded as a distinct disease entity from bipolar disorder and schizophrenia. In addition, based on the DSM-5, the categorical diagnosis of bipolar disorder is regarded as bridging the gap between the diagnoses of psychotic disorders and depressive disorders [6].

Second, in the DSM-5, “mixed episode” has been replaced by “with mixed features,” which can be a transdiagnostic specifier for both depressive disorders and bipolar disorders. The specifier “with mixed features” can be coded during manic, hypomanic, and depressive episodes in the DSM-5. Particularly, in the context of a

depressive episode, coding the specifier “mixed features” requires the presence of at least three among the seven hypomanic symptoms, including elevated mood, inflated self-esteem, pressured speech, racing thoughts, goal-directed activity, involvement in risky activities, and decreased need for sleep [9, 10].

Third, in the DSM-5, the specifier “with psychotic features” can be coded not only for severe major depressive episode (MDE) but also for dysthymic disorder and mild and moderate MDE [9–11], in accordance with rejection of the “severity-psychosis” hypothesis. Since the “severity-psychosis” hypothesis states that psychotic symptoms are dependent on the severity of the depressive episode, coding the specifier “with psychotic features” was permitted only in severe MDE in the DSM-IV. However, the “severity-psychosis” hypothesis has been rejected by several studies [12–14]. Although the preponderance of “mood-congruent psychotic features” rather than “mood-incongruent psychotic features” has been noted in the DSM-IV, the notion is omitted in the DSM-5 [11].

Fourth, the specifier “with anxious distress” has been newly introduced in the DSM-5, based on the overlap in familial or genetic factors, childhood environment, personality traits, and demographic characteristics between major depressive disorder (MDD) and generalized anxiety disorder (GAD). In the context of depressive disorders, coding the specifier “with anxious distress” requires the presence of at least two among the five anxiety symptoms, including feeling keyed up or tense, feeling unusually restless, difficulty concentrating due to worry, fear that something awful will happen, and fear of losing control of oneself. Several studies have reported a closer relationship of GAD with MDD than with other anxiety disorders, including panic disorder, agoraphobia, social phobia, and specific phobia. Although it has been suggested that GAD should be included under the umbrella of depressive disorders, this suggestion was not adopted in the DSM-5. It is speculated that the relationship between MDD and GAD is defined in terms of a continuum from depressive disorders to anxiety disorders, rather than a distinctive difference between depressive disorders and anxiety disorders [6, 15, 16]. However, since the modest association between the different definitions of anxious depression has been reported by Zimmerman et al. [17], it has been suggested that the validity of the specifier “with anxious distress” is weak and requires further evaluation.

In summary, as shown in Fig. 7.1, in the DSM-5, the transdiagnostic specifiers “with mixed features,” “with psychotic features,” and “with anxious distress” can be indicative of quantitative, but not qualitative, overlapping symptoms in the continuum between depressive disorder and bipolar disorder, schizophrenia, and anxiety disorder, respectively [6].

Furthermore, in the revision from DSM-IV to DSM-5, “hopelessness” is newly added to the subjective descriptor of depressed mood, and the “bereavement exclusion” item is eliminated from the definition of MDD. Since “hopelessness” can be present irrespective of depressed mood, it is a cognitive attitude of pessimism, but not a specific emotional state [6, 9, 10]. Also, “hopelessness” is consistent with a “black and pessimistic view of the future” described in the definition of depressed mood in the International Classification of Disease, 10th revision (ICD-10) [18]. The elimination of the “bereavement exclusion” has been supported by the

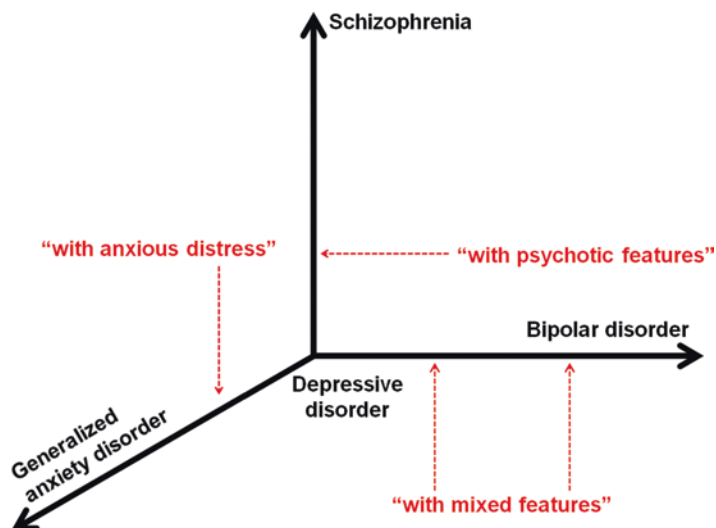


Fig. 7.1 Transdiagnostic specifiers for depressive disorders in the DSM-5. (Reproduced with permission from Park and Kim (2019) [6])

consistent findings that there are no significant differences in genetic or clinical characteristics between bereavement-related depression and any other context-related major depressive episode [19]. Based on the longitudinal two-wave Epidemiologic Catchment Area Study, the general distress symptoms of uncomplicated MDD cannot be easily distinguished from non-pathological intense sadness. Thus, it has been proposed that uncomplicated MDD should be excluded from the MDD diagnosis to clarify the boundary between MDD and normal sadness [20]. However, uncomplicated MDD was maintained in the definition of MDD in the DSM-5. In a more radical interpretation, the elimination of the “bereavement exclusion” item has been criticized as the medicalization of normal grief reaction [21].

In conclusion, in terms of defining depressive disorders, for the symptoms that overlap across diagnostic categories, the following nosological significance can be attributed: blurring of the boundary between depression and bipolar diagnoses may be presented by the specifier “with mixed features.” In addition, different phenomenological symptom experiences can be described by the specifier “with psychotic features.” Moreover, a shift toward broadening the range of experiences captured by the same diagnostic category may be aided by the specifier “with anxious distress.” Therefore, by implementing a pragmatic approach associated with the use of transdiagnostic specifiers, greater clinical flexibility can be provided, and the use of discrete categories of disorders can be eliminated [22]. Herein, it is proposed that the addition of “hopelessness” and elimination of the “bereavement exclusion” may ultimately contribute to lowering the diagnostic threshold of MDD in accordance with a dimensional approach.

7.3 Inevitable Heterogeneity of Depressive Disorders

According to the Rény heterogeneity, which is synonymous with the Hill numbers [23] in ecology or the Hannah-Kay index [24] in economics, the system used to measure heterogeneity may itself be the cause of the heterogeneity [25]. Thus, it is plausible that the current polythetic and operational definition of MDD may contribute to the heterogeneity of depressive disorders. According to Zimmerman et al. [26], a simpler definition for the symptom criteria for MDD, which includes mood and cognitive symptoms such as low mood, loss of interest or pleasure, guilt or worthlessness, impaired concentration or indecision, and suicidal thoughts, has been proposed. Furthermore, in a study of 2,907 psychiatric outpatients at Boston University Center for Anxiety and Related Disorders, both the definition of MDD in the DSM-IV and the simpler definition of MDD reflect an absolute level of agreement (kappa coefficient = 0.88) [27]. However, most diagnostic symptom criteria have only been slightly modified in the revision from the DSM-IV to the DSM-5. Thus, in the DSM-5, nine depressive symptoms constitute the diagnostic criteria for MDE: (i) depressed mood, (ii) markedly diminished interest or pleasure, (iii) significant weight loss or weight gain, (iv) insomnia or hyposomnia, (v) psychomotor agitation or retardation, (vi) fatigue or loss of energy, (vii) feelings of worthlessness or excessive, (viii) diminished ability to think or concentrate or indecisiveness, and (ix) recurrent thoughts of death, recurrent suicidal ideation, suicide attempt, or a specific plan for committing suicide. A diagnosis of MDD requires the presence of at least five depressive symptoms, at least one of which is “depressed mood” or “markedly diminished interest or pleasure” for more than 2 weeks. Thus, as shown in Fig. 7.2, the number of different symptom combinations fulfilling the DSM-5 criteria for MDD is calculated with the binomial coefficient. It is estimated that 227 different symptom combinations meet the DSM-5 criteria of MDD [28, 29]. Surprisingly, from the initial DSM-5 field trials, the inter-rater reliability for the diagnosis of MDD was considered weak (kappa coefficient = 0.28) [30]. However, in 1,566 patients with MDD in the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, 170 different symptom combinations were identified; meanwhile, 119 different symptom combinations were identified in 853 patients with MDD in the Clinical Research Center for Depression (CRESCEND) study [29, 31].

Fig. 7.2 Calculation of the number of different symptom combinations fulfilling the DSM-5 diagnostic criteria for major depressive disorder
n number of depressive symptoms in major depressive disorder

<i>n</i> = 9 :	${}_9C_9 = 1$
<i>n</i> = 8 :	${}_9C_8 = 9$
<i>n</i> = 7 :	${}_9C_7 - {}_7C_7 = 35$
<i>n</i> = 6 :	${}_9C_6 - {}_7C_6 = 77$
<i>n</i> = 5 :	${}_9C_5 - {}_7C_5 = 105$
<i>n</i> = 5-9 :	227

Furthermore, several criteria for the DSM-5 MDD are defined as the composite of more than one symptom. Each of the following constitutes a single criterion: psychomotor agitation and retardation, impaired concentration and indecisiveness, worthlessness and guilt, death wishes, and suicidal ideations [28, 29]. Moreover, it has been reported that the hyperactivation of putative mesocorticolimbic reward circuitry is associated with depression-related increase in appetite, whereas the hypoactivation of the insular region is associated with depression-related decrease in appetite [32]. Although it is speculated that different symptoms of a single criterion may be based on distinctively defined neurobiological underpinnings, the presence of only one of the two symptoms is interpreted as the presence of the single criterion. Thus, by regarding each symptom of these compound criteria as separate domains, 14,528 possible symptom combinations can be calculated [28, 29].

Ludwig Wittgenstein (1889–1951), who worked primarily in the philosophy of language, proposed the following analogy with language games in *Philosophical Investigation* [33].

Consider, for example, the proceedings that we call games. I mean board-games, card-games, ball-games, Olympic games, and so on. What is common to them all? - Don't say: "There must be something common, or they would not be called games" but look and see whether there is anything common to all. For if you look at them, you will not see something that is common to all, but similarities, relationships, and a whole series of them, at that. To repeat: don't think, but look! ... the concept game is a concept with blurred edges. "But is a blurred concept a concept at all?" Is an indistinct photograph a picture of a person at all? Is it even always an advantage to replace an indistinct picture by a sharp one? Isn't the indistinct one often exactly what we need? (Wittgenstein) [34]

From the viewpoint of the Wittgensteinian analogy of "game," the mental phenomena may not be connected by a physical process but may be connected by a thread of concept. Hence, the heterogeneity of depressive disorders can be criticized based on the suggestion that the cases of depressive disorders are related by the "family resemblance," which denotes the extension of meaning but not of the "essence." Although this criticism does not deny the existence of the relevance of the mental process for a distinctive diagnostic entity, it proposes that the operational diagnosis for depressive disorder may not be an indicator for the mental process that is equivalent to the disease [33].

The following is from a systemic review of the biological approaches to the depression subtypes [35]. Depression subtypes, with and without the disturbances in monoamine and catecholamine levels, can be identified by several biochemical studies. In terms of the symptom-based approaches, depression subtypes may be determined by the degree of severity and by weight gain and loss. Despite the lack of replication studies, symptom-based depression subtypes have been supported by differences in biomarker profiles and functional connectivity. Also, depression subtypes might be determined by medication response. A subtype with a distinct pattern of single nucleotide polymorphisms (SNPs) has been identified by one genetic study, but this subtype has not been replicated.

7.3.1 Understanding the Severity of Depressive Disorders

According to symptom-based approaches, severity, as a moderator of treatment response, may determine the subtypes of depressive disorders [25, 36–38]. The severity of depressive disorders is commonly indicated by the number of symptom criteria in the DSM-5 and ICD-10. However, all symptom criteria are equal in terms of severity in the DSM-5 diagnostic criteria, whereas low self-esteem, self-reproach, suicidality, and vegetative symptoms are considered as being more severe than the remaining symptoms in the ICD-10 [39]. From the MIDAS project, suicidal ideation, depressed mood, and anhedonia have been proposed as the best indicators for depression severity in 1,210 outpatients with MDD, whereas some symptoms are not significantly correlated with depression severity [39]. Also from the MIDAS project, for most symptom criteria, the correlation coefficient was higher regarding symptom intensity rather than the mere presence of the symptom. Thus, in terms of the clinical evaluation for depressive disorders, the dimensional symptom severity rating (mild, moderate, and severe) is more pertinent than the dichotomous symptom rating (presence and absence) [40]. Moreover, it has been reported that non-depressive symptoms, including psychic anxiety, somatic anxiety, and subjective anger, are not significantly associated with depression severity [41].

7.3.2 Endophenotypes for Depressive Disorders

In the context of the heterogeneity of depressive disorders, the endophenotypes are proposed as representing an intermediate position that can construct the pathway between genotype and phenotype in the complicated genetics underlying psychiatric disorders such as depressive disorders [42–46]. It has been suggested that, by the endophenotypes, the genetics of depressive disorders can be parsed into smaller, more tractable components [39]. According to the Gottesman and Gould criteria [43, 45–47], the requirements for a construct to be considered an endophenotype can be defined as follows. First, the association with depression is estimated by comparing individuals with and without depressive disorders. Second, heritability is estimated by twin and adoption studies. Third, the state independence is estimated by comparing within individuals or between groups, before, during, and after a depressive episode. Fourth, the cosegregation is estimated by comparison of the relatives who also have a history of depression with the relatives who have never experienced a depressive episode, or currently depressed relatives with relatives who never had depression, in families of probands with depressive disorders. Fifth, the increased rate within an affected family is estimated by comparison of the unaffected relatives of a depressed proband to the general population. Sixth, the psychometric properties are evaluated by the test-retest reliability, internal consistency, and inter-rater reliability for those with and without depressive disorders. Thus, according to Goldstein and Klein [45], neuroticism, morning cortisol, cortisol awakening response, frontal asymmetry on electroencephalography (EEG), probabilistic

reward learning, attention (eye tracking, Stroop, and dot probe), and memory (biased self-referent encoding and overgeneral autobiographical memories) are indicated as the endophenotypes for depressive disorders [45].

Herein, “an operational framework for heterogeneity” of depressive disorders, which is supported by the symptom and neurobiology-based approaches, should be adopted in clinical practice and research [25].

7.4 Network Analysis of Depressive Disorders

Network analysis is a method used to evaluate the network structure and the components proportionally or disproportionally contributing to an adaptive function of the network as a whole [48, 49]. Thus, the network approach has recently been used to explain the complexity of psychiatric disorders for the following reasons [50, 51]. First, the visualization methods in network psychiatry can be used to explore the pathways between variables and identify novel and interesting relationships that may exist between them. Second, network analysis can be used to estimate the properties of the network itself. Third, network psychiatry can identify the variables that are disproportionally related with the network’s adaptive functions. From the perspective of the network analysis approach, the symptoms are not the outcome factors of an underlying disease; alternatively, the symptoms and their associations constitute the disease itself [52]. Thus, the standard reductionistic model supports “top-down” processes, whereas the network analysis approach supports “bottom-up” processes [53]. Since “centrality” denotes the overall symptom connectivity in a network analysis, centrally located symptoms may have a higher impact on the network structure rather than peripherally located symptoms [54–56]. Thus, it is assumed that central symptoms might contribute to the rapid activation of interrelated and intertwined symptoms within a network structure and, thus, may be regarded as potential therapeutic targets [51, 57].

Surprisingly, in a network analysis of the psychiatric symptoms of 3,463 depressed outpatients in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, the DSM symptoms (e.g., sad mood) were not centrally located compared to non-DSM symptoms (e.g., anxiety) [55]. These findings have been replicated by comparing the centrality index of the DSM symptoms and non-DSM symptoms in 5,952 Han Chinese individuals with MDD [58]. Additionally, an unpublished manuscript found that depression symptoms (21 Beck Depression Inventory symptoms) are not more centrally located than anxiety symptoms (21 Beck Anxiety Inventory symptoms) in 223 patients with MDD. Moreover, another unpublished manuscript found that guilt or self-blame is the most central among the ICD-10 symptom criteria in 643 East Asian patients with depressive disorder, followed by fatigue and suicidal thoughts or acts, among others. These findings suggest that the operational definition of depressive disorders may not be equivalent to indicators of MDD. Also, it has been suggested that the organization of symptomatology in depressive disorders may be explored by the strong interconnections within the network structure [59, 60].

7.5 Research Domain Criteria in Depressive Disorders

The Research Domain Criteria (RDoC) has been defined as serving to “develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures” in Strategy 1.4 of the 2008 National Institute of Mental Health (NIMH) Strategic Plan. Thus, since the aim of the RDoC is to link the classification of psychopathology to recent advances in genetics and neuroimaging [61–63], the units of analysis for each domain in the RDoC include genes, molecules, cells, circuits, physiology, behavior, self-reports, and paradigms. Two of the RDoC domains, namely, the Loss construct within the Negative Valence Systems domain and various Reward constructs within the Positive Valence Systems domain, are included in MDD and other depressive disorders [64]. The roles of glucocorticoids, sex hormones, oxytocin, vasopressin, and cytokines are highlighted in terms of the level of the Loss construct. For the genetic level of the Loss construct, the genes that control neurotransmission of serotonin and dopamine (e.g., 5-HTTLPR, 5-HT receptor genes, MAOA, and COMT) are targeted, despite not being identified in the genome-wide association studies (GWAS) [65]. The Loss construct is highlighted not only with the disruption within the cortico-limbic circuitry (increased limbic reactivity to affective salient stimuli, decreased activation in the prefrontal cortex, and reduced functional connectivity between these groups) but also increased activity in the default mode network, which has been studied in the realm of depressive disorders [66–68]. The behavioral level of the Loss construct has heterogeneous features, which are consistent with the DSM-5 diagnostic criteria of MDD, as well as rumination and biases in attention and memory, and the self-report level is represented by attributional styles and symptoms of hopelessness [61]. In addition, the Positive Valence Systems domain denotes the identification and engagement in behaviors for achievement and satisfaction gained from rewards. In terms of the development and course of depressive disorders, a longitudinal association between higher intensity of the Positive Valence Systems domain and attenuation of negative affective symptoms of depression has been identified [69].

Furthermore, environmental influences and development have been proposed as the additional dimensions to the RDoC matrix as follows. First, the vulnerability-stress or diathesis-stress models for depression focus on the influences of the occurrence of negative life events on a person’s level depression risk. Despite lack of replication, the gene X environment (GxE) models for depression risk, which involve the genes with serotonergic or hypothalamic-pituitary-adrenal (HPA) axis function, have been identified [70–72]. Second, developmental shifts have been noted that support not only the GxE models but also the amygdala-prefrontal connectivity, cortisol reactivity to stress, and attentional biases and pupillary reactivity to affectively salient stimuli [73–79]. In addition, there are periods of heightened sensitivity, in which environmental factors may have a stronger impact on the development and function of neural and physiological systems [70].

7.6 Conclusions

For the DSM-5 diagnostic criteria, MDD is defined as a distinctive disease entity parallel to bipolar disorder and schizophrenia, in accordance with the deconstruction of Kraepelinian dualism. Symptoms across different diagnostic categories are described for MDD and other depressive disorders using transdiagnostic specifiers, including “with mixed features,” “with psychotic features,” and “anxious distress.” Due to the addition of “hopelessness” to the category of subjective descriptors of depressed mood and removal of the “bereavement exclusion” item, it is speculated that the diagnostic threshold for MDD may be reduced. As the DSM-5 diagnostic criteria for MDD is defined based on polythetic and operational approaches, the inevitable heterogeneity of the depressive syndrome is apparent. Thus, 227 different symptom combinations fulfill the DSM-5 diagnostic criteria for MDD. We interpreted this heterogeneity using the Wittgensteinian analogy of the language game. Depression subtypes, with and without disturbances in monoamine and catecholamine levels, and those determined by degree of severity and by weight gain and loss, are evidenced by a systemic review of the biological approaches. In particular, depression subtypes determined by degree of severity are supported by biomarker profiles and functional connectivity. According to the Gottesman and Gould criteria, neuroticism, morning cortisol, cortisol awakening response, frontal asymmetry on EEG, probabilistic reward learning, and other variables are evidenced as the endophenotypes for depressive disorders. From the perspective of “bottom-up” processes, network analysis is expected to explore the pathways between depressive symptoms and identify the novel and interesting relationships between depressive symptoms. Therefore, there have been no differences in the centrality index of the DSM symptoms and non-DSM symptoms in patients with MDD. Furthermore, two of the RDoC domains, including the Loss construct within the Negative Valence Systems domain and various Reward constructs within the Positive Valence Systems domain, are included in the diagnosis of MDD and other depressive disorders.

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Chapter 8

Epigenetics: A Missing Link Between Early Life Stress and Depression



Kathleen Saavedra and Luis A. Salazar

Abstract Exposure to early life stress (ELS) represents a major risk factor for the development of psychiatric disorders, including depression. The susceptibility associated with ELS may result from persistent changes in gene transcription, which can occur through epigenetic mechanisms, such as DNA methylation, histone modifications, and microRNA expression. Animal models and reports in humans described that negative stimuli can alter the neurodevelopment of an individual, affecting their behavior and cognitive development. It is currently hypothesized that levels of environmental adversity in this early developmental period are able to shape the experience-dependent maturation of stress-regulating pathways leading to long-lasting alterations in stress responsivity during adulthood. Here, we review key findings from animal and clinical studies examining the effects of prenatal and postnatal environment in shaping development of the neuroendocrine regulation of stress and the role of epigenetic mechanisms in the predisposition of depression.

Keywords Early life stress · Depression · Epigenetics · Prenatal stress · microRNAs

8.1 Introduction

The relationship between adverse experiences during early life and mental health is well described. Various studies in animal models and reports in humans described that negative stimuli can alter the neurodevelopment of an individual, affecting their behavior and cognitive development. These alterations can determine individual differences in the risk to develop stress-related disorders in adult life. The question is

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how these environmental stimuli or personal life experiences can be incorporated into cellular level to determine the risk of development of long-term alterations of mental disorders, including depressive disorder. There are reports that show that depressive disorder is a family disorder, therefore with a strong genetic factor; however, despite describing the different genetic alterations related to the pathophysiology of depressive disorder, it has not been possible to associate a genetic variant to the risk of development of this disease [1]. It has been proposed that depressive disorder may arise from an interaction between genetic alterations and environmental factors, as especially stressors in early life as events during pregnancy that affect the fetus or early traumatic events in the childhood. Thus, these stressors can activate the stress response system and interact with genes involved in the development of depression. The field that studies how the environment affects genes is known as epigenetics and can explain to a large extent how traumatic events condition the development of depressive diseases and why these, despite having a genetic factor involved, are poorly inherited.

8.2 Stress in Early Life Conditions the Development of Depression in Adult Life

Early life traumatic event can condition the ability to respond to stress in the adulthood. Epidemiological studies report that victims of physical, sexual, psychological or emotional abuse in the childhood have considerable increased risk of developing mood disorders in adult life that are associated with depressive syndrome [2]. The degree of risk also depends on the type and number of adverse events faced by the child [3]. Prospective longitudinal studies have confirmed the relationship between abuse and neglect in childhood and major depressive disorder in adulthood (Fig. 8.1)

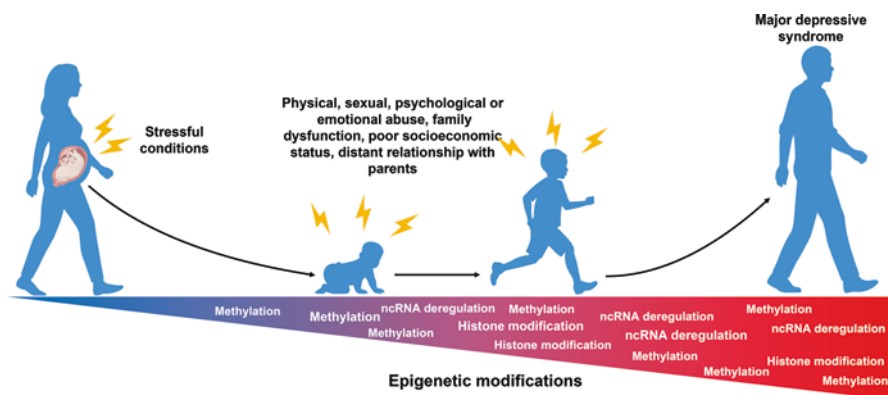


Fig. 8.1 Early life traumatic event can increase the risk of mood disorders in adult life by deregulation of epigenetic modifications

[4]. Other adverse events such as family dysfunction, poor socioeconomic status, distant relationship with parents, strict and inconsistent discipline, among others have also been associated with increased risk of depression, anxiety disorders, poor cognitive and emotional development [5–7]. Initially the idea was emphasized that neural system plasticity was limited to the first stage of life, the perinatal period; however, it is now known that this plasticity is continuous throughout life. From here the hypothesis that suggests that early life traumatic events can cause epigenetics modifications in key genes of the stress response system, mainly hypothalamic–pituitary–adrenal axis (HPA) and that are associated with the development of depression disorder.

8.3 Epigenetic Modifications

Epigenetics is described as the study of changes in gene expression that are not due to alterations in DNA sequence. The concept of epigenetics was first described by C.H. Waddington in 1940, who proposed that phenotypes are the results of an interaction between genotype and the environment [8]. This interaction is mediated by epigenetic modifications that do not affect the nucleotide sequence of DNA. These epigenetic modifications are cell-specific, mitotically and/or meiotically heritable, but at the same time environmentally modifiable, consequently they are a dynamic regulation mechanism and could explain different scenarios in which medical observations confront traditional genetics [9].

Epigenetic modifications can be grouped in DNA methylation, histone modification, and non-coding RNAs. The DNA methylation and histone modification are the best understood epigenetic modifications. These regulate the accessibility to the DNA by regulating the gene expression machinery, thus non-accessible genes are silenced genes, while accessible genes are genes transcriptionally active. The epigenetic modifications allow integrating external stimuli into the genome, regulating the gene expression and thus facilitating cell adaptation, giving the genome a certain degree of plasticity against environmental stimuli that may or may not be unfavorable. In this context, the stimuli perceived in early life can cause changes in the genome that affect the adult life of an individual.

The neuroepigenetics has emerged as a subfield of epigenetic which would explain dynamic regulation mechanisms mediated by epigenetic modifications in cells of the nervous system. Lux [10] distinguishes three types of epigenetic mechanisms in neuronal cells according to their functional context: structural, synaptic and developmental epigenetic mechanisms. Structural epigenetic mechanisms maintain the genomic structure in neuronal cells. Synaptic epigenetic mechanism regulates the gene expression underlying acute synaptic activity, short-term adaptations and synaptic functions. Developmental epigenetic mechanism contributes to the establishment and consolidations of long-term differentiation in structure and functions of neuronal cells. These last could be involved in development of mental disorders in response to early life stress.

8.3.1 DNA Methylation

DNA methylation involves the addition of a methyl group at the 5' position of cytosines (5mC) in cytosine-phosphate-guanine (CpG) dinucleotides [11]. These CpG dinucleotides are concentrated in regulatory regions of the genome, such as gene promoter regions, enhancer elements or repetitive sequences. The DNA methylation is conventionally associated with silencing of gene expression since it reduces the access of transcription factors into regulatory elements. In this way promoter regions and enhancer elements of transcriptionally active genes are usually not methylated, but can be silenced by DNA methylation (Fig. 8.2). The addition of methyl group to cytosine residues is catalyzed by a family of enzymes known as DNA methyltransferases (Dnmts). Dnmt3a and Dnmt3b can methylate unmodified DNA generating a new methylation pattern being known as *de novo* Dnmts. Dnmt1 acts during DNA replication to copy methylation pattern from the parental DNA strand to the DNA of the daughter cell and to maintain the original DNA methylation pattern in the cell lineage; for this reason it is called the maintenance Dnmt. The DNA methylation is a process that can be reversed; however, the exact process by which demethylation occurs is still debated. Different mechanisms have been proposed and described that demethylation occurs through a series of chemical reactions that modify the 5mC by deamination and/or oxidation reactions, then be recognized by the base excision repair (BER) pathway and replace the modified base with a cytosine without modifications. The involvement of the translocation enzyme family of ten once Tet1, Tet2, and Tet3 has also been described. These enzymes agree a hydroxyl group on the 5mC methyl group to form 5hmC. It has been described that this modification seems to be particularly abundant in the brain and could allow the dynamic regulation of DNA methylation, which in turn regulates gene expression [12].

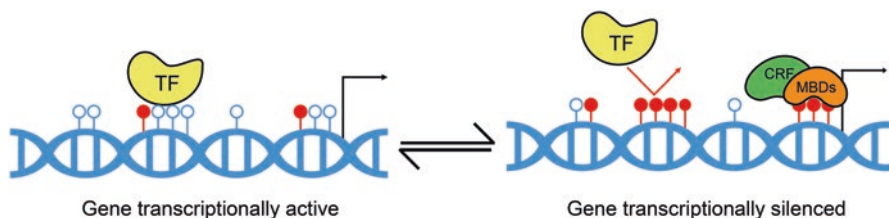


Fig. 8.2 DNA Methylation. CpGs dinucleotides methylated (red), can regulate the gene expression by inhibiting transcription factor binding and recruitment MBDs, CpG rich regions are known as CpG islands and areas around 2 kb away are known as CpG shores, these shores have a CpG density intermediate. TF: transcription factor; CRF: chromatin remodeling proteins; MBDs: methylated DNA binding proteins

8.3.2 *Histone Modifications*

In eukaryotes the DNA is organized in the form of chromatin, its basic unit is the nucleosome, which consists of 147-bp of DNA wrapped in an octamer of histones. The histone tails protrude from the nucleus of the nucleosome and have the ability to interact with adjacent nucleosomes and DNA. All histones may undergo post-transcriptional modifications that affect the histone tail, especially on the tails of H3 and H4. These modifications regulate the chromatin structure and modify the accessibility to DNA, so when it is densely stored, we talk about “closed” chromatin or heterochromatin and when it is stored in a lax form, we talk about “open” chromatin or euchromatin. Histones can be modified at their N-terminal tails, these modifications include acetylation, methylation, phosphorylation, and ubiquitination, SUMOylation and ADP-ribosylation, among others. These modifications can change the DNA-histone interaction, which is involved in gene expression regulation by chromatin remodeling [13, 14] (Fig. 8.3).

8.3.3 *Noncoding RNA*

ncRNAs include PIWI-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), transcribed ultraconserved regions (T-UCRs) and large intergenic non-coding RNAs (lincRNAs); however, the most widely studied class of ncRNAs are microRNAs (miRs), small ncRNAs of 22 nucleotides that mediates post-transcriptional gene silencing by controlling the translation of mRNA [15, 16]. miRNAs are post-transcriptional regulators of gene expression that control many cellular processes, including proliferation, differentiation, apoptosis and development, controlling the activity of approximately 50% of all protein-coding genes. They can regulate one particular target or may regulate the expression of hundreds of genes simultaneously [17]. miRs modulate mRNA expression depending on the number of mismatches between its own sequence and the sequence of the target mRNA, regulating expression by enzymatic target degradation or by preventing mRNA translation into protein due to steric hindrance of the protein synthesis machinery (Fig. 8.4) [18].

8.4 Epigenetic Programing by Prenatal Stress

In mammals, there are specific stages of development during which the epigenome, understood as all epigenetic modifications in the genome, is more labile and sensitive to hormonal variations and environmental stimuli. During the early stages of the development of a mammal, methylation and demethylation cycles occur, which produce a new landscapes of DNA methylation in the developing organism. The first cycle of demethylation of all DNA occurs during germ cell development followed by a remethylation before fertilization where a new DNA methylation landscape is

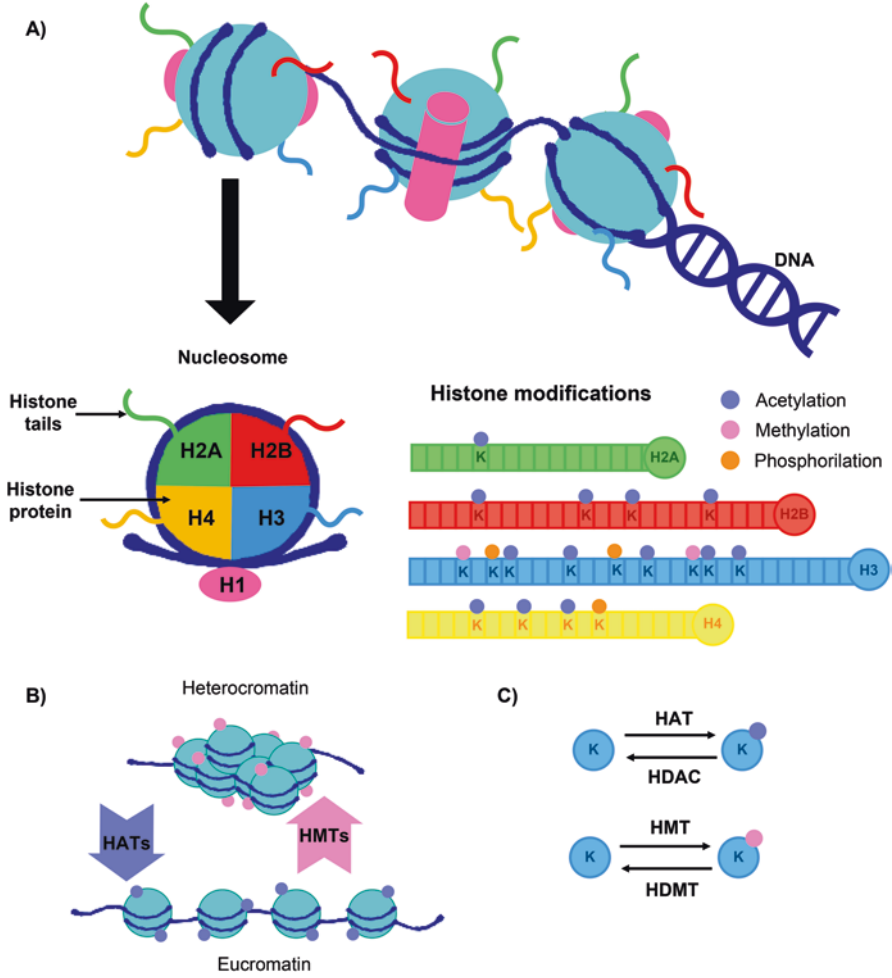


Fig. 8.3 Histone structure and modifications. (a) DNA is coiled around histone octamers, forming the nucleosome. The global patterns of modifications contribute to determine the chromatin state (euchromatin or heterochromatin), the best described modifications are acetylation and methylation. (b) In general, the increased histone methylation is associated with heterochromatin and increased acetylation is associated with euchromatin. (c) HAT and HDAC enzymes, respectively, add and remove acetylation marks on lysine (K) and other residues. Similarly, HMT and HDMT, respectively, methylate and demethylate residues. *HAT* Histone acetyltransferases, *HDAC* histone deacetylases, *K* lysine, *HMT* histone methyltransferases, *HDMT* histone demethylases

established in germ cell precursors. The second cycle of global DNA demethylation occurs after fertilization, in early embryogenesis. This results in the specific methylation of parental alleles in early embryos and the specific expression of parental alleles of associated printed genes of establishing new methylation landscapes [19, 20]. Thus, periods of gametogenesis and early embryogenesis appear to be particularly vulnerable to adverse influences. Likewise, interactions between mother and

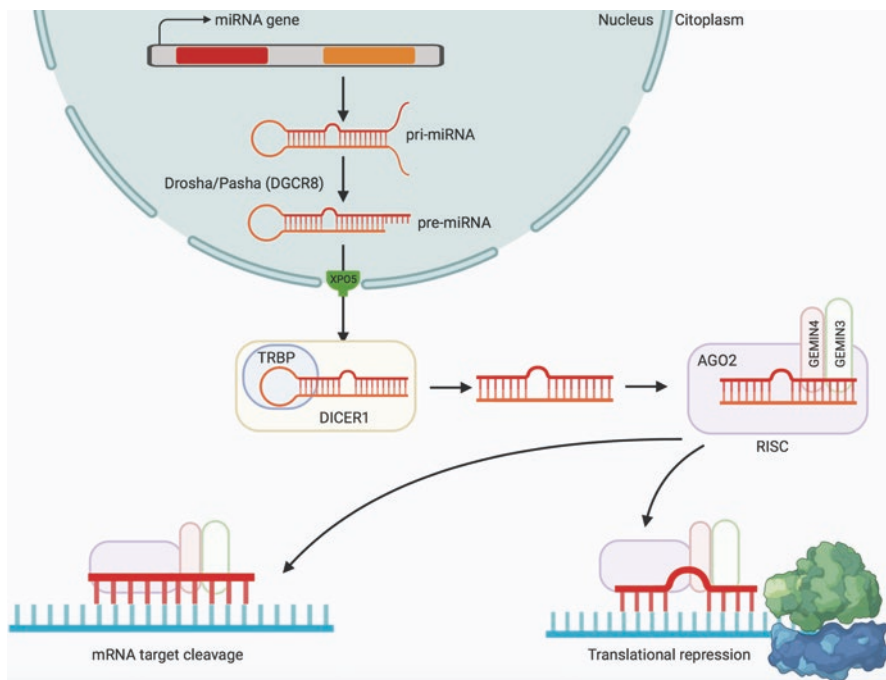


Fig. 8.4 Overview of miRNA biogenesis and effector pathways. The canonical biogenesis includes the production of the primary miRNA transcript (pri-miRNA) by RNA polymerase II or III and cleavage of the pri-miRNA by the microprocessor complex Drosha–DGCR8 (Pasha) in the nucleus into a precursor hairpin (pre-miRNA), this is exported from the nucleus by Exportin-5–Ran-GTP. In the cytoplasm, the RNase Dicer in complex with the double-stranded RNA-binding protein TRBP cleaves the pre-miRNA hairpin to its mature length. One strand of the mature duplex is loaded with Argonaute (Ago2) proteins into the RNA-induced silencing complex (RISC). The miRNA then guides RISC to silence target mRNAs through mRNA cleavage or translational repression, the passenger strand is degraded

fetus are critical for growth and development, alterations in these interactions can have consequences in the adult life for offspring's psychological health.

It is well described that exposure to adverse conditions during prenatal period as unfavorable social environment, anxiety, depression, malnutrition or pain, among others, can cause effects on the fetus that persists in adulthood, these effects can be associated with a variety of pathological psychiatric conditions including schizophrenia, anxiety, and depression [21–24]. These adverse condition stressors expose the fetus to high levels of maternal glucocorticoids that can cross the barrier and disrupt the fetal development of the brain, altering the maternal fetal HPA axis and causing long-term effects [25]. Considering that the HPA axis is developed and functioning at week 22 of pregnancy, maternal stress experience has the potential to alter permanently the functioning of this axis in its offspring, especially because the plasticity of HPA axis is maintained until 2 years of age [26].

There is evidence that demonstrates that HPA axis regulatory genes are regulated by DNA methylation and histone modification [27–29]. Oberlander et al. [28] demonstrated that the prenatal exposure to maternal depressed/anxious mood was associated with the increase the methylation of exon1F of the human gene *NR3C*, responsible for the control of hippocampal glucocorticoid receptor (GR) expression, in newborns. The GR plays a critical role in the regulation of HPA axis through negative feedback on glucocorticoid release. The methylation of *NR3C* results in decreased GR expression and increases the circulating glucocorticoid levels [30]. Similar results were previously described by Hompes et al. [31] who evaluated the association between maternal cortisol and emotional state during pregnancy and the methylation state of the promoter region of *NR3C1* gene. Another important factor in the regulation of the intrauterine level of maternal glucocorticoids is the placental enzyme 11 beta-hydroxysteroid dehydrogenase type 2 (11b-HSD-2) that deactivates cortisol. Animal studies have shown that this enzyme is overexpressed in response to acute stress during pregnancy, while chronic stress and maternal prenatal anxiety cause a decrease in the expression of the enzyme [32, 33]. This decrease in the expression of 11b-HSD-2 has been associated with methylation of *HSD11B2* gene [33].

Parental trauma exposure is associated with greater risk for post-traumatic stress disorder (PTSD) in offspring, this risk could be associated with epigenetic deregulation that occurs in the parent and is inherited to offspring. Yehuda et al. reported the effect to Holocaust exposure on the methylation of *FKBP5*, an important regulator of GR-sensitivity, in parent exposed and their offspring. *FKBP5* methylation was observed both in parents and in their offspring. These effects were observed at bin 3/site 6. Interestingly, in Holocaust survivors, methylation at bin 3/site 6 of *FKBP5* was higher in comparison to controls, whereas in Holocaust offspring, methylation was lower and significantly correlated [34].

8.5 Epigenetic Programing by Early-Life Stress

Just as prenatal care is important in neural epigenetic programming, so is the care of the child after birth. The care received by an infant in its early life can cause changes in the development of neuronal systems that regulate the response to novelty and social behavior. Thus, the quality of maternal care plays a critical role in the formation of adult behavior patterns, regulating stress response, emotional content, learning ability, and memory [35, 36].

Matrilineal transmission of maternal behavior has been described in humans and primates. It is estimated that 70% of abusive parents were abused during their childhood and that at least 20% of abused children could become abusive parents [36, 37]. Similarly, it has been described that institutionalized women who receive less maternal affection during their childhood become mothers with less attachment and sensitivity to their own children [38]. These findings show a strong relationship between maternal care and the behavior of the offspring, studies in primates and

rodents suggest that this inheritance is not mediated by variations in the DNA sequence. However, variations in gene expression and neuroendocrine function are observed. Experiments in rodents where the frequency of mothers in licking/grooming (LG) their pups was evaluated shows that offspring with lower LG have an increase in the activity of the HPA axis as a result of the decrease in the ability to regulate the release of corticotrophin releasing hormone (CRH) and adrenocorticotropin (ACTH) [39].

Another interesting finding in an offspring with low LG is the loss of estrogen sensitivity [40], which translates, among other things, into a decrease in oxytocin receptor levels in the medial preoptic area, being associated with an alteration in the behavior of pup in their adult lives. This loss of estrogen sensitivity is associated with a decrease in the expression of the estrogen receptor alpha ($ER\alpha$) compared with offspring that have received more frequently LG, this difference in the expression appears during the first postpartum week and is mediated by the quality of maternal care [41]. $ER\alpha$ promoter analyzes indicate that it has 14 potential DNA methylation sites. $ER\alpha$ promoter methylation analysis indicates that the medial preoptic area of mice with low LG has methylation levels higher than the high LG offspring. Thus, as adults, the female offspring of mothers who exhibit an increase in pup LG over the first postpartum week show a higher expression of $ER\alpha$ in the medial preoptic area and they are mothers themselves with high LG. Through these pathways there may be a behavioral transmission of maternal care from mother to offspring through epigenetic modification to $ER\alpha$ [36, 40–42]. In humans, low quality of maternal care and overprotection, a ‘style’ referred to as ‘affectionless control’, is a risk factor for depression [43].

Although there is sufficient evidence to deregulation in the expression of miRNAs in depression, no sufficient studies on the contribution of ELS in MDD by alterations in the expression of miRNAs have been reported. The studies to date are mainly preclinical, carried out in animal models of ELS is maternal separation [44]. There is evidence to suggest that dopamine receptor D2 (DRD2) upregulation may be associated with the development of MDD. Zhang et al. [45] increased levels of striatal DRD2 mRNA in adult rats that were maternal deprivation (DM) and increased levels of accumulated DRD2 protein in adult rats subjected to unpredictable chronic stress (CUS). It was found that miR-9 is negatively regulated in the nucleus accumbens (NAc) of CUS rats and in the striatum of MD rats, suggesting that miR-9 in NAc is interrupted by stress in adulthood (modeled by CUS rats), while miR-9 in the striatum is interrupted by early adversity (modeled by MD rats) and when rats were exposed to MD and CUS, miR-9 was more significantly down-regulated in both the NAc and striatum [45]. Huang et al. [46] reported an increase in the expression of mir-504 in the NAc of rats with DM, miR-504 directly marks the 3'UTR region of dopamine D1 receptor gene (DRD1), neurons with DRD1 expression have been shown to play an important role in the development of anhedonic behavior in rodents [47]. Bai et al. [48] is also an MD model in rats, demonstrated the increase of miR-16 expression in the hippocampus compared with control rats and others who received chronic unpredictable stress. Uchida et al. [49] evaluated the expression of miRNAs in rats that had been separated from their

mother for 3 h per day and found an increase in the expression of miRNAs miR-132, miR-124, miR-29a, and miR-9. The miR-9 has been shown to regulate microglia functions through its target HECT domain E3 ubiquitin protein ligase 1 (HECTD1) [50]. miR-132 is related to morphogenesis [51], while miR-124 is related to brain development [52]. One of the targets of miR-124 is FKBP5. Interestingly, it has been reported that miR-124 can play a role in the binding and altered function of FKBP5 through its interaction with GR. It has been shown that miR-124 targets GR and is related to behaviors similar to depression in animal models [53, 54]. Allen et al. suggested the possibility that ELS confers susceptibility to depression through these epigenetic changes involving miR-124 [44]. Recently, Mazzelli et al. [55] investigated the long-term effects of early life stress on the modulation of miR-19 levels in vitro. The results show that ELS can cause a long-term downregulation of miR-19 levels, which may be responsible of alterations in neurodevelopmental pathways and in immune/inflammatory processes, leading to an enhanced risk for mental disorders later in life. In addition, it was suggested that intervention strategies targeting miR-19 may prevent alterations in these pathways, reducing the ELS-related effects.

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Chapter 9

From “Leaky Gut” to Impaired Glia-Neuron Communication in Depression



Leszek Rudzki and Michael Maes

Abstract In the last three decades, the robust scientific data emerged, demonstrating that the immune-inflammatory response is a fundamental component of the pathophysiology of major depressive disorder (MDD). Psychological stress and various inflammatory comorbidities contribute to such immune activation. Still, this is not uncommon that patients with depression do not have defined inflammatory comorbidities, and alternative mechanisms of immune activation need to take place. The gastrointestinal (GI) tract, along with gut-associated lymphoid tissue (GALT), constitutes the largest lymphatic organ in the human body and forms the biggest surface of contact with the external environment. It is also the most significant source of bacterial and food-derived antigenic material. There is a broad range of reciprocal interactions between the GI tract, intestinal microbiota, increased intestinal permeability, activation of immune-inflammatory response, and the CNS that has crucial implications in brain function and mental health. This intercommunication takes place within the microbiota-gut-immune-glia (MGIG) axis, and glial cells are the main orchestrator of this communication. A broad range of factors, including psychological stress, inflammation, dysbiosis, may compromise the permeability of this barrier. This leads to excessive bacterial translocation and the excessive influx of food-derived antigenic material that contributes to activation of the immune-inflammatory response and depressive psychopathology. This chapter summarizes the role of increased intestinal permeability in MDD and mechanisms of how the “leaky gut” may contribute to immune-inflammatory response in this disorder.

Keywords Depression · Leaky gut · Microbiota · Cytokines · Neuroimmunomodulation · Oxidative stress · Glia

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9.1 Introduction

For over four decades, the monoaminergic hypothesis mostly defined our understanding of major depressive disorder (MDD). This hypothesis postulated that deficits in certain neurotransmitters, including serotonin (5-HT), noradrenaline, and dopamine, contribute to MDD symptomatology and that antidepressant treatment improves depressive symptoms due to the restoration of the appropriate neurotransmission. However, in the last two decades, a piece of robust scientific evidence emerged indicating that MDD is accompanied by the low-grade immune-inflammatory response, which has a crucial role in the pathophysiology of this disorder. Consequently, various immune hypotheses of this disorder emerged, including the macrophage hypothesis of depression [1], the monocyte-T-lymphocyte hypothesis [2], a neurodegeneration hypothesis [3], the cytokine hypothesis [4], the glutamate hypothesis [5], “leaky gut” hypothesis [6, 7], or depression as a glial-based synaptic dysfunction [8], to name a few. Those hypotheses reciprocally complement each other and represent a continuum of evolving understanding of depression. It also became clear that the monoaminergic paradigm is just a part of the much bigger and intriguingly complicated psycho-neuroimmunological picture.

Some of the crucial aspects of immune-inflammatory response in MDD include increased levels of pro-inflammatory cytokines, that is, IL-1 β , TNF- α , IL-6 [4, 9], activation of oxidative, and nitrosative stress (O&NS) and decreased levels of crucial antioxidants and total antioxidant capacity in depressed patients [10–13]. Also, it has been demonstrated that O&NS may generate neoepitopes with subsequent autoimmunity in depressed patients [14]. Furthermore, MDD is accompanied by abnormalities in the metabolism of tryptophan and its catabolites in the kynurenine pathway (TRYCATs/kynurenines), which manifests with the decreased amount of tryptophan available for conversion to 5-HT and increased conversion of tryptophan to TRYCATs. Those kynurenines may exert neurotoxic, prooxidative effects on the CNS, and increase glutamate neurotransmission [3, 15–18]. Moreover, MDD is often comorbid with various inflammatory and autoimmune disorders, which could contribute to the activation of the inflammatory response in MDD. Those, for instance, include inflammatory bowel diseases (IBD), that is, Crohn’s disease, ulcerative colitis or irritable bowel syndrome (IBS), further, rheumatoid arthritis, multiple sclerosis (MS), coronary artery disease, chronic obstructive pulmonary disease (COPD), HIV infection (human immunodeficiency virus), Alzheimer’s disease, and their comorbidity reciprocally worsens the course and prognosis. Still, this is not uncommon that patients with MDD do not have defined inflammatory comorbidities, and alternative mechanisms of immune activation in this disorder need to take place.

One of the major contributors to activation of immune-inflammatory response is psychological stress, which with the involvement of hypothalamic-pituitary-adrenal (HPA) axis and the activation of the sympathetic nervous system (SNS), upregulates the expression of nuclear factor kappa beta (NF- κ B) in mononuclear cells, which results with an increase of pro-inflammatory cytokines release [19–21]. Moreover,

catecholamines induce activation of microglia, the release of pro-inflammatory cytokines in the periphery, and within the CNS, and increase the trafficking of macrophages to the CNS. Psychological stress also upregulates the TLR-4 pathway and exacerbates response to bacterial lipopolysaccharides (LPS) [21–24].

Another crucial element that links the effects of psychological stress and immunity is the gastrointestinal (GI) tract with the gut-associated lymphoid tissue (GALT). GI tract, along with GALT, constitutes the largest lymphatic organ in the human body, and it is responsible for the production of 70–80% of immune cells. Given that, in the last decade, there is a growing interest in reciprocal interactions between the GI tract, intestinal microbiota, increased intestinal permeability, activation of immune-inflammatory response, and the CNS. This intercommunication takes place within the microbiota-gut-brain axis or recently proposed the microbiota-gut-immune-glia (MGIG) axis [25], since glial cells are the main orchestrator of the immune response within CNS, and mediate the central response to the systemic inflammation. GI tract forms the biggest surface of contact of the human body with the external environment, and it is the most significant source of bacterial and food-derived antigenic material.

Bacterial LPS/endotoxin, which is a cell wall component of Gram-negative bacteria, along with other bacterial-derived antigenic material including flagellins, lipoproteins, peptidoglycans belong to so-called pathogen-associated molecular patterns (PAMPs) and are recognized by pattern recognition receptors (PRRs) including Toll-like transmembrane receptors (TLRs). TLRs constitute broad antigen sensing “machinery” and, of particular interest, TLR4 are responsible for recognizing bacterial LPS. Those receptors are expressed on various immune and nonimmune cells both in the periphery and within the CNS, such as dendritic cells, lymphocytes, monocytes, macrophages, granulocytes, astrocytes, microglia, oligodendrocytes, and tissues including intestinal tissue [26]. LPS can also activate receptors for advanced glycation end products (RAGE) which can lead to endothelial hyperpermeability [27]. The second group of gut-derived antigens, which could play a significant part in the immune-inflammatory mechanism in MDD are food-derived antigens.

Permeability of the intestinal barrier is the main determinant of the extent of bacterial translocation from the intestinal lumen and subsequent activation of TLR4 receptors. Importantly, this barrier’s permeability may be compromised by a broad range of factors, including psychological stress with the involvement of HPA axis activation and corticotropin-releasing hormone (CRH)-mediated mast cells activation (Fig. 9.1) [28–34]. Also, psychological stress may contribute to increased intestinal permeability via activation of SNS and activation of β 2-adrenergic receptors expressed on epithelial cells [33, 35, 36]. Moreover, factors compromising gut barrier include pro-inflammatory cytokines such as IFN- γ [37], TNF- α [38, 39], IL-1 β [40], O&NS [30, 41], NF- κ B [42], alcohol [43–46], high fat diet [47] and obesity [48], traumatic brain injury [49], food additives and pesticides [50–55], prolonged strenuous exercise [56, 57], heat stress [58], infections [59, 60], some medications for instance, antibiotics [61–64], and nonsteroidal anti-inflammatory drugs (NSAID) [65, 66]. Finally, since gut microbes are the “natural guardians” and modulators of

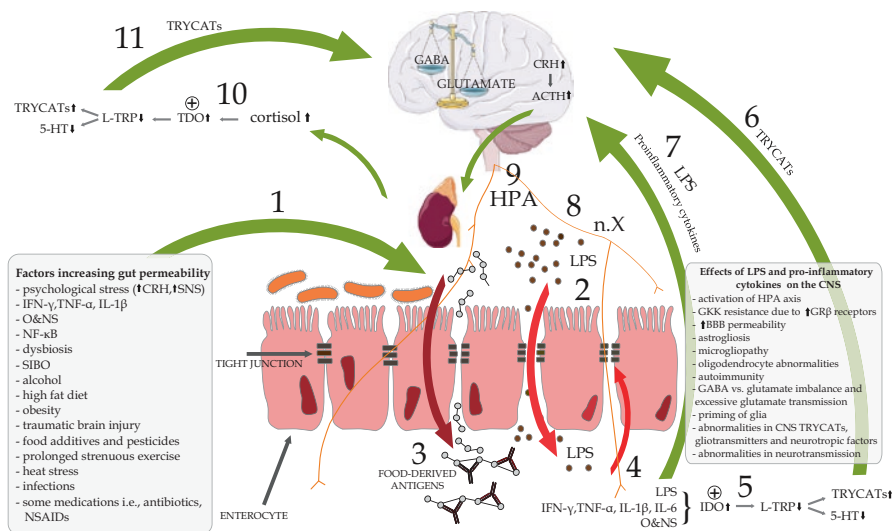


Fig. 9.1 The overview of mechanisms involved in increased intestinal permeability and subsequent activation of the immune-inflammatory response in depression. (Image generated using Servier Medical Art. Partially adapted and modified from Rudzki et al. 2012 [118])

(1) Various factors contribute to increased intestinal permeability (i.e., psychological stress, inflammation, dysbiosis, O&NS, diet); (2) increased translocation of bacterial LPS through the intestinal epithelium and subsequent activation of the immune-inflammatory response (i.e., via activation of TLR4, RAGE, NF- κ B) and increased levels of pro-inflammatory cytokines, O&NS peripherally and within the CNS, LPS may contribute to the peripheral and within the CNS autoimmunity; (3) increased translocation of food-derived antigens and formation of IgG immune complexes and IgG-mediated type III hypersensitivity; food antigen-associated molecular mimicry and covalent binding may lead to peripheral and within the CNS inflammatory response and autoimmunity; (4) further disruption of the gut barrier due to released pro-inflammatory cytokines, O&NS, and activation of NF- κ B; (5) activation of IDO by LPS, pro-inflammatory cytokines, O&NS with subsequent increased synthesis of TRYCATs and decreased availability of tryptophan for conversion to 5-HT and melatonin; (6) detrimental influence of TRYCATs on the CNS; (7) influence of pro-inflammatory cytokines and LPS on CNS by humoral route with subsequent: activation of HPA axis, increase expression of GR β leading to GCC resistance; increase of BBB permeability, astrogliosis, microgliopathy, oligodendrocyte abnormalities, priming of glia, abnormalities in CNS TRYCATs, gliotransmitters and neurotropic factors, imbalance between GABA and glutamate and increased glutamate neurotransmission, abnormalities in 5-HT, NA, and DA neurotransmission; (8) peripheral LPS and pro-inflammatory cytokines activate the CNS inflammatory response via neural route (n.X); (9) activation of HPA axis and subsequent increase in cortisol level; (10) activation of TDO by elevated cortisol with subsequent increase in synthesis of TRYCATs and decreased availability of tryptophan for conversion to 5-HT and melatonin; (11) Further detrimental influence of TRYCATs on the CNS

BBB blood–brain barrier, BDNF brain-derived neurotrophic factor, CNS the central nervous system, CRH corticotropin-releasing hormone, DA dopamine, IgG immunoglobulin G, GABA γ -aminobutyric acid, HPA hypothalamic-pituitary-adrenal axis, GCC glucocorticoids, GR β glucocorticoid receptor β , IDO indoleamine 2,3 dioxygenase, LPS bacterial lipopolysaccharides, L-TRP tryptophan, NA noradrenaline, NF- κ B nuclear factor kappa B, NSAIDs nonsteroidal anti-inflammatory drugs, n.X vagal nerve, O&NS oxidative and nitrosative stress, RAGE receptors for advanced glycation end products, SIBO small intestinal bacterial overgrowth, SNS the sympathetic nervous system, TLR toll-like receptors, TRYCATs tryptophan catabolites, 5-HT serotonin

this barrier’s integrity, abnormalities in their composition, including dysbiosis and small intestine bacterial overgrowth (SIBO), contribute to increased intestinal permeability [46, 67, 68]. Importantly, MDD is accompanied by changes in the intestinal microbiota composition [69–73], and dysbiosis was also demonstrated in other psychiatric disorders, including chronic fatigue syndrome (CFS) [74], schizophrenia and bipolar disorder [75, 76], autism [77–81], and alcoholism [46]. Additionally, psychological stress has a detrimental influence on intestinal microbiota composition, which has a negative impact on mucosal immunity and results with an increase of parameters of peripheral and central inflammation [82–84]. In view of the above, growing scientific data demonstrate that various psychiatric disorders including MDD [6, 7, 14, 76, 85–87], schizophrenia [88–90], bipolar disorder [76], CFS [91, 92], autism [93–95], and alcohol dependence [44–46] are accompanied by increased intestinal permeability. Furthermore, numerous inflammatory disorders, which are comorbid with MDD, including celiac disease, IBD, IBS, rheumatoid arthritis, ankylosing spondylitis, MS, type 1 and type 2 diabetes, asthma, atopic eczema, are also accompanied by increased intestinal permeability [96–99].

Finally, glial cells, which are non-neuronal and most abundant cell types in the CNS, play a crucial role in the brain’s immune response to both systemic and central inflammation, and reciprocally crosstalk with neurons. Those cells include astrocytes, microglia, oligodendrocytes, ependymal cells, Schwann cells, and satellite cells. In particular, astrocytes, microglia, and oligodendrocytes are mainly involved in psychiatric manifestations of gut-derived immune-inflammatory response, and various glial abnormalities accompany MDD. It is noteworthy that these cells express TLR4 receptors for endotoxin, and subsequently, bacterial translocation influenced their functions and structure. Astrocytes are involved in different metabolic processes, including ion and fluids balance and energetic metabolism. Those cells produce a broad range of gliotransmitters, including glutamate, adenosine triphosphate (ATP), D-serine, and are the sources of different neurotrophic factors involved in neurotransmission and synaptic plasticity. Astrocytes play a significant part in the regulation of glutamate and gamma-aminobutyric acid (GABA) neurotransmission and are responsible for the reuptake of about 90% of the glutamate. Subsequently, their dysfunction leads to glutamate excess and inappropriate balance between excitatory and inhibitory neurotransmission (Fig. 9.1). Astrocytes also have a pivotal role in the blood–brain-barrier (BBB) function and its permeability [100]. Abnormalities in astrocytes function and structure, namely, astrogliosis, accompanies MDD, and depressed patients have decreased number and density of those cells in brain regions involved in MDD such as the hippocampus, amygdala, and prefrontal cortex [101–103]. Also, psychological stress has a negative influence on the structure and functions of astrocytes and microglia [104]. Consequently, antidepressant treatment, including antidepressant medication, lithium, and electroconvulsive therapy (ECT) has a beneficial influence on the structure and functions of astrocytes [101, 105].

Microglia is another group of glial cells involved in MDD. Those brain resident-macrophages are mainly participating in immune regulation, and they are “the first line” immune defense of the CNS. Those cells are equipped with a broad plethora

of proinflammatory mechanisms, including cytokines, chemokines, nitric oxide (NO), prostaglandins, prooxidative kynurenines, such as 3-hydroxykynurenine (3OHKYN) and quinolinic acid (QUIN). These immune mechanisms can be life-saving, but when excessively and chronically triggered, can be detrimental to brain functions and mental health. Microglia release neurotrophins, including brain-derived neurotrophic factor (BDNF) and neurotransmitters, that is, ATP and glutamate, and are involved in synaptogenesis, synaptic pruning, sampling, and elimination. Interestingly, glutamate influences microglial chemotaxis, and microglia migrate towards the origin of increased glutamate release [106]. Consequently, abnormalities in microglia proportions (primed vs. resting cells), functions, and morphology, namely, microgliopathy, were demonstrated in MDD and suicidality [107, 108]. It was also shown that antidepressant treatment attenuates microglial activation, including the release of glutamate and pro-inflammatory cytokines [109–111]. Moreover, psychological stress has a negative impact on microglia morphology, particularly in brain areas related to MDD and anxiety, such as the hippocampus, prefrontal cortex, amygdala, hypothalamus, and nucleus accumbens [112].

Last but not least are oligodendrocytes, which are mainly involved in myelin formation. Astrocytes and microglia profoundly influence these glial cells. Pro-inflammatory cytokines, O&NS, and glutamate may compromise functions of oligodendrocytes, particularly myelin formation and abnormalities in oligodendrocytes' function and myelin formation were demonstrated in MDD [113–115].

This chapter will summarize the role of increased intestinal permeability in major depression and mechanisms of how the “leaky gut” may contribute to immune-inflammatory response in this disorder.

9.2 The Evidence of Increased Intestinal Permeability in Depression

9.2.1 Increased Intestinal Permeability to Bacterial Antigens

It is becoming increasingly evident that MDD is accompanied by increased intestinal permeability, which could contribute to the low-grade immune-inflammatory response in patients with MDD (Fig. 9.1). The first evidence of the “leaky gut” in depression was demonstrated in two consecutive studies, which revealed that MDD patients had increased serum levels of immunoglobulins A (IgA) and M (IgM) against LPS of enteric commensal bacteria. Additionally, patients with chronic depression (duration > 2 years) had higher IgM responses compared to nonchronically depressed patients [6, 7]. It was also demonstrated that patients with melancholic versus nonmelancholic depression had higher IgA to gut commensal *Citrobacter koseri*, and Hamilton Depression Rating Scale (HAM-D) score was significantly associated with IgA to *Citrobacter koseri* [76]. Moreover, IgG to oxidized LDL (oxLDL) was significantly associated with increased bacterial translocation, which is consistent with earlier results, which demonstrated that increased

translocation of gut microbes might drive oxidative and nitrosative stress and autoimmune responses against O&NS generated neoepitopes in depressed patients [14, 76]. Another research demonstrated increased plasma levels of bacterial LPS along with increased levels of zonulin and intestinal fatty acid-binding protein-2 (FABP2) in patients with anxiety and depressive symptoms [85]. Zonulin is a regulator of intestinal permeability, and FABP2 is a marker of the defective intestinal barrier. It should be noted that increased zonulin levels were also revealed in various inflammatory and autoimmune disorders, which are often comorbid with MDD [116]. In the same study, patients with depression and anxiety presented with gut dysbiosis and their abnormal intestinal bacterial flora composition was correlated with levels of LPS, zonulin, and FABP2, which indicates that dysbiosis may contribute to increased intestinal permeability in MDD. In another study, patients with MDD had significantly elevated plasma level of 16S ribosomal RNA (rRNA) subunit (16S rDNA) of intestinal microbiota, and this parameter is an indicator of bacterial translocation [117]. Furthermore, patients had increased plasma expression of TLR-4 RNA and protein, increased expression NF- κ B RNA, and increased concentration of IL-6. Strikingly, 16 weeks of cognitive-behavioral therapy (CBT) significantly decreased expressions of TLR-4 RNA and protein, NF- κ B RNA, and reduced level of 16S rDNA, which indicates that CBT contributed to decrease of intestinal permeability. Additionally, greater decrease in pro-inflammatory parameters during CBT was associated with more pronounced clinical improvement in Hamilton Depression Rating Scale (HAM-D). Using another approach of intestinal barrier assessment, namely, measurement of the lactulose/mannitol ratio (LMR), a positive association between intestinal permeability, and depressive symptoms severity in unmediated adolescents, particularly neurovegetative symptoms, was demonstrated [86]. Authors also revealed the association between sympathetic nervous system (SNS) activity and the gut permeability and suggested that intestinal permeability could mediate the association between MDD symptoms and the activity of SNS.

9.2.2 Increased Intestinal Permeability to Food-Derived Antigens

Another aspect of “leaky gut” in MDD is an increased gut permeability to food-derived antigens (Fig. 9.1). It was proposed that increased intestinal permeability to food antigens with subsequent type III hypersensitivity and formation of IgG complexes may contribute to low-grade immune-inflammatory response in MDD [118, 119]. Recently Tao et al. demonstrated that depressed adolescents had a higher rate of serum food-specific IgG that was accompanied by increased serum levels of histamine, S100 calcium-binding protein B (S100B), and homocysteine [120]. S100B is considered as a marker of increased permeability of BBB and is primarily expressed in astrocytes. Authors concluded that IgG-mediated type III hypersensitivity against food antigens could be the principal cause of increased histamine level, which in turn contributed to increased BBB permeability in depressed patients.

It is worth noting that histamine release from mast cells is not exclusively mediated by IgE and that binding of IgG with receptors for the Fc portion of immunoglobulins (FcR), for instance, FcγRIII, also contributes to histamine release [121]. Another study revealed that when depressed patients were tested for IgG levels against 39 selected food antigens, patients had significantly higher serum total IgG and IgG against celery, garlic, and gluten compared to the control group [122]. It was also previously demonstrated that IgG concentration against 5 out of 44 food products (11.36%) positively correlated with the length of depressive episodes [119]. Those results could indicate that the longer duration of depressive symptoms could be related to more pronounced intestinal permeability and subsequent inflammatory response. This seems consistent with the previous report that patients with chronic depression had significantly higher IgM responses against commensal bacteria compared to healthy controls [7]. Still, two scenarios seem plausible regarding the activation of low-grade immune-inflammatory response and “leaky gut” in depression. On the one hand, activation of the immune-inflammatory response can be secondary to increased intestinal permeability. On the other hand, increased intestinal permeability can be secondary to inflammatory factors, that is, activation of HPA axis, pro-inflammatory cytokines, NF-κB, and O&NS which all are the essence of the immune response in various inflammatory disorders.

To summarize, the current literature demonstrates that increased intestinal permeability to bacterial and food-derived antigens accompanies MDD. However, what are the immune consequences and mechanisms which may lead to gut-derived psychiatric manifestations, particularly depressive symptomatology?

9.3 Crossing the Barriers Beyond the Brain’s Privileged Immunity

9.3.1 Central Consequences of Peripherally LPS-Induced Immune-Inflammatory Response

There are various mechanisms of how bacterial LPS contribute to the activation of the immune-inflammatory response both in the periphery and in the CNS (Fig. 9.1). It is, however, important to emphasize that activation of the immune-inflammatory response due to an increase of LPS level in the circulation is not restricted to the periphery but also results with activation of inflammatory response within the CNS and glial cells are primarily involved in this process. Therefore, it is well established that peripheral LPS challenge leads to sickness behaviors, depressed mood, anxiety, and a decline in the cognitive functions both in humans and animals [123, 124]. Peripheral LPS administration also led to robust activation of brain microglia in humans, which was assessed using PET brain imaging [125]. This was accompanied by an elevation of circulating cytokines TNF-α, IL-6, IL-8, and IL-10 and sickness behaviors, including fatigue and reduction in social interest. In addition, peripheral stimulation with LPS induced microglial proliferation in the

circumventricular organs, hypothalamus, limbic system, and medulla oblongata [126]. Consequently, it was demonstrated that peripheral administration of LPS led to increased expression of cortical and hippocampal IL-1 β , TNF- α , GFAP, and iNOS. This was accompanied by decreased expression of BDNF and depressive-type behaviors in laboratory animals. Inhibition of astrocytes resulted in a decrease in above-mentioned neuroinflammatory parameters, reversed LPS-induced decreased in BDNF, and attenuated depressive-like behaviors [127]. Also, lithium prevented LPS-induced activation of astrocytes, TLR4 expression, and proinflammatory cytokine production, and this mood stabilizer also has a strong antidepressant and antisuicidal properties [105]. Consistently, antidepressant treatment with tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), transcranial magnetic stimulation, and electroconvulsive therapy had a beneficial effect on number and morphology of those glial cells [101]. Similarly, TCA and SSRIs inhibited LPS-induced depressive-like behaviors and IL-6 release in laboratory animals [109], attenuated the release of TNF- α , NO [110], and glutamate, and D-serine release by activated microglia [111]. Also, minocycline, which is a tetracycline antibiotic with antidepressant properties, has known anti-neuroinflammatory and microglia modulatory properties [128]. In LPS-stimulated brain microglial cells, minocycline blocked the secretion of pro-inflammatory cytokines. In the second part of this study, minocycline reduced mRNA levels of IL-1 β , IL-6, and IDO in the cortex and hippocampus of laboratory animals, which were peripherally stimulated with LPS. This was accompanied by a reduction in anhedonia and sickness behaviors [129]. Furthermore, LPS have a detrimental influence on oligodendrocytes maturation and myelination [130] and those effects take place due to LPS-induced activation of astrocytes and microglia/macrophages.

Bacterial LPS after translocation binds to PAMP, such as TLR4 and activates MyD88-dependent and MyD88-independent pathways of the innate immune response through NF- κ B signaling, which leads to increased release of proinflammatory cytokines, including IL-1 β , TNF- α , IL-6, and type I interferons (IFNs). Endotoxin can also activate RAGE, which can lead to endothelial hyperpermeability [27]. Moreover, this bacterial molecule can activate the classical complement system, which may lead to neuropathology, including dopaminergic neurons loss [131, 132].

LPS-induced release of proinflammatory cytokines can influence brain and behavior via humoral, neural, and cellular pathways [133]. The humoral pathway includes passage of cytokines through more permeable areas of BBB such as choroid plexus and circumventricular organs, activation of BBB endothelium and subsequent release of second messengers including prostaglandins and nitric oxide which further activate inflammatory cascade within the brain parenchyma. Moreover, some cytokines do have specific transport molecules in the endothelium, which allows for active transport via BBB. Cytokines can also act through neural route, for example, by activating afferent fibers of the vagal nerve. Furthermore, cytokines contribute to the entry to the brain parenchyma of monocytes activated in the periphery. During peripheral inflammation, cerebral microglia recruit monocytes into the brain via the release of cerebral monocyte chemoattractant protein

(MCP)-1 and increased numbers of circulating CCR2-expressing monocytes. Also, peripheral TNF- α is required to stimulate microglia to produce chemokine MCP-1/CCL2 [133, 134]. It was also recently demonstrated that peripheral LPS challenge results with the influx of leucocytes to the brain parenchyma. Respectively, prolonged, repeated exposure to peripheral LPS resulted in microglia activation and increased expression of various chemokines, which attracted neutrophils, monocytes to the brain parenchyma. This led to increased BBB permeability and transient recruitment of neutrophils and monocytes and sustained infiltration of monocytes, T-cells, NK cells, and NK T cells to the brain parenchyma. Interestingly, following consecutive challenges, peripheral tolerance to LPS developed, which manifested with not as pronounced inflammatory response in the periphery, however in the brain, the inflammatory process progressed and manifested with increased transcription of inflammatory cytokines and chemokines [135].

9.3.2 “The TLRs Perspective”

There is a broad presence of the TLR4 microbe sensing “machinery” in different brain cells, including astrocytes, microglia, oligodendrocytes, neurons, perivascular macrophage, endothelium, meninges, and circumventricular organs [136]. Those receptors are also expressed on dendritic cells, lymphocytes, monocytes, granulocytes, and tissues, including intestinal tissue [26]. Such a broad expression of PAMPs within CNS and periphery surely has to serve its purpose and indicates that brain tissue is well familiar with the endotoxin molecule [137]. It is even more so in MDD and various neurodegenerative disorders. However, the latter are beyond the scope of this chapter. When it comes to depression, post mortem study revealed overexpression of TLR3 and TLR4 in the dorsolateral prefrontal cortex of depressed suicide victims and depressed nonsuicide subjects, compared with controls [138]. Animal studies demonstrated that exposure to LPS [139, 140] and psychological stress [141] enhances expression of TLR4 and higher expression of TLR3, 4, 5, and 7 mRNA was demonstrated in peripheral blood of depressed patients [137]. TLR4 mRNA expression was associated with the severity of MDD measured with the Hamilton Depression Rating Scale (HAMD-17). Moreover, it was demonstrated that 4 weeks of antidepressant treatment of MDD patients significantly decreased expression of TLRs [1–9] in peripheral blood mononuclear cells (PBMCs) [142] and lithium inhibited LPS-induced astrocytes activation via inhibition of TLR4 expression [105]. Also, 16 weeks of cognitive CBT significantly decreased the expressions of TLR-4 RNA and protein, which was accompanied by the improvement of intestinal barrier function [117].

9.3.3 *LPS and Kynurenines*

Another essential element in this depression-related inflammatory puzzle is the kynurenine pathway. Bacterial lipopolysaccharides, O&NS, and proinflammatory cytokines, including IFN γ , IL-1 β , IL-6, TNF- α , and cortisol, can activate the first-step enzymes in the kynurenine pathway particularly indolamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) (Fig. 9.1). The former is expressed in antigen-presenting cells during immune reactions, and TDO is mostly expressed in the liver and neurons. Those enzymes are involved in the conversion of tryptophan (5-HT and melatonin precursor) to kynurenine and its further catabolites (TRYCATs), which subsequently decreases the amount of tryptophan available for conversion to 5-HT. TRYCATs perform numerous critical physiological roles, including immunomodulatory functions; however, their excess may have an adverse effect on the CNS functions. For instance, quinolinic acid (QUIN) is an *N*-methyl-D-aspartate (NMDA) receptor agonist and has neurotoxic activity due to stimulation of synaptosomal glutamate release and inhibition of its reuptake by astrocytes. This results in an increase in its concentration in the synapse and excessive stimulation of the NMDA receptors [143, 144], and increased oxidative stress [145]. This is particularly important in the context of glutamate hypothesis of depression where due to dysfunction and decreased number of astrocytes, there is not sufficient reuptake of glutamate, which leads to an imbalance between glutamate and GABA neurotransmission. Therefore, it was demonstrated that activation of microglia resulted in IDO activation, the elevation of detrimental kynurenines, and an increase in glutamate neurotransmission [107]. This also resulted in inhibition of the brain's tropic factors synthesis, including BDNF, and in decreased neurogenesis.

Another kynurenine metabolite 3-hydroxykynurenine (3HKYN) has neurotoxic, neuroapoptotic and pro-oxidative effects and is further metabolized to prooxidative 3-hydroxyanthranilic acid (3HAA). In contrast, kynurenic acid (KYNA) is an NMDA receptor antagonist and modulates acetylcholine 7 alpha nicotinic receptor (α 7-nACh) functions, and it is believed that KYNA counteracts the neurotoxic effects of the above-mentioned QUIN [146, 147]. Accordingly, Myint and Kim proposed the neurodegeneration hypothesis of MDD and demonstrated that an imbalance between neuroprotective and neurodegenerative metabolites in the kynurenine pathway contributes to MDD [3, 15]. Still, it is important to keep in mind that despite “neuroprotective” effects of KYNA and its antagonism to QUIN, those kynurenines, when in excess, contribute to neurodegeneration and cognitive decline, in schizophrenia, bipolar disorder, Alzheimer's, Parkinson's, and Huntington's diseases, dementia related to HIV infection, amyotrophic lateral sclerosis (ALS), post-surgical cognitive decline, etc. [148–150]. The negative impact of QUIN and KYNA on cognitive functions is mainly due to their ability to modulate glutamate and acetylcholine neurotransmission [148]. It is noteworthy that the brain's glial cells are the site of TRYCATs metabolism and tryptophan, and kynurenine after crossing BBB became substrates for further TRYCATs' synthesis within CNS. More precisely, the “neuroprotective” KYNA synthesizing branch is located in astrocytes

and neurotoxic QUIN synthesizing branch is compartmentalized in microglia. Peripheral LPS challenge influences the metabolism of TRYCATs in the brain and in the periphery. LPS challenge increased kynurenine/tryptophan ratio both in the periphery and in the CNS. It resulted in increased expression of proinflammatory cytokines IL-1 β , TNF- α , and IL-6 in the hippocampus, amygdala, and striatum, and was accompanied by an increase of neuroinflammatory glial cellular markers. In addition, kynurenine metabolism in the hippocampus was skewed toward the neurotoxic branch [151]. Also, peripheral chronic, intermittent administration of LPS in laboratory animals resulted in depressive-like behaviors assessed by levels of anhedonia and despair. This was accompanied by hippocampal microglia activation and increased expression of IDO, increased levels of NF- κ B p65 and IL-1 β levels, elevated QUIN/tryptophan ratio, increased levels of kynurenine and QUIN, and decreased hippocampal levels of tryptophan, and 5-HT [152]. Importantly, kynurenine, besides being a precursor for TRYCATs, also has various immunomodulatory roles. For instance, it activates monocytes and astrocytes and is involved in the trafficking of monocytes to the brain, and those neuroimmune mechanisms are accompanied by depressive-like symptoms in laboratory animals [153]. The above-mentioned effects of kynurenine on monocyte chemotaxis take place with the involvement of the aryl hydrocarbon receptor (AhR). Moreover, kynurenine is involved in mast cell activation, also through AhR [154].

Numerous studies indicate the crucial role of kynurenine pathway activation in the pathogenesis of depressive disorders. For example, the interferon- α treatment of hepatitis C patients resulted in depressive symptoms along with changes in the kynurenine:tryptophan (KYN:TRP) concentration ratio and this ratio can indirectly characterize the activity of the enzymes of the IDO and TDO [155]. Besides, the peripheral supply of interferon- α led to an increase in the concentration of KYN in cerebrospinal fluid (CSF) of patients, which was associated with a significant increase in the concentration of QUIN and KYNA in CSF. Also, the levels of these kynurenines correlated with the severity of depressive symptoms [156]. Interestingly, it has been suggested that kynurenines may also play an important role in suicidal behavior. Post mortem study of severely depressed patients, who died due to suicide, demonstrated a significant upregulation of microglial QUIN in the anterior cingulate gyrus [18]. Also, suicide attempters in the course of depression had a significantly increased level of QUIN but not KYNA in CSF [157]. The CSF QUIN level was associated with higher CSF IL-6 levels, and QUIN correlated with suicidality. Moreover, MDD patients who attempted suicide had elevated KYN levels compared to MDD patients who did not have suicidal attempts [158]. Another study demonstrated that adolescents with suicidal tendencies had a reduced level of TRP and an increased ratio of KYN:TRP [159].

9.3.4 *LPS and Glucocorticoids*

Another vital connection between LPS and depression is the involvement of endotoxin in glucocorticoid (GCC) functions and the immune response to those anti-inflammatory hormones. So far, there is compelling scientific data that suggest that LPS may contribute to GCC resistance, which could also highly likely have a negative impact on intestinal barrier function. It is well established that hyperactivity of the HPA axis accompanies MDD, and 50–80% of patients experience hypercortisolemia with the highest rates in severe depression [160], and the severity of depression correlates with cortisol plasma levels [119]. Consistently, it was also proposed that the modulation of glucocorticoid receptors (GR) is one of the mechanisms involved in antidepressants' action [160]. Furthermore, psychological stress and chronic inflammation are known to contribute to GCC resistance [161, 162]. It was previously demonstrated, particularly in patients with Crohn's disease, that GCC treatment decreased intestinal permeability and retightened intestinal tight junctions (TJ) via inhibition of TNF- α -induced increase in myosin light chain kinase (MLCK) protein expression, and GCC beneficial influence on the intestinal barrier was mediated by GR [163, 164]. Unfortunately, it is not uncommon that the longer the time of GCC treatment, the less effective it is due to the gradual development of resistance to those anti-inflammatory hormones. Consequently, the deletion of intestinal epithelial GR receptor NR3C1 led to increased intestinal permeability [165]. It was demonstrated that exposure to LPS increases the expression of GR β in macrophage, which contributed to GR resistance and inhibited the anti-inflammatory action of GCC [166, 167]. Furthermore, LPS led to the loss of the GCC inhibitory effect on the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) [168]. However, the effect of LPS on expression of GR isoforms is not consistent and may vary depending on the cell types [168]. Still, this seems an intriguing direction for further investigations whether the mechanism of GR resistance (due to LPS, pro-inflammatory cytokines, and cortisol) also contributes to intestinal GR resistance and subsequent increased intestinal permeability. This could, for example, take place due to the lack of GCC inhibitory role on TNF- α -induced increased intestinal permeability. Finally, it is worth mentioning that BBB is highly influenced by GCC, which decrease its permeability. There are many analogies between structures and functions of BBB and intestinal barrier, and both those barriers and their permeabilities are susceptible to analogous immune detrimental factors, including TNF- α , IL-1 β , IFN- γ , O&NS, and LPS.

9.3.5 *LPS and Blood–Brain Barrier*

Another essential aspect is the interaction of peripheral LPS with BBB. Crucial questions that call for the answer in this context are whether peripheral LPS can increase BBB permeability and whether BBB is penetrable for those bacterial antigens? And if so, does disruption of BBB integrity accompanies MDD?

Through decades, the common consensus was that the CNS and particularly the brain is an immune-privileged organ well protected by highly selective BBB. However, recent years of research revealed another side to it demonstrating that this barrier might be compromised by multiple factors, including psychological stress via CRH-mediated mast cell activation [169], bacterial LPS, O&NS, pro-inflammatory cytokines (TNF- α , IL-1 β , IFN- γ), and CCL11 (eotaxin) [90, 170–174]. Interestingly, those factors also compromise the intestinal barrier. Additionally, intestinal microbiota modulate BBB permeability and short-chain fatty acids (SCFAs) produced by those bacteria, including butyrate and propionate, have a protective effect on BBB and decrease its permeability [175, 176]. Furthermore, a relatively recent discovery that the central nervous system is equipped with the lymphatic system additionally advocates re-evaluation of the above consensus [177].

A respective number of in vivo animal studies demonstrated that peripheral LPS challenge results in disruption of BBB permeability (for review of the mechanisms see [178, 179]). Varatharaj and Galea, in their systematic review, concluded that 60% of studies included in analysis revealed disrupted BBB after LPS challenge [178]. Authors noted that variability in those results might be attributed to different LPS doses and dosing protocol used in studies, different species, age, health status, the gender of experimental animals, the time course of permeability estimation, and finally, types of solutes used as markers of BBB permeability. Vargas-Caraveo et al. were the first who revealed that LPS could penetrate BBB under physiological conditions and proposed mechanisms for that [180]. The authors demonstrated the presence of two distinct LPS domains, namely, lipid A and core LPS in circumventricular organs, choroid plexus, meningeal cells, astrocytes, tanycytes, and endothelial cells and those domains were colocalized with CD14, TLR-4, and NF- κ B. The results of the study also suggest that LPS crossed BBB via a lipoprotein-mediated transport mechanism.

Regarding human studies, so far, the field of neurodegenerative disorders, which are often comorbid with MDD, gives us the most compelling data indicating that translocation of LPS and other bacterial molecules via BBB is possible and, interestingly, this accounts for not only patients with dementia but also healthy individuals. There is a piece of strong evidence from post mortem studies of patients suffering from Alzheimer's disease, which demonstrated the increased LPS levels in gray and white matter compared to controls [181]. Interestingly, LPS and *Escherichia coli* K99 pili protein were also present in the control group but in a much lower concentration. Moreover, *E. coli* DNA was present in the brain tissues of patients and controls. This indicates that besides increased BBB to LPS in the course of the illness, highly likely, there are also physiological mechanisms of bacterial molecules' translocation via BBB. Also, another study of brain lysates from patients with Alzheimer's disease demonstrated significantly higher LPS concentrations in the hippocampus and neocortex, which in the most severe case reached a 26-fold higher level compared to the control [182].

Regarding MDD, recently, it was demonstrated that depressed adolescents had a higher S100B serum level, and this parameter is considered as a marker of increased BBB permeability and is primarily expressed in astrocytes. Moreover, patients had a

higher rate of serum food-specific IgG, and this was accompanied by increased serum levels of histamine and homocysteine [120]. The authors of this study suggested that IgG-mediated type III hypersensitivity against food antigens could be the principal cause of increased histamine level, which in turn contributed to increased BBB permeability in depressed patients. It was also demonstrated in the course of bipolar disorder that patients with increased BBB permeability had more significant symptoms of depression and anxiety and a more chronic course of the illness [183].

Still, it seems that the permeability of BBB in major depression is not a “black or white” scenario. Likely, it might vary depending on various factors, including genetic ones, the severity of the illness, the level and the source of immune-inflammatory response accompanying the MDD. Moreover, the disruption of BBB is highly dependent on astrocyte function, and their abnormal function was reported in MDD. It also seems likely that interaction between peripheral inflammation, astrogliosis, and abnormal BBB permeability may progress in a vicious cycle manner where progressive dysfunction of those glial cells contributes to increased BBB permeability and subsequently, further neuroinflammatory changes contribute to astrocytic dysfunction and psychopathology.

9.3.6 Lipoproteins—Regulators of the Peripheral Endotoxin Load

As reviewed above, Vargas-Caraveo et al. suggested that LPS can cross BBB via lipoprotein-mediated transport [180]. When discussing the role of lipoproteins in the context of LPS transport, it is also important to point out lipoproteins’ crucial homeostatic role in neutralizing LPS and their elimination in the liver [184, 185]. For instance, high-density lipoprotein cholesterol (HDL-C) and its apolipoprotein A-I (ApoA1) have anti-inflammatory properties and high affinity to LPS and are involved in LPS neutralization and transport to hepatocytes for their degradation. This mechanism prevents further LPS activation of inflammatory response and synthesis of pro-inflammatory cytokines [180, 186]. Consequently, lipoproteins are one of the major determinants of LPS load in the circulation, and likely in CNS, and abnormal lipoprotein concentration may contribute to increased LPS-derived immune-inflammatory response both in the periphery and CNS. Interestingly, the connection between abnormal lipoprotein levels and MDD has been previously established. For instance, MDD patients had decreased HDL-C levels compared to controls, and patients with a history of serious suicide attempts had significantly lower HDL-C compared to MDD patients without such attempts [187–189]. Moreover, patients with chronic depression had significantly lower HDL-C compared to healthy controls, or patients with shorter duration of depression [190, 191], and melancholic features of MDD were independently associated with lower HDL-C [189]. The data above indicate an intriguing connection between increased intestinal permeability, adverse lipoprotein patterns, and depressive symptoms. Further exploration of this area might have implications for MDD treatment.

9.3.7 Increased Intestinal Permeability—The Source of Autoimmunity in MDD

Another crucial aspect of how the “leaky-gut” may contribute to MDD is the involvement of the compromised intestinal barrier in the autoimmunity (Fig. 9.1). This is a very interesting and broad topic an in-depth introduction of which is beyond the scope of this chapter (for further reading see [25]). However, it is briefly worth mentioning that highly likely it is not an epidemiological coincidence that autoimmune disorders increase the risk of major depression and other psychiatric disorders [192, 193], and that there is growing evidence of increased intestinal permeability and dysbiosis in various autoimmune disorders, comorbid with MDD, such as IBD, MS, coeliac disease, diabetes, to name a few [96, 194–196]. On the one hand, bacterial translocation leads to increased O&NS, hypernitrosylation, and generation of immunogenic neoepitopes [14]. On the other hand, food-derived antigenic materials, for instance, lectins and agglutinins, bind with the tissue and form neoepitopes in a covalent-binding mechanism, which leads to autoimmunity. Another mechanism is a molecular mimicry/cross-reactivity, where due to unfortunate molecular coincidence, there is a structural homology between antigenic material (i.e., gut-derived or newly O&NS/hypernitrosylation-formed) and own structure of the organisms, which leads to the autoimmune reaction against this structure, that is, cell membrane, tissue. For instance, molecular mimicry between casein and butyrophilin with myelin, cerebellum, or even a key enzymes responsible for GABA synthesis was demonstrated [197–200]. Those fascinating, but concerning interactions clearly indicate to a substantial role of a healthy intestinal barrier, well-balanced intestinal microbiota and a diet, in the context of inflammation, autoimmunity, and mental health.

9.4 Conclusions

We are facing exciting times in neuroscience and psychiatry research and it is becoming evident that the mind-body connection takes place on the sites of interaction between the immune, endocrine, and nervous systems. Since those interactions are very reciprocal and multifactorial, it is becoming clear that a more holistic approach in the context of mental health diagnosis and treatment is required to warrant its truly efficient and long-term effects. Surely, the intestinal barrier with GALT and intestinal microbiota, which until quite recently remained the “forgotten organ,” does play a major part in the above mind–body interactions. In view of that, it is crucial to promote this knowledge among medical professionals and patients and to implement accessible and cost-effective markers of intestinal permeability, gut-derived inflammation, and autoimmunities driven by bacterial and food-derived antigens. It is also crucial to bring more attention to the prophylactics and the treatment focusing on the improvement of the integrity of the intestinal barrier. This

could include specific supplementation and dietary interventions with known benefits to the gut barrier, and those include, for example, probiotics, prebiotics, turmeric, zinc, and glutamine. Diet is another crucial factor contributing to mental health and the field of nutritional psychiatry is recently receiving growing attention. A diet when is not well balanced, that is, Western, high-fat, high-carbohydrate diet, contributes to neuroinflammation and depression. Contrary, a good quality diet rich in antioxidants, polyphenols, fiber, pre- and probiotics, healthy fats will have a therapeutic value. Making those healthy and conscious choices may be the first step toward wellbeing and a healthy body and mind.

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Chapter 10

Neurogenesis and Neuroplasticity in Major Depression: Its Therapeutic Implication



Michel Bourin

Abstract The neurochemical model of depression, based on monoaminergic theories, does not allow on its own to understand the mechanism of action of antidepressants. This approach does not explain the gap between the immediate biochemical modulations induced by antidepressants and the time required for their clinical action. Several hypotheses have been developed to try to explain more precisely the action of these molecules, each of them involving mechanisms of receptor regulation. At the same time, data on the neuroanatomy of depression converge toward the existence of specific lesions of this pathology. This chapter aims to provide an overview of recent advances in understanding the mechanisms of neural plasticity involved in pathophysiology depression and in its treatment.

Keywords Antidepressants · Depression · Hippocampus · Neurogenesis · Neuroplasticity

10.1 Introduction

For over a century, it has been recognized that the structure of the adult brain remains fixed and that nerve cells in the brain are not replaced, unlike other cells in the body. Indeed, the techniques available until the 1950s did not allow observing dividing cells in the brain of adult mammals and the particularly elaborate architecture of the adult brain made it impossible to add new neurons within this structure. It was, therefore, dogma that we were born with our stock of neurons and that it was decreasing throughout life. Nevertheless, in the late 1950s, the appearance of a new method of detecting cell division—the autoradiography of tritiated thymidine—allowed a major advance in the detection and analysis of neurogenesis. Indeed,

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tritiated thymidine is a radiolabeled analogue of thymidine that is incorporated into the DNA during replication in dividing cells. Since this compound is eliminated by the body in a few hours, its use can then date the birth of labeled cells at the time of injection of this molecule. Using this technique, a first series of studies in rats and cats was published in the 1960s, showing the presence of new nerve cells in different areas of the brain [1–3]. Nevertheless, this work remained largely ignored because it was not possible to unambiguously determine the neuronal or glial identity of these cells. In the 1970s, the advent of electron microscopy techniques confirmed the neuronal status of dividing cells in the adult brain [4]. But again, these last works did not allow shaking the dogma because the idea of the addition of new neurons in the adult brain was in complete opposition to the theoretical conception of the necessity of a structural stability of the neural networks, especially for the long-term maintenance of memory. Various factors ultimately contributed to the abolition of this dogma in the early 1990s: firstly, the demonstration of abundant adult neurogenesis in the bird, especially in the canary learning new songs [5]; then the demonstration of adult neural stem cells in the adult brain of mice [6]; and finally, the arrival of new labeling techniques that distinguish new neurons formed in the adult brain [7]. Indeed, the use of a new thymidine analogue, 5-bromo-2'-deoxyuridine (BrdU), which is incorporated specifically into the DNA of dividing cells and has the advantage of being easily detectable by immunohistochemistry techniques, unambiguously identified the identity of neuronal cells produced by microscopy. Today, the existence of adult neurogenesis is recognized in several animal species including mammals [8].

10.2 Neuroanatomy of Depression

Anatomic changes have been observed in the depression of the hippocampus, amygdala, caudate, putamen, and frontal cortex. All these structures are interconnected and form the limbic-cortico-striato-pallido-thalamic circuit. The neuroanatomical knowledge of depression is based on structural imaging (neuromorphometric MRI) in vivo and postmortem, as well as correlations with functional imaging (PET-scan, functional MRI). In addition, histopathological studies concerning these same structures also show the *existence* of specific lesions [9].

10.2.1 Hippocampus

This is probably the most studied structure [10]. The hippocampus is a bilateral subcortical temporal structure with a laminar organization, each layer having its own characteristic circuits. It has several functions, but is best known for its role in learning and memory, especially in the consolidation of short-term memory in long-term explicit memory. The hippocampus is also involved in the modulation of

emotional responses. This structure has been studied extensively in depressed patients. Numerous studies show the involvement of the hippocampus in learning phenomena and in memory, as well as a deficit of these functions in depression. A meta-analysis in which the different morphological studies centered on the hippocampus were compared [11]. Their results show a volumetric reduction in depressed subjects and, in particular, in the long-term depressed. The age of depressive pathology seems to play a critical role in reducing the volume of the hippocampus. According to another meta-analysis, there is a reduction in hippocampal volume of 8% left and 10% right in comparison with healthy subjects and unipolar depressions only. The hereditary factor is also likely to play a role in the morphometric variations of the hippocampus. For example, it has been demonstrated through a longitudinal study of monkeys the importance that hereditary factors may have on the size of the hippocampus [12]. Studies of patients with major depression have consistently reported reduced hippocampal volumes; however, the exact pattern of these volume changes in specific anatomical subfields and their functional significance is unclear [13].

10.2.2 Amygdala

Functional imaging shows depressive patients hyperactivation of the left amygdala, which standardizes on treatment and this activation, was correlated with the severity of symptoms [14]. The metabolism of the amygdala decreases in parallel with the clinical response to antidepressant treatments [15]. The persistence of an increase in metabolic activity during the remission phase would be associated with a higher risk of relapse. Postmortem histopathological studies have shown amygdala reduction in glial cell numbers in depression, with no change in the number of neurons. More specifically, these modifications concerned oligodendrocytes, the number of microglial cells and astrocytes remaining constant [16]. A decrease in the number of oligodendrocytes may be secondary to an effect on myelin or through demyelination, abnormal development or atrophy of the number of myelinated axons.

10.2.3 Frontal Lobes

The general volume of the frontal lobes does not differ between the depressed and the control subject. On the other hand, volumetric abnormalities were observed in specific structures of the prefrontal cortex (PFC), as well as nuclei of the base and meso-temporal structures [17]. The most significant volumetric reduction concerns the ventral part of the anterior cingulate gyrus where the volume of the gray matter can be reduced by 20–40% in depressed subjects, particularly in the depressed with a pure family history of depression, and in the psychotic depression [18].

The volume of posterior orbital cortex and ventrolateral portion of PFC also appeared decreased in in vivo studies and in histopathological studies [19].

10.3 Neurogenesis

10.3.1 *Originally Neural Stem Cells*

In the adult brain, new nerve cells are produced from neural stem cells [20]. These are cells of glial nature and more precisely astrocytic, which are characterized by:

- Their capacity for self-renewal, that is to say the ability to proliferate and generate at least one daughter cell with the same morphological, biochemical, and functional characteristics as the parent cell, by symmetrical or asymmetrical division.
- Their multipotent nature, that is, their ability to produce the three cell types found in the brain: neurons, astrocytes, and oligodendrocytes.

In the hippocampus, the data show heterogeneity of the nature of the cells at the origin of adult neurogenesis. Indeed, it seems that the stem cells of the dentate gyrus of the hippocampus have a reduced capacity for self-renewal unlike the stem cells of the olfactory bulb [21, 22].

10.3.2 *From a Stem Cell to a Mature Neuron*

Whether for olfactory or hippocampal neurogenesis, new cells are produced in specific areas called neurogenic niches. This is the subventricular zone bordering the lateral ventricles and which supplies the olfactory bulb with new cells and the subgranular zone of the dentate gyrus of the hippocampus [23]. The architecture and functioning of these zones are a microenvironment favorable to the production of new cells [24, 25]. These neurogenic niches are composed of:

- Cells: endothelial cells (blood vessel cells), oligodendrocytes (glial cell), different types of neurons, and astrocytes (glial cell)
- Specific factors: growth factors, neurotransmitters, and epigenetic factors

This particular environment is necessary for the proliferation, differentiation, migration, and functional integration of new neurons within neural networks of the brain. This set of cellular and molecular characteristics make these niches unique environments for the production of new cells.

Regarding the olfactory bulb, the new cells are first produced in the subventricular zone from the stem cells (type B cell) that proliferate [26]. These cells give rise to transient progenitor cells (type C cell), themselves capable of proliferating and

differentiating into neuroblasts [27]. In rodents, the subventricular zone is the largest source of new cells in the adult brain with tens of thousands of cells generated daily [28]. These new cells then migrate along the rostral migration pathway (VMR), over several millimeters [29], to reach the olfactory bulb where they complete their maturation process and become predominantly GABAergic interneurons for a very low proportion of dopaminergic neurons (5%). These new functional neurons then integrate into the pre-existing circuits of the olfactory bulb to participate in its functioning [30].

In the hippocampus, adult neurogenesis originates in the subgranular (SGZ) zone of the dentate gyrus (GD) from stem/progenitor cells (so-called type 1 cells) [31]. After proliferation, these cells give rise to a population of transient progenitor cells (so-called type 2 cells) capable of proliferating abundantly and of differentiating into neuroblasts. The newly formed cells migrate over a short distance (up to 200 μm) into the inner part of the granular layer of the dentate gyrus where they complete their maturation process to become predominantly (60–80%) granular cells integrated into pre-existing networks. About 15% of the cells differentiate into GABAergic cells and about 10% differentiate not only into glial cells, mainly astrocytes but also into microglial cells. In the hippocampus, the cells produced remain in this structure to participate in its functions, including memorization. The production of new cells has also been demonstrated in other brain regions such as certain areas of the cortex, the amygdala, the striatum, the substantia nigra, the vagal complex or the hypothalamus, but also in the spinal cord [32, 33]. However, at present, these areas are not considered neurogenic because the production of new cells in these areas is detected only after stress or pharmacological manipulations and their long-term persistence remains controversial under basal conditions. In addition, the presence of stem cells within these structures has not been demonstrated to date.

10.3.3 Adult Neurogenesis, a History of Maturation, Survival, and Integration

The maturation process results in the morphological maturation of the new neurons, with in particular, the growth of dendritic and axon extensions, the electrophysiological maturation of neurons, the setting up of synaptic connections, and thus their integration into pre-existing neural networks. The new cells produced also undergo a drastic selection process during the first 4 weeks after birth and only a small proportion of them survive in the long term, the others being eliminated by apoptosis (between 50% and 70%). This survival of the new neurons is dependent on their integration within the pre-existing neural networks and in particular on the synaptic activity. The new neurons exhibit functional morphological and electrophysiological characteristics as early as 2–3 weeks of age, but continue to mature until they are 4 months old and present morphology completely similar to pre-existing cells. The transition from an immature neuron to a new, fully functional mature neuron,

inseparable from another mature gyrus neuron, is a complex mechanism with many essential steps for the maturation and perfect integration of new neurons into the networks neurons of the structure in which they integrate [24, 34].

10.3.4 Regulation of Adult Neurogenesis

The different stages of adult neurogenesis, from the proliferation of progenitor cells to the maturation and functional integration of new neurons within hippocampal neural networks, are finely regulated [35–37]. Many factors regulate positively or negatively adult neurogenesis indicating that it is an adaptive mechanism in response to changes in the environment. The intrinsic factors produced directly by the progenitor and/or newly formed cells are distinguished from the extrinsic factors present in the extracellular environment of the neurogenic niche. Intrinsic factors, genetic factors (genetic background and intrinsic cellular programs), epigenetic factors (DNA methylation, post-translational modifications of histones, and regulation/expression of non-coding RNAs, including microRNAs) and transcription factors. Among the extrinsic factors present in the extracellular environment of the neurogenic niche and regulating neurogenesis are the neurotransmitters (glutamate, GABA, serotonin, acetylcholine, norepinephrine, and dopamine), hormones (sex steroid hormones, corticosteroids, and thyroid hormones), growth factors, drugs (nicotine, opiates, and cocaine as well as alcohol) or environmental stimulation (stress, enriched environment, and voluntary physical activity).

10.3.5 The Functions of Adult Neurogenesis

The function of new neurons in the adult brain has been evaluated on the one hand by using production blocking techniques of new neurons (antimitotics that prevent the division of stem cells, irradiation, which causes damage in dividing cells and blocks neurogenesis, genetic models in which the production of new cells is inhibited), or on the contrary by increasing it via genetic models, following exposure to an enriched environment or a period of physical exercise [24]. Different brain functions and processes were then analyzed using these varied models. The majority of studies show a role of adult hippocampal neurogenesis in the processes of learning and memory dependent hippocampus (fine discrimination between two close situations, spatial memory, work, fear, and even episodic) [38], as well as a role of adult olfactory neurogenesis in olfactory learning (perceptual learning, memorization of new smells, representation olfactory, fine discrimination between different odors) [39]. Overall, the absence or decrease of neurogenesis strongly disrupts these different processes, while enrichment and exercise that increase the production of new neurons, improve them. In addition, exercise and learning and memorization modify the number of new neurons produced and their survival, morphological

maturation and integration within neural networks, indicating that new neurons participate in these processes. In addition, the new neurons have a critical period during their maturation (between 1 and 4 weeks after birth in rodents) where they are more likely to participate in the learning and memorization processes, due to some electrophysiological peculiarities such as greater excitability by even low intensity stimuli [40]. The permanent integration of new neurons within the neural networks of the olfactory bulb and the hippocampus allows the systems to be very plastic, and thus to adapt to new environments.

10.3.6 Adult Neurogenesis During Aging

Although adult neurogenesis persists throughout life, it is a highly sensitive process [41, 42]. The production of new neurons decreases with age in rodents and in monkeys. In rodents, the proliferation and survival of progenitor cells decreases from 2 to 5 months of age until 10–12 months of age and then stabilizes until 24–27 months of age. The decrease in adult neurogenesis is also associated with altered dendritic morphology, decreased migration, and decreased neuronal differentiation in favor of increased glial differentiation of newly formed cells. A decrease in neurogenesis is also observed in humans. This decrease in adult neurogenesis during aging may be explained by local and environmental changes in neurogenic niches.

10.4 Neurogenesis in the Depression

10.4.1 The Role of Glucocorticoids

In depression, stress is responsible for hyperactivity of the hypothalamic–pituitary–adrenal axis leading to elevated circulating glucocorticoid levels. However, the hippocampus is particularly sensitive to glucocorticoids. It has a large number of glucocorticoid receptors [43]. A prolonged increase in glucocorticoid concentrations may have different neuroanatomical consequences, such as atrophy of dendritic arborizations, a reduction in CA3 length of apical dendrites, inhibition of adult neurogenesis, and neurotoxic effects. (e.g., atrophy of cells of the C3 layer) [44]. Gradually, this glucocorticoid impregnation could likely lead to a reduction in the ability of neurons to cope with other attacks. These alterations are observed not only in depression but also in Cushing’s disease and in post-traumatic stress. However, several studies tend to qualify the importance of this phenomenon. A reduction in proliferative capacity in hippocampal neural progenitors in animals under stress was shown, with no concomitant elevation of corticosterone levels [45]. There was no correlation between cortisol levels and reductions in hippocampal volume or memory deficits observed in depressed subjects [46]. It, therefore, seems that the reduction in proliferation observed in depression at the level of neuronal

progenitors located in the dentate gyrus of the adult hippocampus is not directly or solely related to the plasma levels of cortisol. On the other end, it was found that CRH could reverse the damaging effects of glucocorticoid on neural stem/progenitor cells (NS/PCs), while its genetic deficiency results in compromised proliferation and enhanced apoptosis during neurogenesis [47].

10.4.2 Inhibition of Neurotrophic Factors

Neurotrophins are a family of growth factors involved in the differentiation and survival of neurons, as well as in synaptic transmission and plasticity. It includes, among many others, BDNF (Brain Derived Neurotrophic Factor) and neurotrophins NT3, NT4, and NT6 [48]. BDNF is an important cell survival factor, implicated in a variety of pathophysiological situations [49]. It acts via two receptors: a high affinity tyrosine kinase (TrkB) and a low affinity pan-neurotrophic receptor (p75NTR) [50]. BDNF is necessary for the survival of not only many neuronal types but also has acute effects on synaptic plasticity and its propeptide [51]. BDNF plays a role in transmission, by promoting the release of glutamate [52], GABA [53], serotonin [54], and dopamine [55]. In this way, it can potentiate both excitatory and inhibitory transmission. However, BDNF is best known for its long-term neurotrophic and neuroprotective effects. Released under stress, BDNF protects neurons, particularly noradrenergic and serotonergic neurons, from neurotoxic (glutamatergic, oxidative or post-corticoid elevation) bypassing their deleterious effects during the process of cell death (apoptosis). It also promotes the growth of axon-dendritic synaptic connections. In animal models, chronic stresses (such as forced immobilization, dominant-dominated confrontation situations, and glucocorticoid treatments) result in reduced levels of BDNF and facilitate neuronal damage in the hippocampus. Demonstration of the central role of serotonergic and β -adrenergic receptors in antidepressant therapy and their regulatory effects on cyclic AMP synthesis and protein kinase activity prompted several researchers to focus more transcription directly downstream of cyclic AMP and, particularly, to CREB (cyclic AMP-Related Element Binding Protein), and its DNA recognition site (CRE) [56].

10.4.3 Neurotoxicity of Glutamate

The hippocampus is rich in glutamatergic neurons [57]. During periods of repeated stimulation, as in learning, glutamate accumulates in synapses of the hippocampus and binds to the corresponding receptors. N-methyl-D-aspartate (NMDA) receptors are one of the subtypes of glutamate receptors and are permeable to calcium. Their activation causes Ca^{2+} entry into the neuron. An extracellular Ca^{2+} flux to the interior of the neurons may also pass through voltage-gated calcium channels that are activated by the depolarization induced by the opening of the channels

associated with the NMDA receptors. Intracellular calcium activates long-term changes in synaptic excitability that is probably the basis of memory processes. But in case of severe stress, hypoglycemia or hypoxia, there is an excess of glutamate in the synaptic cleft which, at sufficient concentration, becomes an excitotoxin. Excess cytoplasmic calcium is mobilized, resulting in overactivity of multiple Ca^{2+} dependent enzymes. This type of cascade then leads to a degradation of certain elements of the cytoskeleton, structural and functional protein modifications and release of free radicals, possibly triggering a programmed cell death process, or apoptosis [58]. NMDA receptor antagonists attenuate the atrophy of the CA3 pyramidal layer observed in the hippocampus under stress, suggesting that this atrophy is, at least in part, dependent on increased glutamatergic neurotransmission [59].

This scheme must be nuanced because, beyond glutamate, it is the energy balance of the cell that determines the process of cell death. The NMDA-dependent mechanism taken alone does not seem to be sufficient to explain the processes of cellular degradation, in particular because the excess stimulation of the NMDA receptors leads to a partial desensitization of these and, therefore, a reduction of affinity for their agonist. In addition, removal of glutamate can only be done via a co-sodium transporter. Therefore, in case of excess glutamate, the preservation of sodium homeostasis implies significant energy expenditure via Na/K ATP-ase. Finally, protons released by anaerobic metabolism decrease the activity of NMDA receptors. All this suggests that the mechanism of atrophy and programmed cell death within hippocampal structures in response to severe or prolonged stress is not limited to glutamatergic excitotoxicity, but obviously involves other complex molecular mechanisms [60]. Recurrent stress may actually lower the cell death threshold in response to a variety of physiological and/or pathological conditions.

10.5 Effects of Antidepressants on Neurogenesis

Serotonin is a neurotransmitter involved not only in the pathophysiology of depression and the mechanism of action of antidepressants but also a key regulator of cell division. Several studies have shown that serotonin can modulate processes such as neurogenesis, apoptosis, and dendritogenesis during brain development [61]. Observations also suggest a central role for serotonin in controlling the proliferation of neuronal precursors in adulthood. Several studies have indeed demonstrated a regulation of the neurogenesis of the dentate gyrus of the hippocampus in the adult brain under the influence of serotonergic antidepressants (e.g., serotonin reuptake inhibitors [62]). However, until now, it has not been possible to demonstrate the clinical impact on depressive pathology. The link between hippocampal neurogenesis and the behavioral effects induced by antidepressants has been demonstrated [63]. Mice were treated with fluoxetine, imipramine, desipramine, haloperidol or placebo for 28 days; then the animals' latency to feed themselves was measured using the novelty suppressed feeding test. This test, in which animals must, in order to feed themselves, overcome the fear of venturing into a scintillating atmosphere,

where the food is. This test had been used previously to test the effectiveness of antidepressants. No change was observed after 5 days of treatment. On the other hand, after 28 days of treatment, it was found a reduction in the time to recharge in all mice treated with antidepressants, but not in those treated with haloperidol or placebo. After it was injected a cell division marker, 5-bromo-2'-deoxyuridine (BrdU), into mice treated with fluoxetine. Mice treated for 11 or 28 days showed a 60% increase in dividing neural progenitors in the serrated gyrus, whereas this difference was not present after 5 days. Cell analysis showed that 70% expressed a neuronal marker and thus differentiated into a neuron while 30% expressed a differentiation marker in glial cells.

10.6 Neuroplasticity and Depression

Depression leads to morphological and functional changes in the brain defining neuroplasticity; these changes occur in the prefrontal cortex, hippocampus and amygdala and have been revealed by advances in neuroimaging [64]. The role of aminergic neurotransmitters—or monoamines—in the mechanism of depression was examined as early as the 1960s. Since the discovery of the efficacy of tricyclic antidepressants (serotonin and norepinephrine reuptake inhibitors) in depression, the hypothesis of central monoaminergic dysfunction—in particular serotonergic—has long predominated. More recently, new data from neuroimaging, neurophysiology and cell and molecular biology have allowed depression to be associated with different neurobiological phenomena, including dysfunction of neuroplasticity. Neuroplasticity corresponds to changes in the organization and structure of certain neuronal elements, producing a modification or a modulation of their function (neurogenesis, apoptosis, synaptic plasticity, reorganization of the composition of neural networks ...). The changes would be a function of factors in the environment in which the subject lives (ex: stress, alcohol) and the environment in which the nervous system is located (e.g., glucocorticoid levels). Knowing that serotonin (5-HT) regulates several aspects of brain plasticity and that most effective antidepressants facilitate 5-HT transmission, it has been proposed that these psychotropic drugs exert their therapeutic effect by promoting neuroplastic processes [65].

Many studies now support the involvement of glutamate in the mechanisms of neuroplasticity [66]. The effects of glutamate on neurons are highly variable depending on its concentration and the duration of the excitation: during a brief exposure of a neuron to glutamate, there is a phenomenon of neurotrophicity, with a development of dendritic spines. But as the exposure intensifies or continues, we observe on the contrary a phenomenon of neurotoxicity, with a dendritic regression. Released during stress, glutamate promotes, through NMDA and AMPA receptors, the release of calcium in the cell, resulting in its death by apoptosis [67].

Glutamate also plays a central role in the long-term potentiation phenomenon (LTP), the inhibition of which, observed in models of depression, is a marker of alterations in synaptic efficiency, and thus of neuroplasticity. This phenomenon,

which occurs in the margins of structural changes (dendritic regression, apoptosis, and hippocampal neurogenesis), confirms the existence of a real toxicity on functional neuroplasticity associated with depression-type behavioral disorders.

Several studies have shown that molecules that act specifically on NMDA glutamatergic receptors (ketamine, memantine) have rapid and prolonged antidepressant effects [68, 69], with an almost instantaneous and sustained decrease in Hamilton depression scale scores. These antidepressant properties have been demonstrated in tests performed in mice and humans: they confirm the role played by glutamate in different depressive phenomena. In contrast, the administration of NMDA receptor antagonists inhibits pyramidal cell atrophy of the hippocampus induced by stress and stimulates neurogenesis.

Morphological and functional alterations related to the duration of exposure to untreated depression are brain scars that would increase the risk of depressive recurrence. However, by acting on the glutamatergic system, some molecules have “neuroreparative” properties, leading to a revival of neurogenesis, an increase in dendritic branches and synaptic connections, all of these phenomena resulting in a restoration of the volume of the hippocampus in stress patterns.

10.7 Antidepressants and Neuroplasticity

The monoaminergic hypothesis of depression is one of the first etiological biochemical models formulated in the 1960s. If the active molecules on norepinephrine and/or serotonin continue to form the main body of antidepressant drugs, other existing molecules are exploring; other pathways involving not only receptors but also processes of intracellular signal regulation, transcription factors and target genes. In particular, glutamate, the main excitatory neurotransmitter in the brain, is one of the most promising lines of research. These results, therefore, demonstrate the existence of at least two possible routes of induction of hippocampal neurogenesis by antidepressants. In addition, the associated blockage of the clinical and neurological effects of fluoxetine suggested that both could be correlated [70]. It is also interesting to note that the effects on the neurogenesis of antidepressants are limited to the subgranular zone (SGZ) of the serrated gyrus and, therefore, are specific to the hippocampus. They do not affect the subventricular zone (SVZ), which is the other area of active neurogenesis in the adult brain [71, 72]. Lithium, which is used in the treatment of refractory depression, also appears to have effects on neuroplasticity. It is involved in various neurotrophic cascades that can increase neuronal survival. Moreover, it also seems that, *in vitro*, lithium protects neuronal cells from the excitotoxicity of glutamate, in particular by the inhibition of NMDA-dependent apoptosis. Finally, it has been shown that lithium administered chronically to mice induces neurogenesis phenomena in the serrated gyrus. In humans, it appears that lithium treatment for 4 weeks would increase neuronal survival, a phenomenon that goes hand in hand with an increase in the total amount of gray matter in the brain.

Electronarcosis treatment is also known to promote the release of BDNF and stimulate neurogenesis. A recent study has shown that hippocampal neurogenesis may account for a large part of the effects of antidepressants [73]. The formal demonstration that the increase in neurogenesis in the hippocampal region modulates the function of the serrated gyrus to induce the antidepressant effect must still be provided. The serrated gyrus and its complex connections with CA3 may be the final common pathway for depression and its treatment.

10.8 Conclusion

The most recent data on the biology of depression confirm the importance of brain plasticity in the pathophysiological processes of mood disorders [74]. The hypothesis of an action of antidepressants via neurogenesis phenomena at the serrated gyrus of the hippocampus is a new way of understanding the biochemical mechanisms underlying their antidepressant action. This hypothesis opens promising avenues for the development of new molecules such as NMDA receptor antagonists (e.g., lamotrigine, memantine) [75–77] AMPA receptor potentiators (another subtype of glutamate-activated ionotropic receptor), or glutamate release inhibitor (riluzole) [78]. The relationships between neuroplasticity, depression and antidepressants are particularly complex. Future steps in this area should improve our understanding of the cellular and molecular mechanisms involved in the etiopathogenesis of depression and the mechanism of action of antidepressants [79].

An analysis of the effects of antidepressants on neuroplasticity is an innovative research theme for a better understanding of the pathophysiology of mood disorders. A body of evidence suggests that the long-term antidepressant efficacy of antidepressants is due to stimulation of neuroplasticity [80]. Prolonged administration in animals of antidepressant treatment (serotonin reuptake inhibitors, monoamine oxidase inhibitors) or electroconvulsive therapy increases the proliferation and/or survival of newly generated neurons in the dentate gyrus of the hippocampus. Conversely, the inhibition of this neurogenic response induces the blocking of the behavioral responses associated with this therapeutics suggesting that the increase of hippocampal neurogenesis is necessary for antidepressant action [81].

The hypothesis of a close relationship among depression, antidepressant treatment, and neurogenesis is reinforced by other experiments showing that the rate of neurogenesis, decreased by glucocorticoid injections (rates equivalent to chronic stress), is normalized as a result of a disturbance in hippocampal neurogenesis would only represent one of the biological processes altered during a depression. It remains to be seen, among the many depressive symptoms, which could be attributed to a deficit in neurogenesis. Cognitive disorders such as concentration problems and memory problems are often reported by depressive patients and may persist after resolution of the mood episode. In addition, cognitive deficits are positively correlated with a high number of depressive episodes. In other clinical situations characterized by an excess of corticosteroids, such as Cushing's disease or

during chronic treatment with exogenous corticosteroids, reversible memory deficits are also reported. In conclusion, a disturbance in hippocampal neurogenesis due to hypercortisolemia could be at the origin of certain cognitive symptoms present during a depressive episode. In addition, prolonged impairment of neurogenesis may explain why some newly euthymic depressive patients complain of residual cognitive deficits a series of electroshocks.

The discovery of adult neurogenesis was quickly followed by an exploration of the many physiological factors regulating it. Despite a significant amount of work in this area, the function of newly generated neurons is still an enigma difficult to solve. The future use of transgenic mice in which it would be possible to specifically and reversibly block hippocampal neurogenesis should provide important elements of response. In addition, better molecular and electrophysiological characterization of new neurons would help us better understand their function. Indeed, it is conceivable that new neurons called “immature” have electrophysiological properties different from older neurons and considered mature. Thanks to these properties, the subgroup of newly generated neurons, even minority ones in the overall population of older neurons, could play a key role in hippocampal plasticity. Thus, only a better understanding of the physiological function of adult neurogenesis will help us to establish the clinical consequences emerging from its disruption. According to an epidemiological study, regular physical activity could protect against depression [82]. In this context, it is intriguing that mice with the opportunity to run in wheels installed in their cages have a much higher level of neurogenesis than sedentary mice [83].

On the other hand, there are many researches in regenerative medicine and in cases of neuronal loss after an injury or stroke inducing a depressive episode [84]. Link between adult neurogenesis and diseases of the nervous system is still much to do in order to understand the role of neurogenesis and its modulation during normal or pathological aging.

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Chapter 11

A Load to Find Clinically Useful Biomarkers for Depression



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Abstract Depression is heterogeneous and complex disease with diverse symptoms. Its neurobiological underpinning is still not completely understood. For now, there are still no validated, easy obtainable, clinically useful noninvasive biomarker(s) or biomarker panel that will be able to confirm a diagnosis of depression, its subtypes and improve diagnostic procedures. Future multimodal preclinical and clinical research that involves (epi)genetic, molecular, cellular, imaging, and other studies is necessary to advance our understanding of the role of monoamines, GABA, HPA axis, neurotrophins, metabolome, and glycome in the pathogenesis of depression and their potential as diagnostic, prognostic, and treatment response biomarkers. These studies should be focused to include the first-episode depression and antidepressant drug-naïve patients with large sample sizes to reduce variability in different biological and clinical parameters. At present, metabolomics study revealed with high precision that a neurometabolite panel consisting of plasma metabolite biomarkers (GABA, dopamine, tyramine, kynurenine) might represent clinically useful biomarkers of MDD.

Keywords Biomarkers · Depression · Serotonin · Dopamine · Norepinephrine · GABA · BDNF · HPA axis · Metabolomics · Glycomics

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11.1 Introduction

11.1.1 *Depression*

Major depressive disorder (MDD) is a complex psychiatric, chronic, and recurring disorder. Its diagnosis depends on the clinical evaluation, usually according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria [1], and subjective description of the symptoms associated with depression. During a 2-week period, besides either a diminished interest or loss of pleasure in activities or a presence of a depressed mood, five of the symptoms should be present to confirm the diagnosis of MDD. These symptoms are related to a major change in weight or appetite, sleep disturbances, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate, inability to make decisions and suicidal behavior, consisting of recurrent suicidal thoughts, ideation, suicidal attempt, or a plan to commit suicide. The presence of these symptoms must cause a substantial distress or deficiency in social, occupational, or other functioning and they are not induced by any medication or drugs.

Depression is one of the most prevalent psychiatric disorders, affecting individuals of all ages. In 2015, 322 million people were estimated to suffer from depression, representing 4.4% of the world's population, and depression was ranked by World Health Organization (WHO) as the single largest contributor to global disability [2]. Clinical presentation ranges from brief and mild episodes to severe, incapacitating conditions that markedly affect lives. According to the DSM-5 criteria, the diagnosis of a major depression episode requires the presence of five or more symptoms within a 2-week period. One of these symptoms should be either a depressed mood or anhedonia. Other symptoms of major depression include appetite and/or weight changes, sleep difficulties, psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidal ideation. Women have a higher prevalence of depression, though this sex difference could have been narrowed recently [3]. The prevalence of depression depends on the population studied and instruments used to detect depression.

MDD is most appropriately diagnosed through direct patient interview, preferably by psychiatrists or other trained professionals. However, self-reported depressive symptoms have been studied more widely—in community settings, among the elderly, or respondents with different somatic illnesses, using scales such as the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale. The inconsistency in incidence and prevalence rates across studies may arise from the lack of universally applied gold standard for the diagnosis of depression and detection of depressive symptoms. In general, the prevalence of depression in studies using self-report instruments was twice as high (17.3% vs 8.5%) compared to those based on interview-based assessment tools [3]. Moreover, various depression screening instruments might also yield different findings. For example, higher prevalence estimates of depression were noted among studies that used Beck Depression Inventory than those which employed Hospital Anxiety and Depression

Scale [4]. The meta-analysis of 90 studies with 1,112,573 adults from all continents, reported that the aggregate point prevalence was 12.9%, one-year prevalence 7.2%, whereas lifetime prevalence was 10.8% in general population [3].

11.1.2 Etiology of Depression

Depression, like any other psychiatric disorder, is the final result of the complex interplay between genetic vulnerability and stressful environment. The risk factors for depression are numerous, and are still incompletely understood. A recent meta-analysis reported that mood disorders share several common genetic associations [5]. Interestingly, genetic liability, presented as polygenic risk scores for major depression, increased the risk for suicide attempt across psychiatric disorders, including MDD [6]. Depression is the common symptom across genetic mood disorder spectrum, with separate clusters for bipolar disorder type 1 and depressive disorders, linked by bipolar disorder type 2 [5].

The underlying pathology of depression is still not clear, and diverse symptoms confirm its heterogeneous and complex etiology and neurobiological underpinning. Due to different symptoms, different neurobiological pathways, circuits and molecules are assumed to be involved in the etiology of depression. A substantially good treatment response, that is, remission, is achieved in only 30% of patients after introducing the first antidepressant medication, while 30% of patients do not enter into remission even after multiple treatments [7]. Consequently, there is a frequent development of a treatment resistant depression (TRD) in patients with MDD, that is, a failure to respond to therapy or to enter remission after antidepressant therapy given in adequate dose and duration [8]. Due to a nonresponse to treatment and a lack of remission, patients with MDD show functional impairment, disability, worse quality of life, and depression elicits significant disease burden [8].

There is a biological link between stress and depression, which has been extensively investigated in animal models. Namely, the innate stress response is considered essential for body homeostasis and survival, whereas the responses to prolonged and intensive stress might become dysregulated, producing changes in neurotransmitter function and neuroplasticity, which might eventually precipitate different symptoms, including depression [9]. In addition, diverse adverse psychosocial factors have been linked to depression, with the interpersonal loss being particularly important. Meta-analytic evidence has shown that parental loss, parental death, and parental separation before the age of 18 [10], spousal loss [11] and work stress, such as job strain [12], increase risks for depression. Importantly, while the highest depression rates occurred in the first month of widowhood, and thereafter it steadily declined, the prevalence of depression was still higher than in general population even after 24 to 60 months after suffering the loss [11]. Depression was also related to nutrition deficits, such as unhealthy dietary pattern [13] and low dietary zinc and iron intake [14]. Protective factors against depression include physical activity [15] and dietary n-3 PUFA intake [16].

Depression is a complex phenotype disorder and can be separated into several subtypes. Among others, depression with psychotic features is less common, with a lifetime prevalence being between 0.35% and 1% [17]. This considerable clinical heterogeneity, might, among others, arise from distinct biological background. It has even been proposed that each symptom of depression might involve unique neuronal circuits [18].

The important goal in research is to assess underlying vulnerability factors associated with development of MDD, as well as to search for biomarkers of MDD and its subtypes [19]. For now, there are still no validated, easy obtainable, noninvasive biomarker(s), biomarker panel or an array of biomarkers that will be able to confirm a diagnosis of MDD, and enhance the diagnostic procedures, predict, or improve the treatment and offer early prognosis, such as theranostic biomarkers [20, 21]. Biomarkers are useful since they can provide insight into molecular underpinning of the underlying alterations in biological systems and pathways in MDD. Biomarkers might be used as objective tool for the accurate diagnosis of MDD or might help in the rational selection of therapy.

11.1.3 Depression and Somatic Disorders

A bidirectional, complex relationship exists between depression and somatic disease(s). While physical illness may produce social and health limitations that facilitate the onset of depressive symptoms, depression is a risk for both the development of somatic disease and preterm mortality. For example, global prevalence of depression is 32.2% in the breast cancer patients [22], 28% in patients with type 2 diabetes mellitus [23], 28.7% in patients with myocardial infarction [24], 30.5% in multiple sclerosis [25], and 21.9% in patients with epilepsy [26], though considerable differences are detected across geographical regions [22–24, 26]. Notably, the highest rates of depression are reported in patients from otolaryngology (53%) and dermatology (39%) departments. However, the interpretation and generalization of meta-analytic data on depression rates should be cautious, because reported prevalence may exceed actual prevalence, given that the majority of studies used different screening tools or rating scales instead of diagnostic interviews, using the term “depression” or “depressive disorders” even though disorders were not assessed [27]. Depression is also common in outpatient, nonpsychiatric units, ranging from 17% to 53% [4].

11.2 Biomarkers in MDD

11.2.1 Neurotransmitter Biomarkers in MDD

11.2.1.1 Serotonergic Biomarkers of MDD

The oldest neurobiological hypothesis of MDD is monoaminergic hypothesis, based on the effectiveness of antidepressant medication that alters levels of monoamines such as serotonin (5-hydroxytryptamine or 5-HT), norepinephrine (NE), or dopamine (DA). The first antidepressants were monoamine oxidase inhibitors (MAOIs: phenelzine, selegiline and tranylcypromine), tricyclic antidepressants (TCAs: amitriptyline, desipramine, doxepin, imipramine, nortriptyline, amoxapine, clomipramine, maprotiline, trimipramine and protriptyline). Later, selective serotonin reuptake inhibitors (SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, and sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs: desvenlafaxine, duloxetine, venlafaxine, venlafaxine XR, milnacipran, and levomilnacipran), and atypical antidepressants (bupropion, mirtazapine, nefazodone, trazodone, vilazodone, and vortioxetine) were synthesized. All antidepressant drugs restore the imbalance in 5-HT, NE, and/or DA neurotransmission. The mechanisms of action of antidepressant medication involve either MAO inhibition, re-uptake inhibition of 5-HT or NE, or antagonistic action on the presynaptic inhibitory 5-HT or NE receptors, leading to the increased 5-HT or NE modulated neurotransmission [28].

Therefore, 5-HT, acting via its receptors (from 5-HT₁-5-HT₇ and their subtypes) and its concentration is regulated by the serotonin transporter (5-HTT), is involved in the neurobiology and etiology of MDD [29, 30]. Namely, 5-HT projections from raphe nuclei innervate hypothalamus, prefrontal cortex, striatum and spinal cord, all regions that are affected by 5-HT deficits, and impaired 5-HT function results in anxiety, depression, low mood, obsessions, and compulsions [28]. There are a lot of studies investigating peripheral indices of the 5-HT system in MDD [31, 32], with aim to detect biomarkers of depression [33], with variable and contradictory results [34]. However, when evaluating validated and confirmed biomarkers related to serotonergic receptors, out of all G-protein coupled or ligand-gated ion channels, only 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₄, 5-HT₆, and 5-HT₇ receptors were found to be involved in the neurobiology of MDD since they modulate cognitive and emotional processing [30]. Among them, 5-HT_{1A} receptor seem to be crucial for MDD diagnosis and prognosis [35]. However, most of the literature findings are inconsistent and biomarkers of MDD are frequently not confirmed in the future much larger studies [19]. In the postmortem studies reduced 5-HT_{1A} mRNA levels in the hippocampus and prefrontal cortex, and lower expression of 5-HTT mRNA in different regions of the brain was found in MDD [20].

Besides 5-HT receptor's biomarkers [30], the most frequently investigated component of the 5-HT system was 5-HTT (a target for all SSRIs), and its functional polymorphism (a serotonin-transporter-linked polymorphic region, *5-HTTLPR*). A

lot of association studies [36] revealed that a repeat length polymorphism (*5-HTTLPR*) in the promoter region of the 5HTT gene (*SLC6A4* or *5HTT*) was associated with depression. Namely, risk alleles of the *5-HTTLPR* (i.e., the less active short (S) allele that leads to reduced expression of the 5-HTT) were significantly associated with depression compared to the long (L) allele [37]. As these findings were not so frequently replicated, this nonreplication was explained by the fact that this association depends on the moderating effect of stress, that is, gene x environment (stress) interaction [38]. Later it was confirmed that people who were exposed to childhood trauma(s) and stressors, carriers of the S allele, were more prone to develop depression than individuals—carriers of the L allele of the *5-HTTLPR* [39]. However, nonreplication of these associations was more frequently the rule than the exception, and therefore recent meta-analyses re-examined this association [40–42]. Although it is expected that an effect of the single polymorphism on the specific phenotype is small in magnitude, and that large sample sizes are needed to detect any significant association, the latest meta-analysis revealed no significant association between *5-HTTLPR* and depression [43]. In addition, in the largest meta-analysis performed so far on more than 40 000 subjects, no significant interaction between stress, depression, and *5-HTTLPR* was detected, and this study did not confirm the finding that *5-HTTLPR* is associated with depression or that *5-HTTLPR* S allele increases the risk of depression in individuals exposed to stress [44].

All these data suggest that there is no simple explanation of the role of 5HT in MDD, and that reduced 5-HT is sometimes, in some patients with a positive family history of depression or in those with previous depressive episodes, associated with depression, but 5-HT definitely affects emotional processing and learning that promote plasticity and improve depressive symptoms [45]. However, validated and clinically useful 5-HT biomarkers of depression are still missing.

11.2.1.2 Noradrenergic Biomarkers of Depression

Noradrenergic pathways and projections innervate different brain regions involved in the regulation of acute and chronic stress response, appetite, emotions, feelings of pleasure, pain perception, and cognitive functions and therefore NE also has a role in depression [28, 46]. Lower NE transmission and signaling are related to reduced vigilance, feelings of exhaustion, executive and social dysfunction, stress-induced depressive symptoms, and troubles with attention and concentration, while antidepressants that increase NE function or restore NE in the brain reduce depressive symptoms [28]. When evaluating peripheral indices of NE function, plasma NE was determined in patients with depression and compared with NE concentration in plasma of control subjects [47]. Although plasma NE concentration was significantly higher in depressed versus control subjects, when controlled for the effect of smoking these differences disappeared [47]. However, this study revealed an association between plasma NE concentration and metabolic variables (lipids in plasma, BMI, waist circumference, blood pressure, insulin sensitivity, and inflammatory markers (hsCRP and IL-6), independent of the presence of depression, suggesting

increased plasma NE associated with increased risk factors for cardiovascular disease [47]. Other study reported increased levels of cerebrospinal fluid (CSF) NE and its metabolite in depression [48]. This finding may be explained by the increased locus coeruleus activity in depression, NE neuronal loss in locus coeruleus, increased synaptic NE or increased availability of the tyrosine hydroxylase, rate-limiting enzyme responsible for the NE synthesis [49].

As the data from the literature show that TRD or absence of remission frequently occurred in patients with MDD, and response to antidepressant treatment can be seen after 3-4 weeks of delay, these facts suggest that monoamine theory of depression, that is, that reduced 5-HT and NE function triggers depressive symptoms, is too simplistic and cannot explain all facets of depression [50]. In line with that, clinically useful noradrenergic biomarkers of depression are still not available.

11.2.1.3 Dopaminergic Biomarkers of Depression

Apart from 5-HT and NE dysfunction, the evidence of involvement of dopaminergic system in depression continues to accumulate. Namely, DA, particularly in the mesolimbic system, plays a central role in regulating motivation, psychomotor speed, concentration, and pleasure. In preclinical trials, dopaminergic abnormalities in models of depression were primarily demonstrated in ventral tegmental area, limbic system, and striatum. For example, mice exposed to chronic social stress had higher dopamine D1 receptor binding in ventral tegmental area, reduced dopamine turnover in nucleus accumbens, blunted dopamine response to dopamine transporter (DAT) inhibitor challenge [51], and reduced expression of dopaminergic genes such as DRD2, Adora2a, and Darpp-32 [52]. These findings suggest diminished mesolimbic pathway functioning, and consequently reduced reward-directed behavior in depression, at least in chronic-stress animal models [51].

In clinical studies, neuroimaging, pharmacological, electrophysiological, and biochemical research have provided further support for dopamine dysfunction in depression. Medication-free MDD subjects displayed slowing of ventral tegmental area dynamics during resting state fMRI [53]. In addition, patients with depression also had lower dopamine D₂/D₃ binding in striatum compared to healthy participants, and, notably, electroconvulsive treatment, despite alleviating depression, did not affect this finding [54].

While the meta-analysis found no alteration of striatal DAT availability in major depression [55], more recent study demonstrated lower DAT availability in bilateral putamen in such patients [56]. Patients with depression also demonstrated lower DAT availability in the midbrain, a region of origin for mesocorticolimbic and nigrostriatal dopamine pathways [56, 57]. Decreased DAT levels (along with tyrosine hydroxylase activity) in the putamen of patients with MDD, in comparison to healthy controls, were further confirmed in postmortem analyses [56]. Lower DAT expression observed in these studies might result from the decreased dopamine availability. If confirmed in the future large studies, these results of the reduced DAT concentration as well as reduced tyrosine hydroxylase activity might offer clinically relevant dopaminergic biomarkers of depression.

However, discrepant findings from various studies might be explained by the great heterogeneity in the clinical presentation of depression. While different aspects of hypodopaminergic state were documented in depression, it might be not being ubiquitous for all patients, and might merely relate to specific clinical presentations [58], such as avolition, psychomotor retardation [59], and poor concentration and anhedonia [18]. Such findings might be clinically important, because only few antidepressants directly target dopaminergic system.

11.2.1.4 GABAergic Biomarkers of Depression

While glutamate is the major excitatory neurotransmitter, gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain. Very precise balance between excitation and inhibition is crucial for the normal brain functioning, and there is evidence on the disruption of this equilibrium in some brain regions in patients with depression [9, 60, 61].

In general, glutamate neuronal atrophy was demonstrated in prefrontal cortex and hippocampus, whereas the hypertrophy of glutamate neurons in amygdala was implicated in depression [62]. The role of GABA neurons includes “fine tuning” of glutamate excitatory signals [61]. However, the expression of GABA interneurons in depression was reduced in many brain areas, particularly in somatostatin GABA neuron populations, which are especially vulnerable, as reflected from their reduced density in depression [61, 62]. Such findings result in cortical inhibitory deficits, which lead to alterations in functional connectivity. There is evidence of decreased cortical GABA levels, decline of GABA neuronal subpopulations, alterations in GABA_A receptors subunit genes expression, particularly in cortical and hippocampal regions, while the participation of GABA_B receptors in the pathophysiology of MDD is less investigated, though there is some evidence of their dysfunction as well [9].

Unlike monoamines, GABA and glutamate might be measured in brain in vivo by proton magnetic resonance spectroscopy ((1) H-MRS). Actually, the most robust evidence on modifications of GABAergic system in depression comes from these studies. Two meta-analyses reported reduced brain GABA levels in symptomatic MDD patients, whereas this finding was no longer evident in patients in remission [63, 64]. Low GABA levels were demonstrated across brain regions, but particularly in regions important for emotional processing, such as anterior cingulate cortex, PFC, and amygdala [61, 64]. Therefore, decreased brain GABA level is candidate for a state-marker in major depression. This GABA deficit was relatively specific for depression, given that apart from acute stress disorder, it was not observed in other psychiatric disorders, such as schizophrenia, bipolar disorder, or posttraumatic stress disorder (PTSD) [63]. The accumulating evidence for diverse defects in GABAergic transmission in depression has led not only to the GABAergic deficit hypothesis of MDD [60], but also to the new avenues of research, assessing potential new antidepressants that directly modulate GABAergic system [65]. As magnetic resonance spectroscopy revealed that besides GABA levels, glutamate

levels were also decreased in anterior cingulate cortex of patients with MDD, these findings do not support the simple hypothesis of the excitatory/inhibitory imbalance underlying depression [64].

11.2.2 HPA Axis Biomarkers in Depression

Depression has been associated with impaired regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis and chronically increased secretion of corticotrophin releasing hormone (CRH) in various brain regions [66, 67]. This hyperactivation of the HPA axis is thought to result in the persistent elevation of adrenocorticotrophic hormone (ACTH) and cortisol levels [68, 69], as well as in altered feedback inhibition by glucocorticoids (GRs), mediated by their binding to the mineralocorticoid (MR) and glucocorticoid (GR) receptors [70–72]. Namely, dexamethasone induces a potent feedback inhibition of the HPA axis in healthy subjects, leading to reduced cortisol levels, whereas in depressed patients an abnormal cortisol suppression was observed after pharmacological challenge using dexamethasone suppression test (DST) [73, 74].

It has been estimated that 20–80% of depressed individuals exhibit some form of HPA hyperactivation [75], and recent meta-analysis demonstrated higher cortisol values in 73%, and higher ACTH levels in 60% of depressed patients in comparison to undepressed subjects [67]. Our previous studies also detected increased plasma cortisol levels as well as DST nonsuppression in depressed patients [76, 77]. It has been proposed that in depression, altered GR expression affects the homeostatic regulation of cortisol [78], leading to its elevated secretion and related changes in 5-HT receptors [79, 80], underlying depressive symptoms [81, 82]. In addition, various studies demonstrated that the severity of depressive symptoms positively correlates with cortisol levels [83]. Higher cortisol response to stress has been associated with acute and severe, but not with mild and atypical forms of depression [84–86]. Namely, individuals with more severe subtypes of depression, such as psychotic [84, 85] and melancholic depressive patients [86], have higher salivary and serum cortisol levels in comparison to patients diagnosed with milder atypical depression. One meta-analysis addressed varying cortisol phases in depressed patients versus controls [87]. Depressed patients demonstrated a relatively flat unresponsive pattern of cortisol secretion with blunted reactivity to stress and impaired recovery phases. This blunted reactivity-impaired recovery pattern was more pronounced in the afternoon studies with older and more severely depressed patients [87]. Moreover, the increased frequency of depression in women is associated with larger cortisol response variability rather than higher baseline cortisol levels [88].

Both susceptible genes and environmental risk factors, such as stress, are implicated in the development of depression. The HPA function is also significantly influenced by the gene x environment interaction. Early life stress has been found to exert long-lasting effects and to induce the abnormal cortisol responses after

exposure to stress in adults [89, 90], potentially via glucocorticoid resistance, increased central CRH activity [91] and alternations in GR and MR receptor binding [92]. Not only stress during childhood, but also stress in adulthood is a risk factor for depression, and data suggested that approximately 80% of community cases of depression are preceded by exposure to different stressors [93].

Various studies suggested that genetic and epigenetic mechanisms link stress, dysregulation of HPA axis function, and depression [94–98]. The variants of CRH receptor (*CRHR1*) gene, GR (*NR3C1*) gene, and gene coding for FK506 binding protein (*FKBP5*) have been shown to interact with early life stress and increase the risk for depression in adulthood [99–103]. Polymorphisms in the promoter region of GR gene, *NR3C1*, have been associated with altered sensitivity to glucocorticoids, as well as with stress-related disorders, including depression [104–106]. Parental care has been shown to influence HPA function through *NRC31* epigenetic regulation and consequently hippocampal GR receptor expression in rats, as well in suicide victims and other subjects with a history of early life stress [94, 107, 108]. In addition, polymorphisms, as well as haplotypes of *CRHR1* gene, in interaction with early life stress are found to increase the risk of depression [101, 103, 109, 110]. Variants of the *FKBP5* gene in interaction with childhood abuse have been associated with the risk of PTSD symptoms in adults [111]. The findings demonstrating the involvement of *FKBP5* gene in response to stress have been further supported by data from the animal studies [112, 113]. The FKBP5 protein, a co-chaperone that modulates the binding of cortisol to GR, presumably disturbs the negative feedback of the HPA axis, resulting in its HPA axis hyperactivity [100], associated with depression.

Numerous studies demonstrate that depression is associated with stress-related variability in the HPA axis response. Increased cortisol levels have been observed in more severe forms of MDD, rather than in chronic or atypical subtypes, suggesting that it cannot be used as a simple biomarker for MDD in general. The imbalance of GR and MR has been also reported in MDD, whereas negative feedback of HPA axis through GR is variably impaired in depressed patients. Genetic and epigenetic influences together with environmental factors such as early life stress significantly affect HPA axis activity; however, the exact brain region-specific roles of enrolled genes are yet to be elucidated. Therefore, multimodal preclinical and clinical research that involves (epi)genetic, molecular, cellular, imaging and other studies is necessary to advance our understanding of the role of HPA biomarkers in depression.

11.2.3 Neurotrophic Biomarkers of Depression

Neurotrophins promote neuronal survival, growth, differentiation and development, and they are the key players in the regulation of neuronal plasticity and function [114]. Neurotrophin family includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3 and NT-4/5. The mature forms of neurotrophins bind to a specific tyrosine kinase receptor (Trk) with high affinity, but

they can also act through pan neurotrophin receptor (p75NTR) [115, 116]. BDNF is a member of the neurotrophin family, widely distributed in the periphery and central nervous system (CNS) [115], which has been comprehensively researched as potential biomarker of depression over the past decade. Binding of BDNF to TrkB causes the autophosphorylation of TrkB and activation of the mitogen-activated protein kinase (MAPK) pathway, phosphatidylinositol 3-kinase (PI3K) pathway, and the phospholipase C-gamma (PLC- γ) pathway [117]. In the end, cAMP response element binding protein (CREB) is activated, leading to the upregulation of *BDNF* mRNA expression [118]. Binding of the precursor form of BDNF (pro-BDNF) to p75NTR activates different signaling cascades, which consequently lead to the activation of apoptotic signaling and synaptic depression mediated by N-methyl-D-aspartic acid (NMDA) receptor [119].

The neurotrophin hypothesis of depression links *BDNF* mRNA and protein expression to pathological changes in different brain areas, including hippocampus [120–122]. This relationship is additionally supported by studies demonstrating the effect of chronic stress on BDNF brain expression in animal models [123, 124]. Evidence from human studies suggests reduced expression of BDNF and TrkB in hippocampus, amygdala and prefrontal cortex [125–127]. However, reduced expression of BDNF in hippocampus was found to be reversible by antidepressant treatment [127, 128]. Due to the limitations of postmortem studies, there is a growing interest in peripheral BDNF as a biomarker in different psychiatric disorders, including depression. Several studies found lower levels of peripheral BDNF (plasma or serum BDNF) in depressed subjects compared to control group [129–133]. There is also evidence of decreased platelet BDNF content [134] and reduced *BDNF* mRNA expression in peripheral blood mononuclear cells [135] of individuals diagnosed with MDD. The potential of peripheral BDNF as a biomarker in depression is supported by the ability of this neurotrophin to cross the blood-brain barrier [136] and by the association between peripheral and central BDNF levels [137, 138]. Antidepressant treatment can increase peripheral BDNF levels [139, 140], demonstrating the potential of BDNF as a marker for treatment response. Studies have shown that antidepressant therapy can reverse peripheral BDNF levels and restore them to a level similar to that in healthy subjects [141–143]. However, it is still questionable whether all antidepressants affect BDNF levels, indicating a different mechanism of action [141]. Furthermore, it was demonstrated that positive response to therapy with classical antidepressants could be predicted from higher BDNF serum levels in depressed patients before the treatment or early after the beginning of treatment [144–147].

BDNF is also a potential contributor to the monoaminergic hypothesis of depression. BDNF promotes development, function and survival of serotonergic neurons. Studies have suggested a feedback loop in which serotonin regulates *BDNF* mRNA expression, while BDNF signaling, through TrkB, leads to the upregulation of tryptophan hydroxylase and 5-HT uptake in serotonergic neurons [148, 149]. It has been suggested that the action of BDNF on serotonergic neurons results in increased cAMP production, leading to an activation of protein kinase A (PKA) and of the transcription factor CREB, promoting BDNF synthesis and induction of

BDNF-TrkB signaling [148, 149]. An association of peripheral BDNF levels and antidepressant treatment, which was demonstrated in different studies [142, 150–154], leads to the conclusion that antidepressants that increase extracellular 5-HT levels, by inhibiting the reuptake of 5-HT by 5-HTT, enhance neurotransmission through different 5-HT receptor subtypes coupled to adenylate cyclase and PKA. Due to interaction between BDNF and serotonergic signaling systems, it is expected that these two systems interact also at the genetic level with synergistic effects. The most studied BDNF polymorphism, rs6265 (Val66Met), is situated in the coding region of *BDNF* gene and it results in a valine (Val) to methionine (Met) substitution in the prodomain of the human BDNF protein at codon 66. This substitution affects *BDNF* mRNA trafficking to dendrites and BDNF protein secretion [155]. Smaller hippocampal volumes were detected in individuals carrying *BDNF* Met66 allele [156] and this variant was associated with altered hippocampal function [155, 157]. Above mentioned facts suggest a possible role of *BDNF* Met66 allele in depression. Reduced hippocampal, parahippocampal and amygdala volumes were detected in MDD patients [158, 159] and *BDNF* Met66 allele was associated with suicidal behavior in depressed patients [160]. Recent studies also suggest that the carriers of *BDNF* Met66 variant are more vulnerable to stress than Val/Val homozygotes [161, 162]. Gene coding for 5-HTT carries a promotor polymorphism (5-HTTLPR) that affects transcription and function of the 5-HTT [163]. The evidence for genetic epistasis between *BDNF* and 5-HTT was presented [164], demonstrating highest depression scores in children with maltreatment history, carriers of the *BDNF* Met66 allele and 5-HTTLPR S/S genotype. Increased prevalence of depression, due to multiple life events, was detected in elderly subject, carriers of 5-HTTLPR S/S genotype and *BDNF* Met66 allele [165]. However, further investigations of genetic interaction between *BDNF* and 5-HTT are still needed and represent a topic with great potential in the search for biomarkers of depression.

Recently, epigenetic modifications have been implicated as a potential mechanism behind BDNF upregulation by antidepressant and behind stress-induced downregulation of BDNF [166]. A number of micro RNAs, including miR-15a, miR-22, miR-26a and miR-26b, miR-30a, miR-124, miR-132, miR-182, miR-195, miR-204, miR-206, miR-210, and miR-376b-5p, have been implicated in regulation of *BDNF* expression. Severity of depressive symptoms was correlated with higher levels of serum miR-132, which is related to *BDNF* gene expression regulation [167]. Studies in rodents also detected an association between increased levels of miR-16, which targets *BDNF* expression, and depressive-like behavior [168]. Antidepressant effect could be mediated through reducing the expression of specific miRNAs, like miR-30a-5p or miR-206, which consequently increase BDNF expression [169, 170]. Monitoring of the alterations in DNA methylation also has a diagnostic potential in depression. Regarding the association of *BDNF* methylation pattern and depression, the most studied are methylation profiles of promotor 1 and 4. Hypermethylation of CpG islands within promotor 4 was associated with suicidal ideation in the Wernicke's area of suicide victims [171] and in the blood samples of depressed patients [172], suggesting a similar DNA methylation pattern of *BDNF* promotor 4 in the brain and in the periphery. Hypermethylation of *BDNF* promotor

4 was also suggested as a vulnerability biomarker in MDD in individuals that experienced stressful life events [173]. Methylation profiles of promotor 1 were also correlated with the diagnosis of MDD [174]. However, further studies are still needed to gain more knowledge regarding epigenetic mechanisms behind vulnerability to depression and antidepressant response.

Decreased peripheral levels of other neurotrophins, like NGF and NT-3, were also associated with MDD [175, 176], but these studies are less prevalent in the currently available scientific literature. Future research on the role of neurotrophins in pathogenesis of depression and their potential as diagnostic, prognostic, and treatment response biomarkers are needed, with a strong emphasis on studies with large sample sizes and reduced variability in different biological and clinical parameters.

11.2.4 Metabolomic Markers of Depression

Metabolomics is a comprehensive and quantitative study of a metabolome [177], providing insight in altered metabolic pathways and metabolites that might represent potential biomarkers in various disorders, including depression [178, 179]. Etiology and molecular mechanisms of depression are complex and still unclear. Hence, metabolic markers might provide information about altered metabolites as potential prognostic or diagnostic biomarkers, might improve treatment and understanding of underlying mechanisms [180]. Different analytical techniques have been used for analyzing various biological samples in order to provide metabolic profiles characteristic for depression. Altered levels of certain metabolites and metabolic pathways have been associated with MDD development. Metabolites that are involved in tricarboxylic acid cycle (TCA) and fatty acid metabolism had been mostly changed in subjects with depression compared to control subjects [178]. Urinary and plasma metabolomics showed altered levels of metabolites that take part in TCA cycle in patients with MDD. While levels of TCA cycle co-metabolites such as α -ketoglutarate, succinate, succinyl-CoA and methylmalonate were increased, decreased levels of malonate, lactate, pyruvate, and glucose have been observed. Such changes indicate succinate dehydrogenase impairment, enzyme that catalyze reaction of succinate to fumarate conversion. Together with decreased levels of malonate, which acts as an inhibitor for succinate dehydrogenase and increased levels of methylmalonate and succinyl-CoA, it is assumed that increased TCA flux is involved in MDD pathogenesis. Altered TCA flux might be associated with glucose impairments, which are characteristic for depression. Decreased levels of sorbitol, metabolite involved in glucose metabolism was observed in MDD [181]. Consequently, lack of glucose in certain brain areas was noticed in patients with depression [182]. Therefore, altered metabolites involved in citric acid and glucose metabolism might represent biomarkers for MDD [181, 182].

Alterations of gut microbiota are assumed to be associated with MDD pathogenesis. It is known that subjects with MDD show symptoms of disrupted microflora and often develop irritable bowel syndrome (IBS). Metabolites produced

exclusively by gut microbiota, such as hippurate, trimethylamine-N-oxide, dimethylamine, dimethylglycine, and m-hydroxyphenylacetate were decreased in MDD subjects compared with healthy controls [182]. Moreover, studies on animal models of depression showed that observed behavioral alterations are associated with microflora impairment [182]. These findings indicate that changes in gut microbiome might contribute to the development of MDD symptoms and hence represent potential biomarkers of disrupted gut-brain axis in subjects with MDD [182].

Various metabolites that take part in fatty acid metabolism are altered in depression. Triglycerides, low density lipoprotein and very low-density lipoproteins were significantly increased in MDD subjects compared with concentrations found in healthy controls [183]. While fatty acids and fatty amides were decreased, glycerophospholipids were increased in subjects with MDD [178]. Levels of medium-chain fatty acids, oleate, stearate, palmitate, myristate were altered in MDD subjects [184]. Lysophosphatidylethanolamines, lysophosphatidylcholines, phosphatidylethanolamines, and phosphatidylcholines were significantly increased in patients with depression compared with healthy controls [179]. Phosphoethanolamine, as part of a fatty acid metabolism might represent potential biomarker in subjects with MDD. It is a precursor of phosphatidylethanolamine and it is involved in membrane stability, neuromodulation, and osmoregulation [185]. Decreased levels of carnitines and deoxycholic acid were observed in subjects with depression compared with controls [178], while other bile acids, such as glycochenodeoxycholic acid, glycodeoxycholate, and taurochenodeoxycholate were significantly increased in MDD subjects [179]. Numerous studies also found elevated levels of bile acids, which correspond with alterations of gut microbiota in MDD. It has been assumed that during depression development, production of bile acids was enhanced [186].

Altered neurotransmission, including neurotransmitters DA, glutamate, and GABA, and their metabolites might represent important, potential biomarkers for depression [181, 187]. Reduced levels of excitatory neurotransmitters and elevated levels of inhibitory neurotransmitters, such as GABA have been shown in subjects with depression [181], but these findings differ in depressed vs. remitted patients [63]. Increased plasma levels of GABA have been associated with depression, anxiety, and schizophrenia [187]. In addition to GABA, catecholamines were upregulated in plasma of MDD subjects [187]. According to these findings, it was assumed that disbalance between inhibitory and excitatory neurotransmitters could be implied in MDD development [187], although this hypothesis was questioned [64]. Tryptophan-nicotinic acid metabolism is another metabolic pathway involved in MDD pathogenesis. Tryptophan is a precursor of serotonin, and its levels were significantly reduced in brain or plasma samples of MDD subjects [179]. Moreover, increased N-methylnicotinamide levels also indicate impaired 5-HT synthesis and altered upregulation of tryptophan-nicotinic acid metabolism [182]. These changed metabolites are in accordance with the theory that metabolites that are part of serotonergic neurotransmission are altered in MDD [182, 187].

Numerous other studies identified metabolites that contribute to high differentiation between MDD subjects and healthy controls. Mostly, they were myoinositol, certain amino acids and sugars, sorbitol, N-acetylglycoprotein, creatine, creatinine,

oleic, and linoleic acid. Altered levels of amino acids, including alanine, phenylalanine, serine, aspartate, aspartic acid, γ -glutamyl glutamine, and γ -glutamyl leucine have been observed in subjects with depression, compared with healthy controls [184, 188]. Altered levels of metabolites that take part in pentose phosphate and propanoate metabolism, dicarboxylic acids, purine, and pyrimidine metabolites and degradation products of aromatic compounds were observed in MDD subjects [188, 189]. However, it is assumed that antidepressant treatment might regulate or normalize certain altered metabolic pathways, which is why patients in remission might have similar metabolic profile as healthy controls compared with metabolic profiles of MDD subjects [190]. Due to heterogeneity of MDD, underlying molecular mechanisms are still unclear; however, detection of potential measurable biomarkers would largely contribute to prediction of disease and improved therapeutic approach [191]. Various studies have shown that certain metabolic pathways are involved in MDD pathogenesis. Altered neurotransmission and metabolites that take part in fatty acids, bile acids, tryptophan, glucose, citric acid, and gut microbiota metabolism are involved in MDD development and could represent potential diagnostic and predictive biomarkers for MDD [179].

11.2.5 Glycomic Biomarkers of Depression

Majority of biological processes, especially those included in signal transduction and immunological response, are influenced and to some degree regulated by glycosylation of proteins, that is, posttranslational enzymatic attachment of oligosaccharide residues to nitrogen atom on asparagine (N-glycans) or oxygen atom on serine/threonine (O-glycans) in conserved amino acid sequence in polypeptide backbone [192]. Biological role of proteins, as well as their affinity to target cells or ligands, can be drastically changed depending on type, number, and attachment site of glycan species [193]. Since protein glycosylation does not have predefined template and is highly time- and tissue- dependent [194], it could be considered as mediator between environmental stimuli and genetic predisposition; thus, it potentially provides more precise input into various pathophysiological states. N-glycosylation pattern substantially changes with age and relative abundance of specific N-glycan species could be considered as an indicator of the biological age of individual [195–197]. Changes in N-glycome have already been reported in age-related diseases such as dementia and Alzheimer's disease [196, 197], cancer [198–201], several autoimmune diseases [199, 202], but also in neuropsychiatric disorders [203, 204], such as PTSD [205, 206], schizophrenia [207, 208], and attention-deficit hyperactivity disorder (ADHD) [209].

There are several studies [210–212, 215] showing changes in glycosylation in MDD. A significant decrease in agalacto core- α -1,6-fucosylated biantennary glycans (NG1A2F) was detected in the serum of female patients with MDD compared to control subjects, matched by sex and age, along with significant elevation of nonfucosylated biantennary N-glycans (NA2) and triantennary N-glycans (NA3FB)

in women with MDD [210]. These alternations were more prominent in patients with more severe depressive symptoms, as well as with a history of childhood sexual abuse; however, no significant differences between serum N-glycan profile between nondepressed control subjects with or without history of childhood sexual abuse was detected [210]. This points to the conclusion that childhood abuse is associated with adverse biological alternations that could affect susceptibility to MDD and clinical course of depression later in life [211].

Association of N-glycosylation and severity of depression, as well as response to antidepressant treatment has also been reported in a recent study [212]. Relative abundance of highly branched and sialylated (tri- and tetraantennary) N-glycans in plasma positively correlated with severity of depressive symptoms, especially in male patients with MDD. Although noticeable alternations in total plasma N-glycome depending on severity of depression were less prominent in female patients, significant changes in two immunoglobulin (IgG) glycoforms containing bisecting N-acetylglucosamine showed strong positive correlation with symptom's severity [212]. Additionally, plasma and IgG-attached N-glycans were significantly altered between female patients with MDD who responded well on antidepressant therapy and those who did not, and correlated significantly with changes in total scores measuring depressive symptoms; specifically, relative plasma abundance of high-mannose N-glycoforms decreased with more intense symptoms of depression in female patients [212]. These results could potentially offer a tool to monitor and diagnose severity of depression in both male and female patients and possibly to predict the efficacy of antidepressant therapy, but only in female patients.

This finding is in accordance with animal study [213] that reported diminished depressive-like symptoms, such as reduced immobility, increased cage exploration, and decreased social investigation that could possibly be linked to hyperactivity and mania, but not to depression, in male mice lacking N-acetylglucosaminyl-transferase 5 (*MGAT5*^{-/-} mice). *MGAT5* is main enzyme included in β 1,6 branching of N-glycans; thus, the absence of this enzyme significantly decreases the abundance of highly branched N-glycan species [214]. This study suggests that tri- and tetraantennary glycoforms deficiency is linked to absence depression or depressive-like symptoms or their diminishing [214]. Sia- α 2-6Gal/GalNAc glycan structures were reported as potential plasma biomarkers of depression, based on their significant alternations in chronic ultra-mildly stressed mice who exhibit depression-like symptoms and in human patients with MDD (depressed and remitted) compared to nonstressed animals and healthy control subjects, respectively [215]. Additionally, expression of α -N-acetylgalactosaminide α -2,6-sialyltransferase 2 (*ST6GALNAC2*) protein, included in sialylation of (glyco)proteins, was significantly decreased in leukocytes of remitted patients compared to depressed ones, thus confirming the association of dysregulated sialylation and MDD [215].

These studies indicate potential role of sialylation and branching of N-glycans in development and progression of depression or depression-like behavior in human subjects and in animal models. This pattern of N-glycosylation is also reported in other neuropsychiatric disorders such as schizophrenia [208] and PTSD [206], as well as inflammation [216] and carcinoma [200, 201, 217]. This is not surprising

since there is growing number of evidence showing that chronic inflammation lies in the biological background of various neuropsychiatric disorders, including depression, and malignant diseases [218, 219].

11.3 Conclusion

Of note, for the studies of biomarkers of MDD, no monoaminergic, neurotrophic, HPA axis or any other neurotransmitter system cannot be examined in isolation, given the extensive mutual connections between diverse neuronal pathways. Due to the complexity and heterogeneity of MDD, the search of clinically useful biomarkers of MDD is difficult. Therefore, the use of the first-episode depression with patients who were antidepressant drug-naïve, that can significantly reduce the heterogeneity of MDD, would be able to offer some highly sensitive and highly specific biomarkers of MDD [187]. The metabolomics study detected plasma metabolites from GABAergic, catecholaminergic and serotonergic pathways, and this neurometabolite signature was able to differentiate with high accuracy patients with MDD from healthy controls and also from patients with bipolar disorder [187]. This study revealed that metabolomics data related to GABAergic and catecholaminergic, and to a lesser extent serotonergic pathway, might have a real diagnostic potential for MDD [187]. Glycomic studies detected altered sialylation and branching of N-glycans in development and progression of depression; however, these changes are also associated with inflammation [211, 212]. Therefore, a neurometabolite panel consisting of plasma metabolite biomarkers (GABA, dopamine, tyramine, kynurenine) might represent clinically useful biomarkers of MDD [187].

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Chapter 12

Genetic Architecture of Depression: Where Do We Stand Now?



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Abstract The research of depression genetics has been occupied by historical candidate genes which were tested by candidate gene association studies. However, these studies were mostly not replicable. Thus, genetics of depression have remained elusive for a long time. As research moves from candidate gene association studies to GWAS, the hypothesis-free non-candidate gene association studies in genome-wide level, this trend will likely change. Despite the fact that the earlier GWAS of depression were not successful, the recent GWAS suggest robust findings for depression genetics. These altogether will catalyze a new wave of multidisciplinary research to pin down the neurobiology of depression.

Keywords Depression · Genetics · Association studies · Candidate genes · Genome-wide association study · GWAS · Depression genetics

Abbreviations

5-HTTLPR	Serotonin-transporter-linked polymorphic region
BDNF	Brain-derived neurotrophic factor
COMT	Catechol-O-methyltransferase
DSM-5	<i>Diagnostic and Statistical Manual of Mental Disorders</i> , Fifth Edition
GWAS	Genome-wide association studies
LD	Linkage disequilibrium
MAF	Minor allele frequency
MD	Major depression
PRS	Polygenic risk score

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RDoc	research domain criteria
SNP	Single-nucleotide polymorphism
TDT	Transmission disequilibrium test

12.1 Introduction

Brain information processing depends on the integration of excitatory and inhibitory circuits orchestrated by the spatially and temporally regulated gene expression that is also susceptible to environmental modulation [1]. Thus, as described by neuroplasticity, the brain is an adaptive organ in response to environment. Neuroplasticity is the basis of natural brain functions such as learning and memory [2], but neuroplasticity may also give rise to the development of diseases such as depression [3].

Depression is a brain disease characterized by either a depressed mood or anhedonia (loss of interest or pleasure) accompanied by the symptoms such as appetite or weight changes, sleep difficulties (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidality. The prevalence of depression is estimated as 6.9% in the EU [4] and 6.7% in the USA [5]. This represents about 35 million adults in the USA that will experience at least an episode of depression in their lifetime [6]. In India, 45.7 million people have been diagnosed with depression in 2017 [7]. In fact, depression is the leading cause of disability globally [8], and the World Health Organization (WHO) projected depression as the first leading cause of burden of disease by 2030 [9].

But what causes depression exactly? Is it caused by the disruption of neuroplasticity mechanisms such as maladaptation of the stress system which normally serves for the assurance of homeostasis [10]. It is well known that environmental stressors increase the risk of depression, but cumulative genetic risk factors appear to determine who is going to get depressed under stress [11]. This is not surprising as the heritability of depression has been estimated as 37% [12] suggesting the role of the genetic predisposition in the etiology of the disease.

On the other hand, genetic factors involved in the etiology of depression are not well known. This is well reflected by the lack of adequate treatments. The antidepressant treatment of depression does not benefit patients as desired, since 50% of the patients do not respond to treatment fully [13]. The lack of objective diagnostic criteria derived from biological markers is another indication of the problem. Biological markers for disease subtyping and treatment prediction are especially needed, but the attempts to identify such biomarkers remain in the theoretical level [14, 15]. At present the diagnostic criteria of depression are based on the subjective clinical signs and symptoms which are clinically reliable but lack biological validity [16]. As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) the symptoms such as depressed mood, anhedonia, fatigue, and reduced ability to concentrate represent the subjective clinical signs without any direct and objective biological link. This in turn caused a bottleneck [17] for

top-down research to pin down the genetic associations for depression. Thus, hunting for the causative genes under the lack of objective biologically defined criteria has led to the identification of many candidate genes without robust and consistent results. For example, until 2013, about 200 candidate genes had been reported as associated with depression, but only a few of them yielded statistically significant results after meta-analysis [18]. While the initiatives such as the research domain criteria (RDoc) [19] aim to resolve the diagnostic bottleneck, it is just one dimension of the enormous complexity masking the neurobiology of depression. The role of multiple common genetic variants with small effect sizes and environmental factors generate a very complex array of interactions. These altogether require attacking the problem from multiple sites and by different ways so that top-down research and bottom-up research together with *in vivo*, *in vitro*, and *in silico* methods can be integrated profitably (Fig. 12.1). Interestingly, the recent findings of

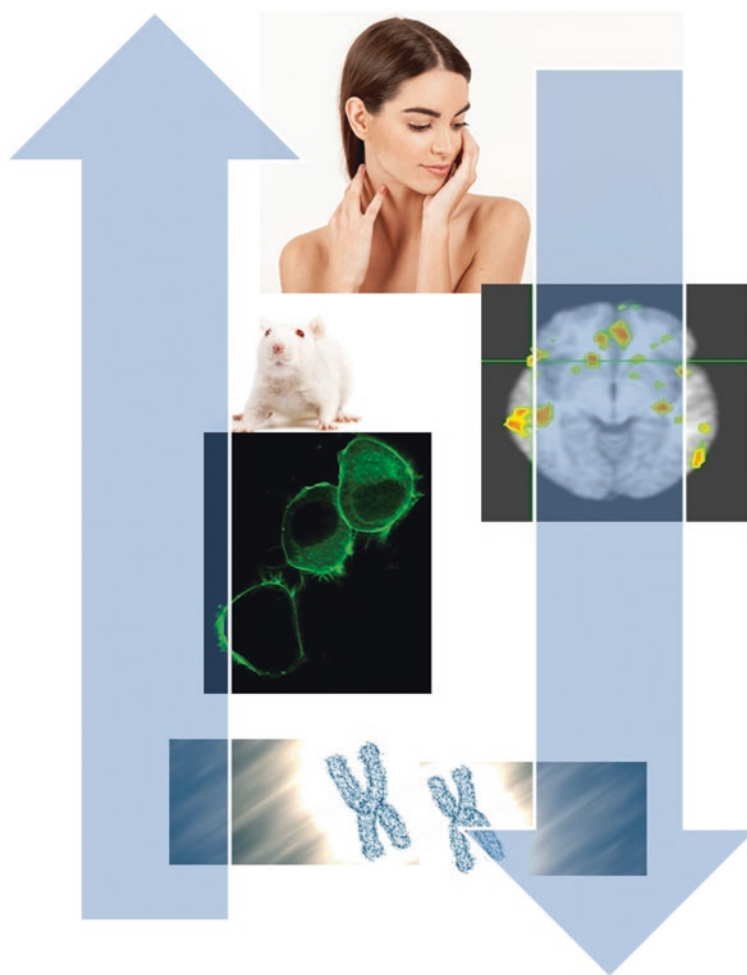


Fig. 12.1 The strength of the psychiatric genetics depends on the profitability of the multidisciplinary research both in top-down and bottom-up directions

genome-wide association studies (GWAS) have made this possible. Several genetic loci exceeding genome-wide significance levels have been found as associated with depression recently, and this has caused an increasing effort to study the function of these genetic variants in different levels of complexity. For example, SNP rs35936514 in the LHPP gene has been reported to be significantly associated with depression at a genome-wide level [20]. LHPP encodes for an enzyme known as phospholysine phosphohistidine inorganic pyrophosphate phosphatase, and it is expressed in various tissues including the brain [21]. Consequently, several studies reported this variation associated with depression during resting state activity [22], with structural and functional connectivity of hippocampal-corticolimbic neural circuitry [23]. Similarly, SIRT1 (Sirtuin 1), a protein mediating the deacetylation of transcription factors and enzymes/proteins [24–27], has been reported as significantly associated with depression at a genome-wide level [20]. SIRT1 is widely distributed in the brain with high levels in the hippocampus and cortex [28] besides its expression in metabolically relevant areas, especially in the hypothalamic arcuate; ventromedial, dorsomedial, and paraventricular nuclei; and the area postrema and the nucleus of the solitary tract in the hindbrain [29]. Thus, after decades of research with mostly unsatisfactory findings, the new studies have led to the identification of novel candidate genetic loci which represent a significant progress in search of the genetic predisposition of depression. These new studies involve the second-generation GWAS of depression designed with special emphasis on increased sample size or homogeneity. In this chapter, first we will summarize the earlier studies of depression genetics in the pre-GWAS era. Then we will introduce first- and second-generation GWAS and future prospects.

12.2 Depression Genetics: Earlier Studies

Earlier studies of depression genetics refer to pre-GWAS period of depression research. Here, historical candidate genes of depression have been identified and/or tested mostly by genetic linkage studies and association studies.

Genome regions which contain disease predisposing genes can be identified by genetic linkage analysis. In genetic epidemiology, two coronations are present: a) linkage and b) linkage disequilibrium (LD). If two genetic loci are transferred simultaneously under independent inheritance from parent to offspring more frequently than expected, the link is present. Additionally, the link of the two loci depends on the occurrence of recombination between them, if the probability is less than 50% during meiosis [30]. As if these two genetic loci are located on the same haplotype more common than expected, the LD is existing between them. LD possesses shorter regions of the genome relative to linkage. The LD between two loci declines when the recombination emerges constantly in the population, and it is conserved if these loci are at most close to each other. The linkage analysis, which provides to identify the genomic regions broadly, is promising in the genetic investigation of a trait [31].

Despite there are over ten linkage studies of depression that have been found in the literature as of 15 Jan 2020, these linkage studies of depression have not been fruitful. In a recent review which performed the partitioned LD score regression, the results did not show any significant overlaps with present GWAS in depression [32].

Besides, different approaches such as examination of pedigrees with various affected individuals to detect genomic regions inherited from a common ancestor and present in affected individuals have been tried [32]. This approach was fruitful for other biomedical conditions (despite more simple genetic architectures) but not for depression: this design was followed by several studies performed between 1998 and 2010 [33–44]; however the results did not develop as replicable.

There are several reasons why genetic linkage studies have not produced significant results. The partial success of the linkage analysis in depression is related with the small size which may preclude to detect the genes with small or modest effect. The interpretation of the findings depends especially on the power which is affected by genotyping error, also [45]. Genotyping errors can be recognized effortlessly due to the Mendelian inconsistencies in large pedigrees; however the identification of these errors would become more challenging with insufficient family data and when only affected siblings are genotyped [31].

Like linkage studies, genetic association studies have not been fruitful either [46]. There are miscellaneous designs available for examination of the associations such as cohort, cross-sectional, family studies, extreme values, and case control. The studies of genetic association might be performed as candidate gene association and genome-wide association.

The association studies of candidate gene are usually performed in several particular candidate pathways that are related with the generation of the disease, and these studies are hypothesis-driven. The selection of candidate genes is frequently made according to the previous pharmacological findings (e.g., the action sites of several antidepressant drugs, the genetic variation of the serotonin transporter). However, the candidate gene approach yielded contradictory results due to the frequent cause of false-positive results [47, 48]. In one recent candidate gene study, the researchers assessed 18 candidate genes for multiple depression phenotypes which were constantly evaluated in previous studies (e.g., gene encoding for brain-derived neurotrophic factor (BDNF), SLC6A5 gene encoding for the presynaptic glycine transporter, HTR2A encoding for the G protein-coupled receptor for serotonin, and COMT encoding for the catechol-O-methyltransferase that degrades catecholamines such as dopamine). The sample size of the study was larger than the previous counterparts, and it ranges between 62,138 and 443,264 across subsamples. The authors emphasized the probability of false-positive findings in previous studies because they were not able to show the significant contributions of these commonly studied candidate genes to liability for depression [32, 49].

In 2003, Caspi et al. conducted one specific candidate gene study to explore the “SLC6A4/HTTLPR” gene-environment association with the early stress for the estimation of depression risk [50]. However, the significant findings in this study could not be replicated in subsequent studies [51, 52]. In one of the controversial studies that performed with the same design (longitudinal birth cohort study), the

researchers focused on the childhood development and its risk for the future mental disorders. In this study, a total of 104 regression models were conducted for MD, depressive symptoms, suicidal ideation, and anxiety disorder with the usage of various life course stressors from childhood and adulthood. The results did not show any association between elevated responsivity to life stressors and “s” alleles of serotonin-transporter-linked polymorphic region (5-HTTLPR) [52]. In a similar vein, one meta-analysis ($n = 38,802$) did not corroborate the earlier findings of Caspi et al. [50] ($n = 837$). However, the candidate gene approach yielded inconsistent results in the past; currently there are more suitable ways to assure the replicable findings. According to the suggestion of the National Institute of Mental Health genomics panel, unbiased and well-powered association studies should take part instead of the candidate gene studies performed with cognitive, behavioral, or psychopathology phenotypes [53]. The candidate gene era may last longer, if only it strictly bonds with the reproducibility under high statistical power [32].

Consequently, the vast majority of genetic association studies were not able to imitate their initial affirmative findings among independent populations [46, 54]. The major reasons that contributed to this failure in case-control genetic association studies are often related with methodological flaws in data analysis and study design; however they are not well reported, specifically [55–58]. These flaws derive from the problems such as complexity of depression genetics, gene environment interactions, and phenotype bottleneck [17].

In association, the same allele (or alleles) is associated with the trait in an identical way through the entire population. On the other hand, linkage differs from association in which different alleles can be associated with the trait in distinct families. The human populations own shared pedigree, and as a consequence the genetic associations can be studied. The association study is deemed as an exceptional form of linkage study which utilizes the wider population on behalf of the extended family. The data gathered from distantly related individuals is healthier than the data from closely related individuals in linkage analysis while identifying the small effects, but extending over shorter distances in distantly related individuals requires better density of markers; therefore the advantage of linkage analyses is counter-vailed by the recombination.

The association analyses are more powerful than linkage studies in identification of small effects; however it also requests several more markers to be tested. Indeed, the association maneuvers only over short distances in the genome, and as a result the association studies cover a prominent place in mapping genetic loci originally recognized by linkage. Many genes with small effects may play a role in genetic liability to common multifaceted disorders. Owing to the lowered genotyping costs and the documentation of vast numbers of single-nucleotide polymorphisms (SNPs) throughout the genome, the association studies thoroughly partake in genetic epidemiology [59].

However, as described above, genotyping is just one part of the story. Multifactorial diseases are quite complex and have impact on various systems, as a result generating quite heterogeneous phenotypes. Accordingly, multifactorial diseases such as depression might be quite challenging for researchers because of the intrinsic phenotypic complexity [60].

The choice of disease or trait is the salient point for efficacious phenotyping. Traits might be continuous (quantitative) and discrete (dichotomous, qualitative) [61]. The quality of a genetic association study depends on the exact phenotyping of cases; therefore the case classification should be executed according to the biological markers rather than clinical observation for assuring the homogeneity of the group [61]. However, such a strategy is not possible for depression due to the lack of biological diagnostic criteria [14, 15]. Thus, approximately 200 genes have been tested, many by compound groups [62, 63]. The main problem in this field is the lack of mutual agreement between groups. In order to overcome this difficulty, a meta-analysis was run by Flint and Kendler (2014) [18], and 7 out of 26 genes were found to be significant: 5HTTP/SLC6A4, APOE, DRD4, GNB3, HTR1A, MTHFR, and SLC6A3.

In summary, genetic linkage and candidate gene association studies were not successful to produce robust genetic findings linked to etiology of depression. However, this is not surprising as understanding the biological bases of depression is very challenging and appears to be a harder task than mapping the genes of other complex disease such as schizophrenia in which more progress has been made [15, 64]. There are some characteristics of depression making its genetic analysis very difficult. Although these factors are common to majority of multifactorial diseases, their impact is higher in the case of depression. Among these, involvement of many genetic variants with small effects can be exemplified to describe the genetic complexity factor. Linkage and candidate gene studies have indicated the polygenic foundation of depression. Thousands of loci with minor effect are thought underlying the heritability of depression [32]. Majority of the meta-analyses are focused on identifying genes in schizophrenia, and in a recent review of meta-analysis, they found a significant gene effect for 50 genes (97 variants) for schizophrenia which 199 meta-analyses confirmed. In the same review, they only found 43 meta-analyses confirming 27 genes (27 variants) for depression [65]. Also, the lack of gene-dose relationships makes it even more complex.

Moreover, when the population stratification is performed in the study, the significant effect may not be related to the existent association between gene variant and disease. The differences in disease prevalence and genotype frequencies between populations may lead the observation of the effect, instead. If the observed effect is small or moderate, it is vital to consider the population stratification in regard to likelihood of enhanced or diminished associations of the trait and genetic variant. There are several methods proposed to alleviate the potential population bias such as statistical methods [66–68], use of the transmission disequilibrium test (TDT), and family-based studies [69].

Naturally, under such complexity, the typical experimental and statistical methodologies in turn become inadequate. For instance, up to 30% of misclassification may occur due to the genotyping error, and it may lead to the severe over-transmission of common alleles. Accordingly, the elevated false-positive rates may be observed in genetic association studies.

Additionally, the frequency of the predisposing allele determines the essential sample size in genetic association studies [70, 71]. The required sample size

diminishes when the frequency of the predisposing allele and effect size (allelic odds ratio) increase. Odds ratios often remain low due to the small contribution of the genetic variant of the particular event relative to the overall risk in the individual across genetic association studies of multifactorial diseases [72]. In order to reveal the significant associations of small effect sizes and rare alleles, several 10s of 1000s of subjects are required in the study. In a similar vein, more than 10,000 subjects are compulsory to detect an odds ratio of 1.1, even with common alleles present in up to 20% in controls. Therefore, the studies that explore the negative findings should have sufficient power to support their claims. The studies with low power are not likely to be published in numerous journals when they find negative results [61].

12.3 Genome-Wide Association Studies

The genome-wide association studies (GWAS) strive to isolate the associations between traits and genetic variants within populations. GWAS evaluate the differences in allele frequencies among disease and control groups at millions of common SNPs across the genome. These differences may signify loci which are transmitted in LD with a causative polymorphism or may be functionally related to the disease. The association between a trait and a genetic variant at a genomic locus may not be straightforwardly illuminating the target gene or the mechanism whereby the variant is linked with phenotypic alterations; therefore the pathway from GWAS to biology is often sophisticated. Nevertheless, novel molecular technologies, innovative analytical procedures, and different types of data have provided opportunities to shed light on this track. Now, GWAS have also been utilized for identifying the relative role of environment and genes in disease risk estimation, aiding in risk prediction (allowance of personalized treatment), and examining the differences in natural selection and population [73]. There are plenty of conditions needed to be considered in order to estimate the statistical power while exploring the associations between a trait and DNA variants: a) the size of the sample, b) the frequency of unknown causal genetic variants which segregate in the population, c) the distribution of effect sizes of unknown causal genetic variants, and d) the LD between unknown causal variants and observed genotyped DNA variants.

Hence, the success rate of a GWAS for a disease or a specific trait stands on five anchors: 1) the number of loci affecting the segregation of the traits in population, 2) the combined distribution of allele frequency and effect size at loci (genetic architecture), 3) the panel of genome-wide variants utilized in GWAS, 4) the experimental sample size, and 5) the heterogeneity of the evaluated disease or the trait (the capability of accurate diagnosis or assessment and the biology of the trait are critical) [73].

The knowledge of the genetic architecture of a disease or a specific trait is the key step to perform optimal experiments for identification of particular variants. Before GWAS, there were many attempts done by the theoretical studies with regard to the probable association between trait loci and allele frequency; however such limited data were gathered [73]. The individual genome variations can emerge from

either missing pieces of DNA (deletion), excess pieces of DNA (insertion), or single-nucleotide mutations. If these mutations are represented in more than 1% of the population, they are acknowledged as SNP [74].

GWAS have been expedited by the development of relatively inexpensive, commonly used SNP arrays which contain 200,000 to more than 2,000,000 SNPs. Recently, common variants with $\geq 1\%$ minor allele frequency (MAF) and rare variants with $\text{MAF} < 1\%$ were defined. GWAS assess the genetic variants which are widespread in the population, and these variants typically comprise of MAF with $\geq 1\%$.

GWAS cannot be considered as sole array-based assessment of common variants; particularly whole-genome sequencing (WGS) studies also partake as GWAS. The differences between GWAS (based on SNP arrays) and WGS are a) the variants' MAF spectrum, b) the concentration of coverage of variation in the genome, and c) the cost of the experiment [73].

Generally, LD between genetic variants is usually estimated as squared correlation (r^2). The linear nature of this measurement provides better estimation in the sample size that is essential for revealing the association between unobserved causal variant and observed genotyped variant. GWAS (based on SNP arrays) cannot identify the associations sufficiently due to the sample size considerations, rare causal variants, and small LD r^2 estimations (large r^2 is achieved only if matching of the allele frequencies at the two loci is present). The lost information due to the insufficient LD between unobserved causal variants and unobserved genetic variants may be avoided by statistical imputation [75–77].

The statistical imputation is empowered by the haplotypes observed from a totally sequenced reference panel and multiple observed SNPs which predict the genotypes of unobserved genetic variants [73]. WGS can detect associations of variants that have a frequency of 1/1000 with the aid of statistical imputation; however for ultra-rare variants which have a frequency of 1/100,000, WGS requires large effect size of polymorphisms (mutations) [78]. For instance, in such rare variants with an effect size of 1 phenotypic standard deviation (SD) unit (about 5 BMI units or 7 cm for height), more than one million samples are mandatory (i.e., an allelic count of ten). The effects sizes of $\beta = 0.01$, 0.1, and 1 phenotypic SD correspond to odds ratios of 1.02, 1.2, and 4, respectively, in case-control studies for the disease if the assumption of population prevalence and allele frequency are 0.01 or lower [79]. The family-based experimental design is recommended for identification of monogenic traits, if the certain families have the observable segregation of rare variants with exact large effects. Furthermore, if the GWAS are not accessible, WES and WGS studies (other genome-wide scans) provide the evaluation of the burden of the rare variants across common functional units (e.g., genes) [73].

Many complex traits are defined across a wide range of domains by GWAS results: brain imaging phenotypes, quantitative traits (risk factors), common diseases, behavioral and social traits (e.g., educational access, subjective well-being), and genomic measures (e.g., gene expression and DNA methylation). Approximately, 10,000 associations were reported between complex traits and genetic variants. The defined associations were statistically significant with p value threshold of 5×10^{-8}

[80]. GWAS have demonstrated replicable associations, both within and between populations with the assumption of adequate sample sizes [81, 82].

The data obtained from GWAS shed light on novel methods in analysis: a) to identify new gene loci and new variants based on GWAS summary statistics [83–85], b) to better model the affiliation and population structure between individuals in a sample through association analyses [86–92], c) to infer the causality [93–95], and d) to estimate and to subdivide genetic (co)variance [96, 97].

Besides, the proportion of total additive genetic variation due to segregating variants in the population tagged by imputed and genotyped SNPs can be predicted by GWAS. This prediction of “SNP heritability” is enlightening when the unknown genetic architecture of the trait is considered. SNP heritability has warranted to guide the design of experiments in terms of efficacy to identify the novel trait locus associations based on empirical data (i.e., expanding sample size of GWAS).

Classical prediction of total narrow-sense heritability (anticipated from phenotypic records of samples from family members) seizes the count of additive genetic variance in the population irrespective of effect size and common distribution of allele frequency [98]. On the contrary, SNP heritability (calculated upon minute genetic relationships from unrelated individuals) captures only the ratio of additive genetic variance due to LD between the unknown causal variants and imputed SNPs.

Estimation and subdividing of additive genetic variation for quantitative traits and liability to disease have recommended that the imputed and joint genotyped SNPs can tag one-third to two-thirds of genetic variation at causal variants through LD [74, 99]. It is challenging to indicate the contribution of causal variants with frequencies less than 1% to the total additive genetic variation. The imputed genotype data for height emphasized that the variants with $MAF < 10\%$ explained more additive genetic variation than expected with an evolutionary neutral model which is consistent with purifying selection of the height-associated loci [100]. After the determination of additive genetic variance from WGS data in large samples is achieved, the involvement of observed low-frequency and rare variants can be estimated accurately [73].

Theoretical and empirical observations imply a place for non-additive genetic variation; however, the attempts with GWAS data were ineffective to detect epistasis. The potential reasons are aligned as follows: a) limited evidence regarding the representation of large fraction by non-additive genetic variation in total genetic variation, thus larger sample sizes are required relative to sizes for main effects, and b) imperfect LD between causal variants and genotyped SNPs induces more loss of information for interactions than main effects (e.g., information loss for additive effects is proportional to the LD r^2 , but r^4 is for additive-additive interaction and dominance effects) [73].

GWAS data was used to generate genetic predictors of complex traits and disease by predicting the effect size at multiple loci in a discovery sample and operating the estimated SNP effects among independent samples. Additionally, they have formed polygenic risk score (PRS) per individual [101, 102].

The accuracy of prediction is mostly affected by the size of discovery sample which is used for appraising the effects of individual variants. PRSs have been

utilized broadly to construct novel discoveries and state-of-the-art experimental designs; however they are not used for the disease risk estimation of healthy individuals in clinical settings.

PRS is not the most suitable way to inform an individual in regard to disease risk; however PRS can elucidate adequate proportion of variation (1–15% at present for highly polygenic traits without a major gene) to discriminate the groups such as lowest and highest risk. PRS can correlate phenotypes in a cohort or sample with the genetic prediction of another trait that is also advantageous for identifying new trait associations.

When the discovery sample is entirely independent from the new sample, this design selection becomes more effective, because an identified association between a genetic predictor and a complex trait from the discovery sample must be related to the genetic factors; besides no environmental factors are shared [73]. One or more causal variants which are accountable for the observed GWAS signals can be identified by fine-mapping of SNP-trait associations. The LD and experimental sample size could limit the fine-mapping merely by statistical association. In order to distinguish a variant in LD and a causal variant, the statistical evidence should be in proportion to $n(1-r^2)$. Fine-mapping is also limited by the imputation error, if causal variants do not exist in the data (e.g., not genotyped). A little number of variants which are in tremendously high LD might be classified as conceivable set of variants that retain higher odds of holding causal variants after the progress of statistical power in fine-mapping by the availability of the data belongs to the large sample sizes in WGS and SNP-array-based GWAS. Preceding knowledge in regard to location, neighboring DNA motif(s), and potential function of specific variants could be exploited to diminish the set of statistical candidates [103, 104]. The integration of disease/trait GWAS results and tissue gene expression is beneficial for the bioinformatics and statistical fields [105–107]. The anticipated acceleration in GWAS data on cell-specific and tissue gene expression may expedite the resolution of fine-mapping [73].

For the present one of the GWAS analysis characteristics is entirely exclude individuals outside ethnicity margins based on SD unit's principal-component dimensions. Nonetheless, by the aid of larger sample sizes, the mixed ethnicity can be utilized as an advantage. The LD structure and dissimilar allele frequencies across populations may assist fine-mapping of causal variants. Novel methods have been discovered to overcome the data problems [85, 108]; therefore this field can become one of the productive areas in discovery and method development in the following years [73].

12.3.1 Early GWAS of Depression

GWAS are characteristically executed in two phases: 1) the entire genome is checked (discovery phase), and 2) a subset of SNPs is assessed in an independent cohort (replication phase). Several studies indicated the discovery and replication findings separately; on the other hand, some studies merge the p values of the

studies (including the discovery sample) in a meta-analysis. The GWAS studies were not promising for MD, initially [109], and the previous studies have acknowledged the irrelevant findings (no SNPs exceed the genome-wide significance threshold) even with the comparable sample sizes to other psychiatric disorders [18, 110]. In a similar vein, CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium declared no significant genetic associations in a GWAS for depressive symptoms conducted with around 30.000 people [109]. Nevertheless, one genome-wide association for MD was denoted in recent meta-analyses: a marker within a gene desert on chromosome 12 [111]. The researchers emphasized the prominence of this fundamental finding on chromosome 12, and they also recommended not to disregard the null findings.

The common variation in the genome is assessed by the GWAS, and it requires more than 5% variant frequency and a genome-wide significance threshold of 5×10^{-8} [112].

It is noteworthy that the population history affects the level of LD, and consequently the genotyping arrays catching genomic information are population specific, partly. Therefore, the LD is likely to increase as the population recedes away from Africa [113]. This finding confirms the hypothesis that migrated population from Africa underwent severe blockages on the way colonizing the rest of the world [114, 115]. GWAS with standard approach do not function decently across African populations [116].

The failure in genotyping the causative variants or markers (adequately close ones) may be one of the difficulties for GWAS in MD. Among non-African populations, the blocks of linkage disequilibrium provide the efficacious GWAS which identifies a large set of significant common variants (odds ratio > 1.2) that contributes to complex traits. For instance, in one GWAS, Affymetrix 500 K genotyping array was utilized with the entire variants in HapMap [117]. This relatively restricted array (existing platforms probe millions of variants) yielded an odds ratio of 1.2 with 82% power ($n = 9000$) to identify a locus, when compared to 88% with the complete set of SNPs [18]. Moreover, one of the largest discovery sample size consisted of 9240 cases in GWAS for MD [118].

Another clarification for the difficulties of GWAS in MD is the underpowered nature to discover the causative loci [119]. GWAS performs adequately in common variants; however, large sample sizes are needed to reach sufficient power to detect variants of small effect (odds ratio < 1.2). The relationship between effect size and sample size is non-linear among common variants. Approximately sample sizes with tens of thousands are mandatory to identify the loci with the odds ratio ≤ 1.1 (based on disease prevalence, the assumption of MD prevalence is set to 10%). One large sample-sized GWAS for MD recruited 9519 controls and 9240 cases. The power obtained from the sample was around 90% to identify loci with the odds ratio of 1.2, and it isolates the effects at more than 93% of whole acknowledged common variants [118] (2013b). One discovery sample consists of 366 controls, and 353 cases were used to discover the relationship between a marker nearby SLC6A15 gene and MD at genome-wide significance [120]. Although this finding is immense, without any replication in the following years, it may be considered as false positive and ambiguous.

12.3.2 *Recent GWAS of Depression*

There has been an expansion in GWAS studies of depression in recent years. Although a mega-analysis [118] has failed to show any replicated variants associated with MD and a meta-analysis that involves depressive symptoms also failed to find replicated variants [121], following studies begin to change this course. CONVERGE consortium was first to show replicable genetic variants for depression. They discovered two significant loci associated with recurrent, severe MD [122]. Later on Hyde et al., using the data from 23andMe, Inc., the personal genetics company, have found 15 associated loci [123]. And recently by using UK Biobank, Howard et al. have found 17 variants that were associated across three depression phenotypes [124]. And a meta-analysis conducted by Wray et al. (PGC) has showed 44 loci that were significantly associated with depression phenotypes [125]. Another recent promising meta-analysis has detected 102 common genetic variants related with MD [124].

One study operated the low-pass sequencing data implied a role of genetic variation on mitochondrial DNA; however this finding was not replicated [20]. The sequencing studies of type 2 diabetes mellitus and schizophrenia emphasized the importance of large sample sizes which ensures the significant findings in this analysis (e.g., entire exome data of 25,000 cases with <10 significant associations each) [126]. The substantial role of structural variation is exhibited in schizophrenia; however, this genetic variation is not well defined in MD. The findings from the current studies demonstrated that the variants with rare copies do not have a significant role in MD relative to other psychiatric disorders (e.g., schizophrenia) [127]. On the other hand, cases have more common rare copy variants than controls. A recent meta-analysis including four cohorts with a total of 6626 controls and 5780 cases revealed that amplified number of short deletions lead to rare copy number variants which is predisposing for MD [128]. It was proposed that rare copy number variants alter the gene expression, and this distortion intensifies the MD risk [32].

By expansion of sample sizes, the total count of related variants can increase such as in other disorders; however, currently these variants occupy a narrow genetic contribution in MD. The polygenic nature of MD limits the value of longitudinal follow-up studies which probe for specific variants, because the risk of MD is affected mildly by each variant. Nevertheless, GWAS may be more effective to analyze the effects of variant groups; besides more advanced technology can be utilized to explore genome-wide results [129]. Table 12.1 shows a summary of the results of the recent GWAS data together with relevant information such as the genes in the closest proximity (for intergenic variants) and their functional expression. Our genetic knowledge of MD is enriched by the evaluation of risk at individual level, estimation of heritability, enlightening the associations with treatment, identifying pleiotropy, and identification of the pathways and/or genes noticeable in disease [32].

The heritability of MD was estimated as 8.9% (95% confidence interval 8.3–9.5%), and the heritability in twins rises up to 37% in a genome-wide study

Table 12.1 A summary of the recent depression GWAS findings and their genomic context, expression, and function

SNP	Chromosome location or location in bp	Gene context	Function	Expression or localization
rs12415800 [20]	12q21.31	Sirtuin 1 SIRT1	Deacetylation of transcription factors and enzymes/proteins involved in diverse functions including metabolism [24–27, 132]	Widely distributed in the brain with high levels in the hippocampus and cortex [28] Expressed in metabolically relevant sites, especially in the hypothalamic arcuate; ventromedial, dorsomedial, and paraventricular nuclei; and the area postrema and the nucleus of the solitary tract in the hindbrain [29]
rs35936514 [20]	10:126244970	LHPP (phospholysine phosphohistidine inorganic pyrophosphate phosphatase)	Increased amplitudes of low-frequency fluctuations (ALFF) in the left superior temporal gyrus and occipital cortex, lowered ALFF in bilateral lingual gyri [22] T allele-carrier group showed significantly higher fractional anisotropy (FA) values in the fornix as well as increased functional connectivity from the hippocampus to the rostral part of the anterior cingulate cortex (rACC) [23]	Effects found in the bilateral lingual gyri, bilateral dorsal lateral prefrontal cortex (dlPFC), and left medial prefrontal cortex (mPFC) [22], involvement of the structural and functional hippocampal-corticolimbic neural system [23]

(continued)

Table 12.1 (continued)

SNP	Chromosome location or location in bp	Gene context	Function	Expression or localization
rs7973260 [133]	12q 118,375,486	KSR2 (kinase Suppressor of ras 2)	Association with depressive symptoms [133] Increased risk of metabolic syndrome (MetS), severe hypertriglyceridemia (HTG), and diabetes, regulates multiple signaling pathways by binding kinases such as Raf and AMP-activated protein kinase [134]	Expressed in COS-7 and 293 T cells, detectable at neuronal cells, skeletal muscle, liver, and adipose tissue [135]
rs62100776 [133]	18q 50,754,633	DCC (deleted in colorectal cancer)	Encodes a transmembrane receptor involved in axon guidance that responds to netrin-1 [109] Affect the adolescent expansion of mesocorticolimbic dopamine pathways and vulnerability to putative mesocorticolimbic-related psychiatric disorders [136]	Expressed in dopamine cell bodies and terminal regions, including the SN, VTA, striatum, hippocampus, and cerebral cortex [136]
rs10514299 [123] rs454214 [123]	87663610 88003403	TMEM161B (transmembrane Protein 161B) MEF2C (myocyte enhancer factor 2C)	Plays a role in synaptic Learning and memory [109] Shows decreased levels of repressive dimethyl histone H3 Lys9/Lys27 methylation in response to social isolation [123] Influence on striatal BOLD responses during reward/loss anticipation in alcohol dependence [137] MEF2C involved in brain development that has been associated with epilepsy, intellectual disability, and hyperkinesis [137]	Expression on putamen during reward processing in alcohol dependence [137]
rs2422321 [123] *rs11209948 [123]	72811904 73293393	NEGR1 (neuronal growth regulator 1)	Associated with major depression [109, 123, 138]	Expressed in brain tissues [123]

(continued)

Table 12.1 (continued)

SNP	Chromosome location or location in bp	Gene context	Function	Expression or localization
rs1518395 [138]	2q 58208074	VRK2 (vaccinia-related kinase 2)	Affect neuronal proliferation and migration via interacting with multiple essential signaling pathways [139]	Potential roles in the central nervous system, involved in multiple other congenital deficits related to the malfunction of neurodevelopment [139]
rs2179744 [138]	22q 41621714	L3MBTL2	Associated with major depression [123] Alzheimer's disease [140], schizophrenia [141], and neuroticism [142] Role in neural development [140] Its function in neural system remained unclear [140]	Highly expressed in neuron [140]
rs301806 [138] rs159963 [125]	1q 8482078 1q 8.390–8.895 (associations could not be assigned to RERE)	RERE (the arginine-glutamic acid dipeptide (RE) repeats gene)	Associated with white matter alterations [143]	Found in the anterior thalamic radiation and cingulum, corticospinal tract, inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, right superior longitudinal fasciculus, uncinate fasciculus, forceps major, and forceps minor [143]

(continued)

Table 12.1 (continued)

SNP	Chromosome location or location in bp	Gene context	Function	Expression or localization
rs10786831 [138]	10q 106614571	SORCS3 (sortilin-related VPS10 domain containing receptor 3)	Associated with major depression [109, 123, 138] Altered synaptic plasticity leading defects in spatial learning and modulation of fear memory, indicating involvement of SORCS3 in anxiety-related hippocampal activities and long-term depression [144]	Highly expressed in the CA1 region of the hippocampus, localizes to the postsynaptic density [144]
rs12552 [138]	13q 53625781	OLFM4 (olfactomedin 4)	Associated with major depression [109, 123, 138], increased reporting of panic attacks, use of medication to treat mental health problems, prescription sleep aids, and pain medication, BMI greater than 27, earlier age-of-onset of MDD, and associated with lower continuous age of onset [123]	Expressed in the brain, including amygdala and medial temporal lobe [123]
rs802523 [138]	15q 37648402	MEIS2-TMCO5A (Meis homeobox 2-transmembrane and coiled-coil domains 5A)	Associated with major depression [109, 123, 138] MEIS2; role in adult olfactory bulb neurogenesis [145], cleft palate,cardiac septal defects, and intellectual disability [146] TMCO5A; involved in the process of spermiogenesis [147]	MEIS2, expressed in neuroblasts of the subventricular zone and rostral migratory stream and in some of the olfactory bulb interneurons [145] TMCO5A, found to be distributed in the endoplasmic reticulum-nuclear membrane of spermatid cells as a membrane-associated protein ²⁷

(continued)

Table 12.1 (continued)

SNP	Chromosome location or location in bp	Gene context	Function	Expression or localization
rs1656369 [138]	3q 158280085	<i>RSRC1-MLF1</i> (arginine and serine-rich coiled-coil 1-myeloid leukemia factor 1)	Associated with major depression [109, 123, 125, 138, 148] and schizophrenia [124] (differential activation of the dorsolateral prefrontal cortex in working memory tasks measured by functional MRI) [149] <i>RSRC1</i> ; involved in both constitutive and alternative mRNA splicing [149]	Ubiquitously expressed [149]
rs2125716 [138]	12q 84941429	<i>SLC6A15</i> (solute carrier family 6 member 15)	A neuron-specific neutral amino acid transporter [120] Associated with a downregulation of the expression of this gene in the hippocampus [120], alterations in hippocampal volume and neuronal integrity [120], altering neuronal circuits related to the major depression [120]	Expression in the hippocampus [120]
rs7044150 [138]	9q 2982931	<i>KIAA0020-RFX3</i> (pumilio RNA binding family member 3-regulatory factor X3)	Associated with major depression [109, 123, 138, 143, 150] <i>RFX3</i> ; regulates the expression of genes required for the growth and function of cilia [151]; regulates the expression of <i>D2lic</i> , a gene that is implicated in intraflagellar transport [152] <i>KIAA0020</i> ; regulate mRNA stability and translation [153]	<i>RFX3</i> , expressed in ciliated cells of the node [152] <i>KIAA0020</i> , localized to multiple foci within the nucleus of HeLa and HEK293T cells [153]

(continued)

Table 12.1 (continued)

SNP	Chromosome location or location in bp	Gene context	Function	Expression or localization
rs6476606 [138]	9q 37005561	PAX5 (paired box 5)	Associated with major depression [109, 123, 138] Encodes the B-cell lineage specific activator protein that is expressed at early, but not late, stages of B-cell differentiation, role in neural development and spermatogenesis [154]	Detected in developing the central nervous system and testis [154]
rs1475120 [123]	6q 105389953	HACE1-LIN28B (HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1, lin-28 homolog B)	HACE1; responsible for Rac1 degradation following activation by a migration stimulus [155], role on cell migration independently of growth factor stimulation [155] LIN28B; association with increased expression of several genes in the hypothalamus and the pituitary in humans, including estrogen receptor 1 (ESR1) and proopiomelanocortin (POMC) [156]	LIN28B, highly expressed in the testis, fetal liver, placenta, and primary human tumors and cancer cell lines [157] HACE1, expressed in natural killer (NK) cells [158]

[124]. Moreover, it was assumed to increase with larger sample sizes in GWAS. Currently, the PRS which represents the rough genetic liability to MD can be computed for each individual with the aid of genome-wide studies. PRS reveals the total number of risk alleles in an individual and gauges each variant according to the effect size (log (odds ratio)). The genome-wide substantial loci may limit the PRS; however the usage of an independent set of genome-wide loci (~100 k variants) can decrease the p value threshold, and this may result in more accurate prediction of PRS. PRS are acknowledged to be higher among cases with MD relative to controls due to the greater number of risk alleles. PRS discriminates case-control status (2% accountability of variants in case-control status for MD); moreover it provides insight for the genetic contribution of variants to disease subtypes (PRS is greater for recurrent depression relative to early onset or single-episode depression). Additionally, PRS is beneficial to determine the genetic overlap between disorders. Therefore, PRS for schizophrenia has the potential for predicting MD. PRS reforms a large genotype matrix into a single variable for an individual. PRS reflects a statistical significance, but the score can be attributed to a minor fragment of the disease and/or subtype risk (e.g., PRS in top decile exhibits 2.5-fold increased risk for MD relative to PRS in the lowest decile) [125]. It is acknowledged that the genetic

component of MD demonstrated in existing studies is more beneficial for exploration of the disorder-level characteristics than the determination of disease risk level [32]. To improve our knowledge in MD genetics like other mental disorders such as schizophrenia, GWAS with gross sample sizes are essential. The future challenge is to display molecular mechanisms mediated by GWAS loci and to transform this information as therapeutic targets and novel biomarkers. The previous studies shed light on the genetic variants of MD; now there is an opportunity that arises to benefit from these biological findings as prospective clinical tools [109].

12.4 Conclusion

Recent GWAS data of depression caused some progress in our understanding of the genetic architecture of depression and provide novel insights for future research. The variants found in the intergenic or intronic regions are one prominent characteristic of the findings of the GWAS of depression. This will in turn require an in-depth analysis of these variants by means of biological pathways within the specific brain circuitry. Besides, gene-gene and gene-environment interactions will have to be explored in this specific context. Another characteristic is that there is a significant overlap observed in the genetic architecture of depression and other psychiatric disorders such as bipolar disorder and schizophrenia [130] (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). This suggests some specific effects such as pleiotropic effects and neurodevelopmental mechanisms that may underlie the neurobiology of depression. As these characteristics refine the genetic architecture of depression, future research faces new challenges as explained above in addition to old ones such as “missing heritability” [131]. Thus, we are still far from a detailed knowledge of the genetic architecture of depression which underlies the neurobiology of this disease, but recent progress caused an excitement to take these challenges into priority.

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Chapter 13

Pharmacogenetic/Pharmacogenomic Tests for Treatment Prediction in Depression



Farhana Islam, Ilona Gorbovskaya, and Daniel J. Müller

Abstract Genetic factors play a significant but complex role in antidepressant (AD) response and tolerability. During recent years, there is growing enthusiasm in the promise of pharmacogenetic/pharmacogenomic (PGx) tools for optimizing and personalizing treatment outcomes for patients with major depressive disorder (MDD). The influence of pharmacokinetic and pharmacodynamic genes on response and tolerability has been investigated, including those encoding the cytochrome P450 superfamily, P-glycoprotein, monoaminergic transporters and receptors, intracellular signal transduction pathways, and the stress hormone system. Genome-wide association studies are also identifying new genetic variants associated with AD response phenotypes, which, combined with methods such as polygenic risk scores (PRS), is opening up new avenues for novel personalized treatment approaches for MDD. This chapter describes the basic concepts in PGx of AD response, reviews the major pharmacokinetic and pharmacodynamic genes involved in AD outcome, discusses PRS as a promising approach for predicting AD efficacy and tolerability, and addresses key challenges to the development and application of PGx tests.

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13.1 Introduction

Antidepressant (AD) medications have become one of the primary means of treating major depressive disorder (MDD) since its clinical introduction in the 1950s [1]. Despite the current availability of more than 40 different AD drugs on the market, response to these medications remains highly variable: two-thirds of patients continue to experience depressive symptoms with first-line pharmacological treatment, one-third of patients fail to show remission after four treatment attempts, and 10–20% of patients remain refractory despite multiple drug therapies [2, 3]. In addition to variability in treatment response, ADs are associated with interindividual differences in tolerability contributing to occurrences of adverse drug events.

Presently, the selection of pharmacological treatments for patients diagnosed with MDD is based on a trial-and-error process taking into consideration both the clinician's preference and evidence-based guidelines on treating the “average” patient [4, 5]. This “one-size-fits-all” heuristic approach results in a substantial proportion of patients experiencing continued suffering due to little to no significant changes in their depressive symptomatology and/or serious side effects contributing to noncompliance and premature termination of their pharmacological treatment [6]. Therefore, personalizing therapy by identifying the most effective medication for each patient and being able to predict treatment resistance and drug-related adverse events would dramatically improve the quality of care for patients with MDD [2] (Fig. 13.1).

Since an estimated 42% of variance in AD response is attributable to genetic polymorphisms [7], molecular genetics is a promising avenue to explain and predict interindividual differences in therapeutic response and the emergence of side effects. Studies have shown that AD response is similar among family members [7], and patients subgrouped by genetic variants demonstrate similar patterns of improvements in depressive symptoms [8], suggesting a genetic component contributing to AD outcome. Pharmacogenetics and pharmacogenomics are the study of the contributions of genetic variability to phenotypes of drug response, which have become widely recognized as promising tools to guide efforts for the development of new ADs and for individualizing treatment plans using existing pharmacotherapy options with the ultimate goal of optimizing care for MDD patients [9, 10].

Therefore, the present chapter aims to provide a comprehensive review of (1) key concepts, definitions, and principles of pharmacogenetics/pharmacogenomics of ADs; (2) important genes influencing AD metabolism, bioavailability, and excretion (pharmacokinetics) and its effects at the site of action (pharmacodynamics);

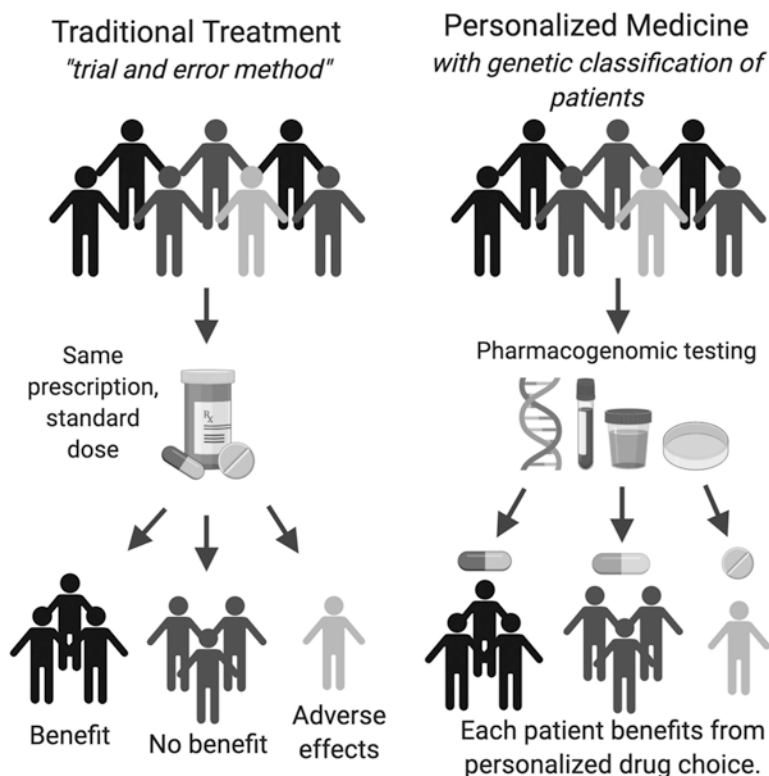


Fig. 13.1 Traditional “one-size-fits-all” versus the precision medicine approach of AD treatment selection. (Image created using BioRender)

(3) polygenic risk scores (PRS) as a promising approach for predicting AD efficacy and tolerability; and (4) key challenges of incorporating pharmacogenetic/pharmacogenomic tests into clinical practice to improve patient outcomes.

13.2 Key Concepts, Definitions, and Principles of Pharmacogenetics/Pharmacogenomics

13.2.1 Objectives of Pharmacogenetics/Pharmacogenomics

The term “pharmacogenetics” was coined by Friedrich Vogel in 1959 to define a branch of science that combines genetics and pharmacology to study inherited differences in drug response [11]. The term “pharmacogenomics” was introduced in

the late 1990s just prior to completion of the first draft of the human genome and realization of the polymorphic nature of many genes [12]. Although pharmacogenetics usually refers to the contributions of one gene to drug response, while pharmacogenomics encompasses all genes in the genome associated with variations in drug response, both terms are often used interchangeably. Both have the objective of identifying gene variants associated with treatment response to pharmacological agents with the ultimate goal of applying these tools to improve treatment outcomes. From this point forward, both pharmacogenetics and pharmacogenomics will be referred to in the chapter using the shorthand, PGx.

13.2.2 Single-Nucleotide Polymorphisms (SNPs)

Most commonly studied in PGx studies are SNPs (single-nucleotide polymorphisms), which are single base-pair substitutions that are the most common form of variation in humans present at a level of more than 1% of the population. When the nucleotide substitution occurs within the coding region of the gene, it can be a synonymous SNP, which has no significant effects on the protein, or a non-synonymous SNP, which leads to changes in amino acid residues of the protein sequence and contributes to altered protein function consequently giving rise to an altered phenotype. SNPs on non-coding regions are not on protein encoding regions of the gene and may be found on the gene's regulatory sequences; these SNPs will not necessarily change the protein function, but may influence its expression and splicing, among other regulatory factors. PGx studies attempt to identify functionally relevant SNPs or other genetic variation, such as copy number variants, that may contribute to drug response or adverse events. If clinically relevant, such information between SNPs and treatment outcome can be translated into pharmacogenomic tests.

13.2.3 Candidate Gene and Genome-Wide Association Studies (GWAS)

PGx studies use candidate gene or genome-wide approaches to identify gene variants associated with drug response and toxicity. The candidate or targeted gene approach is hypothesis driven for their known or suspected involvement in drug efficacy and toxicity with the aim of typically identifying a small number (i.e., less than 50) of genetic polymorphisms. Genes can encode proteins that influence “pharmacokinetic” factors, including drug metabolism and distribution, and “pharmacodynamic” factors, such as the interactions of the drug at the target organ and its effects on downstream signalling. The genome-wide screen approach is hypothesis-free and discovery driven for the identification and confirmation of gene variants that may contribute to variability in drug response and adverse drug reactions.

13.2.4 Identification of Patient Phenotypic Subgroups for the Application of Pharmacogenetic/Pharmacogenomic Tools

PGx approaches can be used to identify subgroups of patients who are genetically predisposed for high drug efficacy and those who are at risk for developing adverse reactions to certain therapies. Such studies can identify genetic subpopulations through, for instance, revealing a clear difference in drug response in heterozygous and homozygous individuals of a given SNP, which can aid treatment and dosage selection and contribute to drug development [13]. Currently, well-established examples of genetically determined variability in drug response mostly involve SNPs that are common in a population, have functional impact, and have established clinical validity [12].

A wide variety of nomenclature systems have been developed to describe genes associated with drug response [14]. The “star” (*) nomenclature arose in an effort to standardize annotations for genetic polymorphisms in cytochrome P450 genes, which was then adopted by pharmacogeneticists to describe gene variants underlying variability in drug response [12, 14]. In most cases, *1 is the default reference sequence (wild-type or fully functional) against which other polymorphic sites (e.g., *2 or *3) are compared [15]. However, *1 is not necessarily the most common allele in all populations, although it may be common in the subpopulation within which it was originally studied [15]. Some star alleles can include multiple variant alleles existing on the same chromosome that demonstrate a functional effect on the protein (e.g., *CYP2D6**17), which poses a challenge when distinguishing this allele from those carrying only one of the SNPs [12]. As the understanding and discovery of the number of variants in important pharmacogenes increase, alternate variant nomenclature, such as the Reference SNP (rs) nomenclature, is becoming more commonly used [15]. The rs ID number corresponds to a variant in a specific genomic location and is available for the majority of commonly studied SNPs [15]. However, this nomenclature system is also not without issues. In some cases, SNPs described by rs IDs can refer to more than one SNP and may result in multiple haplotype designations [15]. A more standardized and streamlined system for reporting and annotating pharmacogenetic variants remains to be developed for accelerating the implementation of PGx tools in clinical practice.

The pharmacogenetic phenotype, referring to the activity or function of enzymes, transporters, or drug targets, can be predicted by testing pharmacogene variants using *in vitro* or *in vivo* methods [15]. Further, as a supplement to the functional, benchtop analyses of these gene variants, clinical studies are used to validate phenotypic effects of pharmacogenes within populations. Since the star nomenclature system is a very limited method of annotating phenotypic effects of corresponding alleles, a standard set of definitions of pharmacogenetic phenotypes have been adopted within the field for pharmacokinetic genes including normal (or extensive) metabolizers (NMs or EMs) carrying functional alleles, intermediate metabolizers (IMs) carrying one loss-of-function allele, poor metabolizers (PMs) carrying two

loss-of-function alleles, and ultrarapid metabolizers (UMs) carrying gain-of-function alleles or duplications of normal alleles [12].

13.3 Genes Influencing Antidepressant Pharmacokinetics

A drug's pharmacokinetics determines its absorption, distribution, metabolism (i.e., biotransformation), and elimination over time. Variations in pharmacokinetic genes can contribute to large interindividual differences in AD concentrations in plasma or serum and possibly contribute to variations in therapeutic response to the medication [16, 17]. AD concentrations in plasma measured through chemical assay methods, such as gas-liquid chromatography (GLC) and high-performance liquid chromatography (HPLC), have been used in PGx studies to examine the contribution of pharmacokinetic genes on the relationship between interindividual differences in AD plasma levels and therapeutic response.

13.3.1 Cytochrome P450 Enzymes

Gene variants encoding the cytochrome (CYP) P450 hepatic enzymes that mediate the phase I metabolism of some ADs have been shown to significantly influence clinical efficacy [18]. CYP enzymes are involved in the biotransformation of a medication, in some cases into active metabolites, by aromatic and side-chain hydroxylation occurring predominantly in the liver (although some of these enzymes are also expressed in other tissues). Genetic variability in CYP enzymes can lead to increased, decreased, or absent CYP enzyme function, which influences plasma concentrations of the drug and its metabolite. In turn, this enzymatic variation can impact the effectiveness of drug therapy, with adverse effects occurring at high concentrations and no clinical benefits experienced with lower to absent concentrations, especially if the drug has a narrow therapeutic index [19]. Phenotyping CYP polymorphisms is conducted using *in vitro* methods, including liver microsomal preparations, or *in vivo* studies, including research subjects or patients. Individuals are categorized by expected phenotypes as described in Section 2.4. Out of the 57 human CYP P450 enzymes, isoenzymes of CYP2D6, CYP2C19, CYP2C9, CYP1A2, and CYP3A4 play a major role in AD metabolism [2].

13.3.1.1 CYP2D6

CYP2D6 genotyping is currently the most widely used application of PGx testing in psychiatric practice due to its involvement in the metabolism of many psychotropic medications, particularly ADs. Genetic variability is the main factor contributing to interindividual differences in *CYP2D6*'s catalytic activity [16]. As a result, the

molecular genetics of *CYP2D6* and its clinical relevance have been well studied with more than 100 allelic variants and subvariants identified [20]. The *5 allele indicates deletions, and gene duplications are expressed using “xN” following the allele [20]. Carriers of *CYP2D6* NM (or EM) phenotype demonstrate the genotypes *1/*1, *1/*2, *2/*2, or one duplication allele (*2X2 or *1X2) plus one deficient allele (*3, *4, *5, or *6) [16]. The *CYP2D6* PM phenotype is inherited as an autosomal recessive trait resulting from a combination of two partially or completely nonfunctional alleles (e.g., *5/*5, *3/*4), whereas *CYP2D6* UMs express duplication of functional alleles [21].

Clinical studies have demonstrated that genetic variants of *CYP2D6* have an influence on plasma concentrations of ADs and their metabolites, including escitalopram [22, 23], fluvoxamine [24, 25], imipramine [26], paroxetine [25, 27, 28], venlafaxine [29], and other second-generation ADs [30]. However, results from studies on the association between *CYP2D6* metabolizer status and AD efficacy and tolerability have been mixed due to the heterogeneity of the studied populations. Some studies have shown an association between *CYP2D6* gene variants and AD response for *CYP2D6*-dependent antidepressants, including escitalopram [23, 31] and mirtazapine [32], whereas other studies observed a lack of association between *CYP2D6* gene variants and response to citalopram [33], desipramine [34], paroxetine [35, 36], venlafaxine [37], and others [30, 38]. Some authors reported an association between *CYP2D6* polymorphisms and occurrence of side effects in response to fluvoxamine [39], venlafaxine [37], and other *CYP2D6*-dependent antidepressants [31], whereas other studies report a lack of association for citalopram [33] and venlafaxine [40].

13.3.1.2 CYP2C19

CYP2C19 is the second most relevant enzyme for AD metabolism following *CYP2D6*. Similar to *CYP2D6*, it is highly polymorphic with more than 35 known allelic variants and subvariants identified ranging from null to increased enzymatic activity [41]. *CYP2C19**1 is the wild-type allele encoding a fully functioning enzyme. Those carrying two inactive alleles (*2 to *8) are classified as PMs, and those carrying one active and one inactive allele are classified as IMs (e.g., *1/*2) [42]. The increased function allele is *17, which causes enhanced gene transcription; therefore those carrying *1/*17 and *17/*17 genotypes are considered UMs [42].

It has been demonstrated that genetic variants of *CYP2C19* have an influence on the pharmacokinetics of ADs and their metabolites, including citalopram [43], escitalopram [22, 44], imipramine [45], and sertraline [46, 47]. Polymorphisms of *CYP2C19* have also been associated with therapeutic failure to escitalopram [44, 48] and citalopram [48] with discontinuation of treatment occurring more frequently among non-NMs compared to NMs of *CYP2C19*. In terms of tolerance, *CYP2C19* non-NMs also demonstrate less tolerance to citalopram [49] and other ADs [50]. In contrast, studies have also reported a lack of association between *CYP2C19*

genotype and response and tolerance to ADs [37], including escitalopram and nortriptyline [51]. As a result, more data is required to describe the association between CYP2C19 genotype and AD efficacy and tolerability.

13.3.1.3 CYP2C9, CYP1A2, and Other CYP Isoforms

CYP2C9 is partially involved in the metabolism of several common ADs, including amitriptyline, fluoxetine, and trimipramine [18]. The most common alleles of *CYP2C9* with functional consequences are *2 and *3, which code for enzymes with decreased enzymatic activity compared to the *1 wild-type allele. Variability in the *CYP2C9* gene have been associated with steady-state plasma concentrations of fluoxetine, with increased plasma concentrations of fluoxetine and norfluoxetine detected in carriers of *2 and *3 than those with the *1/*1 genotype [52, 53]. However, the overall effect of *CYP2C9* and plasma levels of those ADs appear limited and not of meaningful clinical relevance [54].

CYP1A2 is another important polymorphic enzyme that metabolizes many common ADs, such as fluvoxamine and paroxetine. The *1F allele has been associated with higher enzyme inducibility by substances including tobacco smoke and caffeine, thereby increasing the clearance of CYP1A2 substrates. Two *CYP1A2* SNPs, rs4646425 and rs2472304, have been reported to demonstrate significant associations with remission after 8 weeks of treatment with paroxetine in a sample of Chinese MDD patients [55].

Other isoforms including CYP2B6, CYP2E1, and CYP3A4 are also involved in the metabolism of some ADs [56]. However, the associations between these isoforms and AD treatment response and tolerability remain inconclusive due to the availability of limited data.

13.3.2 P-Glycoprotein

Since the target molecules by which most ADs exert their effects are located in the brain, the brain concentration of the drug is important to consider in regard to its therapeutic efficacy. Many ADs are substrates of the P-glycoprotein (P-gp), which is an efflux pump with broad substrate specificity located in the plasma membrane of the BBB and belonging to the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily [57]. Polymorphisms in the *ABCB1* (or *MDR1*) gene that encodes P-gp may lead to changes in its protein structure, thereby altering its functionality and ability to bind to and selectively extrude psychoactive medications from the brain across the BBB [58]. As a result of being able to limit drug exposure to the brain, variability in the *ABCB1* gene can influence the clinical effects of many ADs that are substrates of P-gp, including tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, and trimipramine; SSRIs such as escitalopram,

citalopram, fluoxetine, and sertraline; and serotonin norepinephrine reuptake inhibitor (SNRI), such as venlafaxine [59].

Clinical studies have shown that *ABCB1* gene variants are associated with treatment outcome in patients treated with ADs that are P-gp substrates [60]. A systematic meta-analysis of PGx studies focusing on the association of *ABCB1* gene variants and AD treatment outcome revealed a nominally significant association of *ABCB1* SNP rs2032583 with treatment outcome across all studies, while the SNPs rs2032583 and rs2235015 were significantly associated with treatment response for inpatient samples [59]. Furthermore, the clinical application *ABCB1* genotyping has possible benefits with one pilot study showing that patients who received *ABCB1* genotyping demonstrate higher remission rates and lower Hamilton Depression Rating Scale (HAM-D) scores in comparison to patients who did not receive *ABCB1* genotyping [61].

13.4 Genes Influencing Antidepressant Pharmacodynamics

Pharmacodynamics refers to the interaction of the medication with various target physiological systems and encompasses all of the processes involved in the drug's resulting effects [62]. Pharmacodynamic genes code for drug targets, such as the serotonin (5-HT) transporters and receptors, and those that are indirectly involved in drug action, such as genes coding for proteins downstream of or influenced by the activation and modulation of the monoaminergic system (e.g., ion channels, growth factors, neuropeptides, etc.) [62]. Although the interaction of the drug at its primary target is mostly known, this relationship is nonlinear. All of the physiological processes that contribute to the resulting drug effects are often unclear. Thus, the majority of candidate pharmacodynamic genes relevant for drug response remains to be elucidated. Thus far, much of the investigations on pharmacodynamic genes associated with AD response have been on the monoaminergic system. However, more research is being conducted on the possible influence of downstream pathways and the stress hormone system on AD response.

13.4.1 Serotonergic System

The most investigated gene in relation to AD response is *SLC6A4* since it encodes the serotonin transporter (SERT), which is the principal site of action for many ADs [62]. Although several polymorphisms have been described for the *SLC6A4* gene, the serotonin transporter gene promoter polymorphism (5-HTTLPR) has been the most studied in the PGx of ADs [62]. 5-HTTLPR is polymorphic because of an insertion/deletion region of 44 nucleotides in its 5' promoter region resulting in a short (S) allele that is 44 base pairs shorter than the long (L) allele [62]. The S

variant results in decreased transcriptional efficiency of the *SLC6A4* gene promoter leading to decreased SERT expression and 5-HT uptake [63].

An association between *5-HTTLPR* polymorphism and AD response has been reported in some of the largest available AD clinical trials. Specifically, a positive association was reported between the *L* allele and better response to citalopram [64] and escitalopram [65]. In a meta-analysis of more than 30 studies, an association between *L* allele and both response and remission to SSRIs was observed in Caucasians, while a small effect of *5-HTTLPR* on remission was detected in Asians [66]. Differences in results between Asian compared to Caucasian samples may be due to the ethnic differences in allele frequencies, with 50% of Caucasians and 75% of Asians expressing the *S* allele [62]. The *L* allele frequency is smaller in Asians, which may possibly hamper the detection of an association between this genotype and better AD outcome [62].

Furthermore, *5-HTTLPR* genotype has been reported to have an effect on adverse effects associated with SSRIs with the *L* allele associated with lesser adverse effect burden to patients treated with citalopram [67] or other SSRIs [68]. The association between *5-HTTLPR L* allele with better response and fewer adverse effects is consistent with the hypothesis that individuals with high-expression *SLC6A4* genotypes (e.g., *LL*) have higher SERT density to which SSRIs can bind to in order to exert its therapeutic effect. Those with low-expression genotypes (e.g., *SS*) have reduced SERT density, which may result in greater saturation when exposed to the same SSRI dose and lead to excess central and peripheral 5-HT availability that manifests as adverse drug events [68].

Besides the *5-HTTLPR* polymorphism, there are other SNPs within the *SLC6A4* locus that influence SERT function and may possibly contribute to AD response. Biochemical experiments show that this SNP disrupts the consensus sequence of activator protein 2 transcription factor, which is believed to play an important role in regulating neural gene expression [69]. Because rs25531 is located just upstream of *5-HTTLPR* and is also in linkage disequilibrium with *5-HTTLPR* ($r^2=0.75$), it may influence *5-HTTLPR* associations with AD response [62]. Nonresponse has been reported to be associated with the *L* allele of *5-HTTLPR* expressed in the presence of the *G* allele of rs25531 and also with the *S* allele of *5-HTTLPR* expressed in the presence of the *A* allele of rs25531 [62].

Other possible candidate pharmacodynamic genes for PGx studies are those coding for 5-HT receptors. The *G* allele of the *C-1019G* polymorphism in the promoter region of the *5-HT_{1A}* gene (rs6295) showed a nominally significant association with response to various ADs. Those expressing the *-1019G/G* genotype demonstrated significantly less response to ADs and were twice as likely to be non-responders compared to the *-1019C/C* genotype [70].

For the *5-HT_{2A}* receptor gene, there are three most widely investigated polymorphisms: *A-1438G* (rs6311) and *C-102T* (rs6313) in the promoter region and a mis-sense substitution, *His452Tyr* (rs6314) [71]. For the *A-1438G* polymorphism, patients with the *-1438G/G* genotype showed better response to fluvoxamine [72] and citalopram [73] than patients with the *-1438A/-1438A* or *-1438A/-1438G*

genotypes. Further replicating these results, the *C-102T* polymorphism, which is in linkage disequilibrium with *A-1438G*, showed an association with AD response with patients with one or two *-102C* alleles showing significantly greater improvement in depressive symptomatology [74].

For the 5-HT₆ receptor gene, *C267T* variant (rs1805054) has been investigated for its association with AD response with mixed findings. Individuals with *-267C/T* genotype showed significantly better AD response compared to those with the *-267C/C* and *-267T/T* genotypes [75]; however other reports showed no significant associations [76].

The tryptophan hydroxylase gene (*TPH*) codes for the rate-limiting enzyme that is involved in 5-HT biosynthesis. Two major polymorphisms of this gene in strong linkage disequilibrium have been investigated for their association with AD response: *A-218C* and *A-779C* [62]. Association between *TPH* and response to fluvoxamine [77] and paroxetine [78] was reported with *-218A* allele carriers demonstrating poorer response.

13.4.2 Other Neurotransmitter Genes

Genetic variations in dopamine receptors have been investigated for associations with AD response with reports of mostly negative findings. *Ser311Cys* polymorphism of the dopamine receptor D2 (*DRD2*) gene and the *VNTR* polymorphism within exon 3 of the dopamine receptor D4 (*DRD4*) gene were found to be not significantly associated with treatment response to fluvoxamine or paroxetine [79]. In contrast, other findings have been reported that out of 21 polymorphisms tested to detect the genetic basis of AD response, a statistically significant difference was observed between responders and non-responders only for the *DRD4* exon 3 *VNTR* genotype with the homozygous 7-repeat genotypic group having twice the number of responders compared to non-responders [80].

Only a few studies have investigated the noradrenergic pathway genes in relation to AD response. Functional polymorphism in the G protein-associated $\beta 1$ adrenergic receptor (*ADRB-1*) resulting in an amino acid variation at codon 389 (*Gly389Arg*) has shown an association with AD response with those homozygous for the *C* allele demonstrating faster and better response to AD medications [81]. However, these findings failed to be replicated in patients treated with citalopram [82].

13.4.3 Other Important Genes: Signal Transduction Pathways, Growth Factors, and the Stress Hormone System

GNB3 encodes the $\beta 3$ subunit of the G protein complex, which is present in all cells and plays a key role in the downstream signalling cascade following monoamine receptor activation. The most investigated variant within *GNB3* for its possible

involvement in AD response is the functional *C825T* polymorphism (rs5443). Yet the findings pertaining to this polymorphism are inconclusive. While some studies reported that the *TT* genotype is significantly associated with better response to ADs [83–85], including nortriptyline [86], others have reported an association of the *T* allele with poorer response to nortriptyline [87] and mirtazapine [88] or no association of *C825T* polymorphism with AD response [89].

Brain-derived neurotrophic factor (BDNF) has been implicated in contributing to neuroplastic changes as a result of long-term AD treatment [62]. Studies on the influence of *BDNF* gene variants on AD response have also yielded mixed findings. The *G196A* (*Val66Met*) polymorphism within this gene has been the most investigated with studies reporting an association between the heterozygote (*G/A* or *V/M*) genotype and better response to fluoxetine [90], fluvoxamine [91], and milnacipran [91], while others have reported an association between the *M* allele and better treatment outcome to citalopram [92].

Dysregulations of the stress hormone system play a major causal role in the development of MDD [93]. AD treatment seems to normalize the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis that is observed in patients with depression and may be important to achieve clinical response to AD treatment [62]. Within the stress hormone system, two genes most investigated for their involvement in AD response are the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene and the glucocorticoid receptor (*GR*) gene; however, the findings of these studies are inconclusive and remain to be replicated [94]. Overall, there is a paucity of data related to the stress hormone system and AD response, which should be addressed in future studies (Fig. 13.2).

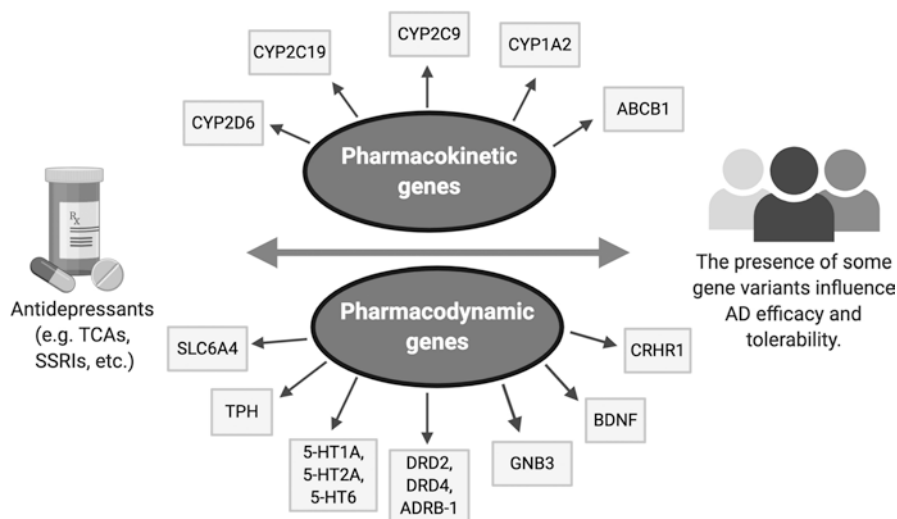


Fig. 13.2 Important candidate genes associated with AD outcome. (Image created using BioRender)

13.5 Polygenic Approach to Pharmacogenomics in Depression

Numerous studies have utilized the candidate gene approach in attempts to explain variance in AD response and yielded mostly inconclusive findings. These candidate gene studies often demonstrate small effect sizes, include underpowered samples, lack consideration for interactions between gene variants, and show variable effects in different ethnic populations [6]. More recently, focus has shifted from an individual candidate gene approach to a genome-wide genotyping approach identifying millions of variants within the genome associated with AD response. GWAS have been useful in providing hints at explaining the genetic contributions to the variance observed in AD response. This in turn aided the discovery of new polymorphisms, such as in non-coding regions, by bypassing the need for a priori hypotheses [6]. Nevertheless, most associations identified by GWAS have been inconclusive or not able to be replicated [95]. Furthermore, there are difficulties in prioritizing variants identified in GWAS and distinguishing between false negatives and true negatives [6]. Taken together, this suggests that the phenotype of AD response is likely a polygenic trait that involves a large number of polymorphisms with small effect sizes [95].

Given the challenges of candidate gene and traditional GWAS approaches in accruing sufficiently robust evidence to confirm association of a single SNP with AD response, alternative aggregated genome-wide approaches, such as polygenic risk scores (PRS), are being considered to identify genetic component of AD response [6]. PRS is a single variable that is created by taking alleles across the genome up to varying thresholds of significance from a GWAS discovery sample, weighed by their effect sizes, to predict a trait in an independent target sample [6]. In GWAS analysis, only a few SNPs with relatively high impact that reach stringent significance levels are considered, while SNPs with low impact are ignored. In contrast, PRS are calculated from multiple SNPs with lower evidence of association that may not necessarily meet the genome-wide significance threshold. The assumption is that these SNPs, when considered together, may have good predictive power and allow for the classification of patients within a risk spectrum [2]. Furthermore, consideration of functionality and heritability when estimating weights assigned to each variant in PRS can improve prediction of the trait in the sample [6].

Currently, PRS has not yet been widely applied in GWAS investigating AD response and side effects. One promising study has shown that the additive effects of common variants across the human genome explained 42.0% of individual variation in AD response [91]. With more evidence and validation supporting the usefulness of PRS, designing genotyping arrays to include the variants needed to calculate PRS may allow for the prediction of the risk of AD non-response for each patient.

13.6 Current and Future Clinical Applications

Several genes confirmed to influence AD response, described in this chapter such as CYP2C19 and CYP2D6, are now included in commercially available PGx testing panels. However, there are notable differences in panel composition between tests [96]. Almost 40 commercialized PGx tests are available claiming to predict AD outcome, of which 5 have been tested in randomized control trials (RCTs) at the time of writing this chapter [6]. These RCTs evaluated the benefits of PGx testing for drug therapy guidance on patient response and tolerability compared to standard care. Results for GeneSight® [97], CNSdose® [98], YouScript® [99], Neuropharmagen® [100], and NeuroIDgenetix® [101] showed that PGx testing significantly improved the likelihood of response in patients diagnosed with MDD and, in some cases, also reduced the burden of side effects. Although these results remain to be validated, even modest benefit from PGx testing could alleviate patient suffering and reduce healthcare costs.

The implementation of PGx testing into clinical settings also comes with its own challenges. There is a need to standardize and streamline education, training, and support for providers, including clinicians, pharmacists, and genetic counsellors, so that they are able to interpret the results for the patients and, in some cases, their families [96]. The development and dissemination of universal clinical practice guidelines for evaluating and utilizing PGx tests are also crucial to facilitate its introduction into clinical practice [96].

13.7 Conclusions

PGx is a relatively new field of research in psychiatry and holds great promise for refining and optimizing the treatment of depression. Limitations of existing PGx studies, including small sample sizes, insufficient independent replications, and the lack of standardized study design, make it difficult to compare results from independent studies. This signifies a need for a paradigm shift to one that captures the complex, polygenic nature of AD response. Furthermore, there is a pressing need to lessen the gap that remains between research and clinical implementation. This can be accomplished with strong evidence supporting the clinical benefits of PGx testing and by making available standardized training and education to providers for the clinical application of PGx tests. Despite the work that remains to be done, PGx is a powerful tool to personalize treatment and improve outcomes for patients suffering from depression (Table 13.1).

Table 13.1 An overview of genetic variants and candidate genes investigated for association with antidepressant treatment response in patients with depression

Most investigated polymorphisms	Antidepressant	Positive associations		No associations			
		Refs.	n	Ethnicity	Refs.	n	Ethnicity
<i>CYP2D6</i> *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35, *41, and <i>CNVs</i>	Various CYP2D6-dependent ADs	[31]	28	Not reported	[30]	136	Caucasian
	Citalopram				[38]	278	Caucasian
	Desipramine				[33]	1,229	Various
	Escitalopram	[23]	100	East Asian	[34]	31	Not reported
	Mirtazapine	[32]	109	Caucasian	[40]	106	Various
					[36]	246	Various (predominantly Caucasian)
	Paroxetine				[35]	56	Japanese
					[36]	246	Various (predominantly Caucasian)
					[102]	71	Various (predominantly Caucasian)
	Venlafaxine				[37]	100	Caucasian
				[40]	106	Various	
<i>CYP2C19</i> *1, *2, *3, *2- *10, *12, and *17	Various CYP2C19-dependent ADs				[38]	278	Caucasian
Citalopram	[49]	1,074	Caucasian	[33]	1,953	Various	
	[50]*	2,558	Various				
	[48]	263	Not reported				
Escitalopram	[50]*	2,558	Various	[23]	100	East Asian	
	[44]	2,087	Not reported				
	[48]	263	Not reported				
Venlafaxine				[40]	106	Various	

(continued)

Table 13.1 (continued)

Most investigated polymorphisms	Antidepressant	Positive associations		No associations			
		Refs.	n	Ethnicity	Refs.	n	Ethnicity
CYP1A2							
*1A, *1C, *1E, and *1F	Paroxetine	[55]	241	Han Chinese			
	Escitalopram				[103]	158	Han Chinese
ABCB1							
rs1045642, rs1128503, rs2032582, rs2032583, rs2235040, and rs2235015	Citalopram	[104]	54	Turkish			
	Escitalopram	[105]	683	Various (with white subsample)			
	Fluoxetine	[106]	112	Taiwanese			
	Sertraline	[105]	683	Various (with white subsample)			
	Various	[59]*	2,695	Various			
	Venlafaxine	[105]	683	Various (with white subsample)	[107]	52	Turkish
		[106]	112	Taiwanese			
SLC6A4							
5-HTTLPR and rs25531	Various ADs	[66]*	5,479	Caucasian and Asian			
	Citalopram	[64]	1,074	Caucasian	[108]	1,914	Various
					[67]	1,131	European
	Fluoxetine	[69]	96	Various (predominantly Caucasian)			
	Mirtazapine				[109]	124	Various (predominantly Caucasian)
	Paroxetine	[109]	122	Various (predominantly Caucasian)			
Various SSRIs		[110]*	1,435	Caucasian and Asian subsamples	[111]*	5,408	Various

<i>5-HT_{1A}</i> <i>C-1019G (rs6295)</i>	Fluoxetine					[112]	222		Chinese
	Various SSRIs or SNRIs	[70]	118		Not reported				
<i>5-HT_{2A}</i> <i>G-1438G (rs6311)</i>	Citalopram	[73]	71		Korean				
	Fluvoxamine	[72]	49		Japanese				
	Paroxetine	[72]	56		Japanese				
	Various	[73]	173		European				
<i>5-HT₆</i> <i>C-267T (rs1805054)</i>	Fluoxetine					[76]	57		Chinese
	Venlafaxine					[76]	57		Chinese
<i>TPH</i> <i>A-218C (rs1800532)</i>	Various	[75]	91		Korean				
	Fluvoxamine					[77]	217		Not reported
<i>DRD2</i> <i>C957T (rs6277), TaqIA (1800497), and Ser311Cys (rs1801028)</i>	Paroxetine	[78]	121		European	[113]	54		Japanese
	Fluvoxamine					[79]	266		European
<i>DRD4</i> <i>48bp exon 3 VNTR</i>	Paroxetine					[79]	98		European
	Various	[80]	97		Not reported				
<i>ADRB-1</i> <i>G-1165C (rs1801252)</i>	Fluvoxamine					[79]	266		European
	Paroxetine					[79]	98		European
	Various								
	Citalopram					[82]	873		Various
	Various	[77]	259		European				

(continued)

Table 13.1 (continued)

Most investigated polymorphisms	Antidepressant	Positive associations		No associations			
		Refs.	n	Ethnicity	Refs.	n	Ethnicity
GNB3							
C-825T (rs5443)	Fluoxetine				[89]	224	Chinese
	Fluvoxamine	[84]	362	European	[87]	87	Various (predominantly Caucasian)
	Mirtazapine				[88]	101	Korean
	Nortriptyline	[86]	811	European			
		[87]	82	Various (predominantly Caucasian)			
	Paroxetine	[84]	128	European			
	Various	[79]	78	Not reported			
		[85]	106	Korean			
	BDNF						
Val66Met (rs6265)	Citalopram	[92]	83	Korean			
	Fluoxetine				[90]	152	Chinese
	Fluvoxamine	[91]	54	Japanese			
	Milnacipran	[91]	80	Japanese			
CRHR1							
rs1876828, rs242939, and rs242941	Desipramine	[114]	80	Mexican-American			
	Fluoxetine	[114]	80	Mexican-American			
GR							
ER22/23EK (rs6189 and rs6190) and rs41423247	Citalopram				[115]	84	Korean
	Fluoxetine	[116]	100	Caucasian			
	Various	[117]	490	Caucasian			

*meta-analysis

Peer-reviewed studies written in English were identified systematically using any combination of the keywords “depression,” “antidepressant,” “response,” “remission,” “treatment,” “outcome,” and “tolerability,” along with the gene variants or polymorphisms of interest. Further studies were identified through the references of relevant articles and reviews.

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Chapter 14

The Role of Neurotrophic Factors in Pathophysiology of Major Depressive Disorder



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Abstract According to the neurotrophic hypothesis of major depressive disorder (MDD), impairment in growth factor signaling might be associated with the pathology of this illness. Current evidence demonstrates that impaired neuroplasticity induced by alterations of neurotrophic growth factors and related signaling pathways may be underlying to the pathophysiology of MDD. Brain-derived neurotrophic factor (BDNF) is the most studied neurotrophic factor involved in the neurobiology of MDD. Nevertheless, developing evidence has implicated other neurotrophic factors, including neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), glial cell-derived neurotrophic factor (GDNF), and fibroblast

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growth factor (FGF) in the MDD pathophysiology. Here, we summarize the current literature on the involvement of neurotrophic factors and related signaling pathways in the pathophysiology of MDD.

Keywords Neurotrophins · Neuroplasticity · Brain-derived neurotrophic factor · Glial cell-derived neurotrophic factor · Major depressive disorder

14.1 Introduction

Major depressive disorder (MDD) is a common, devastating, and lethal illness resulting in elevated suicide risk. In addition, cerebrovascular disorders, cardiac disease, and other medical causes of mortality are among the leading contributors to the profound social and economic burden of this disorder [1–4]. Although complex interaction between a variety of genetic, epigenetic, endocrine, and environmental risk factors mediates susceptibility for MDD, the neurobiological mechanisms underlying its pathophysiology remain poorly understood [1]. Molecular and cellular changes induced by stress and (or in combination with) other risk factors on synaptic connectivity and functional, as well as structural, connections of specific neural circuits related to mood regulation have been suggested to be underlying the MDD pathophysiology [1]. Clinical and experimental studies have found an association of MDD with structural and cellular alterations in cortico-limbic brain regions responsible for regulating mood and emotions [5].

According to the neurotrophic hypothesis of MDD, reduced expression of growth factors can lead to a decrease in the neuroplasticity, neuronal atrophy, and/or aberrant neurogenesis in key brain areas related to mood and memory, including the amygdala, prefrontal cortex, and hippocampus [6, 7]. Neurotrophic factors function as critical regulators of the formation and plasticity of neuronal networks [8] comprising the neurotrophin family including neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) [9, 10], and other neurotrophic factors, such as members of the insulin-like growth factor (IGF), glial cell-derived neurotrophic factor (GDNF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) families [11, 12].

An increasing body of evidence shows that MDD and stress could decrease the expression of neurotrophic factors in limbic structures, including the hippocampus [6, 11, 13]. Stress impairs downstream targets of signaling pathways implicated in neuroplasticity by suppression of growth factor expression, such as VEGF and BDNF that possibly are enhanced by antidepressant therapies [14–17]. Therefore, identifying the intracellular signaling cascades mediating neurotrophic/growth factor receptor signaling will contribute to the development of future antidepressant targets [18]. In addition, measurement of neurotrophic factors in peripheral circulation has been suggested as a probable putative peripheral biomarker for identifying

MDD and examining antidepressant response to pharmacological and non-pharmacological interventions [9, 12].

Here, we summarize the current literature addressing the implication of neurotrophic factors and associated signaling pathways in MDD. First, a brief overview of the role of neurotrophic factors and related signaling pathways in neuroplasticity is described. Further, evidence for the involvement of neurotrophic factors and associated signaling pathways implicated with neuroplasticity changes in MDD is highlighted. We also examined peripheral levels of neurotrophic factors and expression levels of neurotrophin receptors in the *postmortem* brains of depressive individuals as an important step in understanding the significance of the role of neurotrophins in the pathophysiology of MDD.

14.2 Neurotrophin Signaling Pathways

Selective binding of different neurotrophins to two classes of signaling receptors, including the Trk family of receptor tyrosine kinases and the p75 neurotrophin receptor (p75NTR), accounts for their facilitating effect responsible for mediating trophic properties in neurons. NT-4/5 and BDNF bind preferentially to tropomyosin receptor kinase B (TrkB); NT-3 binds to TrkC with high affinity but also exhibits low affinity for TrkA and TrkB. NGF shows high affinity for TrkA, and all four neurotrophins interact with p75NTR [19–21]. GDNF, as a member of the transforming growth factor- β (TGF- β) family, exerts its effects primarily through binding to GDNF family receptors α 1 (GFR α 1) and activation of tyrosine kinase signaling (Fig. 14.1) [12]. A multi-component receptor system composed of a high-affinity ligand-binding component (GFR α 1–GFR α 4) and a common transmembrane receptor tyrosine kinase (RET) mediates the effects of members of the GDNF family of neurotrophic factors including GDNF, neurturin (NTN), artemin (ART), and persephin (PSP) [22].

The binding of neurotrophins to their receptors activates different intracellular signaling cascades, including the MAPK/ERK, PI3-K, and PLC γ [23], which stimulate neuroplasticity particularly neuronal survival, growth, and differentiation, synaptic plasticity, and neurotransmission [2]. Together, these signaling cascades mediate both distinctive and overlapping functions of neurotrophins in the nervous system [24].

Mitogen-activated protein kinase (MAPK) signaling pathways comprise a complex network of signaling cascades that, via transduction of extracellular signals to cytoplasmic and nuclear effectors, regulate the genes involved in various cellular processes such as apoptosis and synaptic plasticity [25, 26]. These MAPK family members include extracellular signal-regulated kinase (ERK) 1/2, extracellular signal-regulated kinase 5 (ERK5), ERK6, ERK7, C-Jun N-terminal kinases, and p38 MAPKs [27–29]. Activation of Ret can initiate a variety of intracellular signaling pathways similar to signal transduction pathways elicited by other tyrosine kinase receptors, including the mitogen-activated protein kinases (MAPKs) ERK1

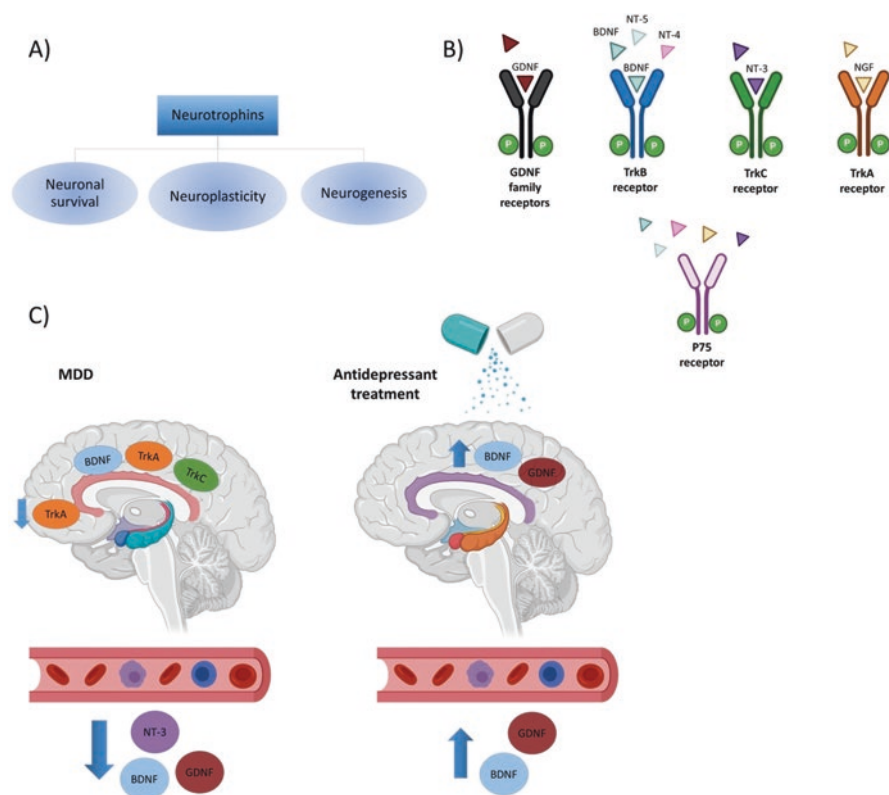


Fig. 14.1 *Neurotrophins and major depressive disorder (MDD)*. Neurotrophins are important family proteins involved in process such as neuronal survival, neuroplasticity and neurogenesis (a). Glial cell-derived neurotrophic factor (GDNF) binds in a GDNF family receptors; brain derived-neurotrophic factor (BDNF), neurotrophin 4 (NT-4), and NT-5 bind with more affinity in tropomyosin receptor kinase B (TrkB); NT-3 has more affinity for TrkC receptors; nerve growth factor (NGF) binds preferentially in TrkA receptors; both BDNF, NT-3/4/5, and NGF also bind in less affinity in p75 receptors (b). In MDD individuals and animal models of depression BDNF levels are decreased in brain structures, mainly hippocampus (CA1 and dentate gyrus), and anterior cingulate cortex. Receptors such as TrkA and TrkC also are reduced in hippocampus and PFC. In periphery neurotrophins such as BDNF, NT-3, and GDNF are decreased in blood and white blood cells from depressed individuals (c). On the other hand, antidepressant treatment increases BDNF and GDNF levels in both brain (astrocytes and neurons) and periphery (c)

and ERK2, PI3K/AKT, and phospholipase C γ pathway [30–34]. FGF1 and FGF2 by binding to four FGF receptor subtypes activate the phospholipase C γ (PLC- γ 1), MAPK, and AKT pathways [35, 36].

14.3 The Role of Neurotrophic Factors in Neuroplasticity

There is growing evidence that neurotrophic growth factors and related signaling pathways play major roles in neuroplasticity [17]. Reorganizing of structure, function, and connections of the nervous system induced by the response to intrinsic or extrinsic stimuli has been defined as neuroplasticity [37]. Different mechanisms may mediate neuroplasticity including neurogenesis, modification of mature neuronal morphology, synaptogenesis, long-term potentiation (LTP), and transcriptional regulation of genes involved in neuroplasticity by epigenetic mechanisms [38]. Long-term potentiation (LTP) and long-term depression (LTD) are two well-known forms of long-term synaptic plasticity that result in strengthening or weakening of synaptic connections, respectively, and persistent modifications of synapses [39]. It has been well established that neurotrophic factors that are produced and secreted in an activity-dependent manner tightly control synaptic plasticity [40, 41]. Many physiological functions underlying neural plasticity have been associated with Trk receptor activation, including improvement of synaptic neurotransmission and cell survival [42]. It has been shown that p75NTR negatively modulates dendritic morphology in adult hippocampal pyramidal neurons [43] and deletion of p75NTR induced a significant impairment in LTD without affecting LTP [39, 44] indicating its role in negative regulation of plasticity. p75NTR stimulates several proapoptotic pathways that directly promote cell cycle arrest and apoptosis, such as Jun kinase signaling, while Trk receptors suppress c-Jun kinase as the major proapoptotic signaling pathway initiated by p75NTR [45, 46]. The MAPK cascade also is implicated in signaling to the nucleus and the induction of long-lasting synaptic plasticity in the hippocampus, amygdala, and cortex [47–50]. For example, this cascade of kinases is critical for the induction of long-term potentiation (LTP) as a prototypic form of synaptic plasticity that is extensively assumed to represent cellular mechanisms underlying hippocampus-dependent memory formation [51].

BDNF is an important neurotrophic factor involved in the survival, growth, and differentiation of neurons, as well as in the regulation of neurogenesis and synaptic plasticity [52]. NGF has been implicated in regulating hippocampal plasticity [53] and neurogenesis in the striatum [54, 55]. GDNF, due to its neuroprotective properties, plays a crucial role in the survival and maintenance of both dopaminergic and serotonergic neurons [12, 56, 57]. The FGF family plays an important role in proliferation and maturation of neurons in two well-known proliferative areas involved in the formation of newborn neurons or neurogenesis, including the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus [58]. FGF1 and FGF2 play a critical role in the regulation of synaptic plasticity [59] and neurogenesis [60–63]. Vascular endothelial growth factor (VEGF) is

involved in growth, differentiation, and axonal outgrowth, as well as neuroprotection, neuronal survival, and regeneration, which are known to be involved in the pathophysiology of MDD [64]. VEGF as a potent neurotrophic factor could induce neuronal survival and proliferation, glia survival, glia migration, and neurogenesis [65–67]. IGF-1, by influencing processes, was implicated in the formation of synapses, the release of neurotransmitters, and the excitation of neurons by controlling the efficiency of synapses and plays role in synaptic plasticity [68]. IGF-1, through binding to tyrosine kinase receptor, mediates multiple roles in neuroprotection, neurotrophic mechanisms, and neuronal signaling [69]. VEGF and BDNF regulate neurogenesis likely through mechanisms that were initially implicated in the induction of LTP, such as activation of CREB [17, 70–72]. Survival-promoting effects of IGF-1 involve activation of the PI3K/AKT or MAPK/ERK signaling pathways [69]. Activation of signal transduction pathways induced by binding of BDNF, VEGF, IGF-1, and FGF2 to tyrosine kinase receptors triggers various cellular functions including the expression of genes involved in neuroplasticity [18].

14.4 The Role of Neurotrophic Factors in Neuroplasticity Changes in MDD

Substantial evidence suggests that the impaired mechanisms of neuroplasticity induced by stress contribute to the pathophysiology of MDD; antidepressant treatments might affect the same mechanisms and have the opposite effect [17]. Abnormal trophic support and impairment in growth factor signaling in cortico-limbic regions might be associated with MDD [17, 73]. Growing clinical and pre-clinical evidence indicates that abnormal structural and cellular alterations in the cortico-limbic regions, such as neuronal loss and synaptic dysfunction, lead to impaired functioning of cortico-limbic regions regulating mood and emotions that may take part in the pathophysiology of MDD [5]. MRI studies have revealed structural changes such as reduced hippocampal volume during a depressive episode [74].

In addition, numerous studies have reported impairment of synaptic plasticity and neurogenesis, increased hippocampal dendritic atrophy and cell death, reduced LTP, and increased LTD in MDD [75–79]. MDD patients showed lowered gene expression of BDNF and VEGF in dentate gyrus (DG) and CA1 regions of hippocampus [80], which both of these growth factors are necessary for hippocampal LTP [81, 82]. Involvement of trophic factors BDNF, GDNF, and VEGF in maturation and maintenance of developing neurons and modulation of adult neurogenesis may contribute to generation of neuroplasticity abnormalities in MDD [12, 57, 83]. It has been suggested that disturbances in the IGF-1 system by influencing on many processes, such as synaptic plasticity and adult neurogenesis, might be involved in MDD development [69].

It has been revealed that p75NTR plays a role in the mediation of cell death, and increased expression ratios of p75NTR to Trks might be associated with

pathophysiology of mood disorders and suicide [42]. Depressed suicide individuals showed dysregulated levels of growth factor receptor including lower mRNA levels and phosphorylation of TrkA and TrkC in the hippocampus, decreased mRNA level of TrkA in the PFC, and an increased mRNA level of p75NTR in both PFC and hippocampus [42]. Human cortical and hippocampal brain areas highly express both Trk receptors and p75NTR [84–86]. When p75NTR is co-expressed with Trk receptors, it can modify the binding and function of neurotrophins [87, 88]; on the other hand, in the absence of Trk receptors, neurotrophins may via p75NTR induce neuronal apoptosis [89, 90].

14.5 The Role of Neurotrophins in Anti-Depressive Responses

It has been suggested that similar molecular and cellular mechanisms are involved in neuroplasticity and MDD, especially those underlying synaptic plasticity and the anti-depressive response [17]. Such signaling systems activate the regulation of transcription factors in the nucleus, such as transcription factor cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) that induces effector genes, prominently BDNF, and contribute to long-lasting synaptic change [17].

Chronic antidepressant administration could increase activation of neurotrophin-mediated signaling cascades, including phospholipase C (PLC) gamma 1 phosphatidylinositol 3-kinase (PI3K) and MAPK, which converge to activation of the CREB-mediated gene transcription [17, 91–93]. Interestingly, antidepressant treatment successfully could upregulate neurotrophic factors related to neuronal growth and survival [6], and neuroplasticity [94, 95]. The antidepressant fluoxetine could increase expression of neurotrophic factors likely by activation of mitogen-activated protein kinase (MAPK) cascades, including extracellular signal-regulated kinase (Erk) and p38 mitogen-associated protein (MAP) kinase cascades in cultured rat astrocytes (Fig. 14.1) [96]. It has been suggested that the antidepressant amitriptyline may induce GDNF synthesis and release in rat astrocytes through regulation of extracellular signal-related kinase (ERK) kinase (MEK)/MAPK signaling [97]. Central administration of IGF-I and BDNF could produce long-lasting antidepressant-like effects in rats [83]. VEGF as an angiogenic factor also plays a role in the promotion of neurogenesis and is involved in the mechanism of action of antidepressants [98]. It has been demonstrated that growth factors BDNF and VEGF, by activation of the MAPK signaling cascade, play roles in the regulation of synaptic plasticity and are implicated in the actions of antidepressant treatments [17, 70]. The BDNF/TrkB signaling pathway has been suggested as the main mechanism underlying the development and course of MDD, as well as the action of currently available antidepressants [2]. Therefore, the TrkB receptor and new

molecules that directly target TrkB signaling might be main molecular targets for treating MDD [99, 100].

14.6 Neurotrophic Factors as Biomarkers for MDD: Evidence from Clinical Studies

Development of clinically useful biomarkers for MDD will improve diagnostic precision and therapeutic strategies [101]. Although increasing evidence demonstrate that GDNF, IGF-1, and VEGF might have an important role in the pathophysiology of MDD, large-scale studies are still warranted to verify the worth of these trophic factors as clinically useful biomarkers for depression [12, 102]. *Postmortem* hippocampus and PFC of suicide victims showed a reduced expression of BDNF and TrkB [103, 104]. In addition, *postmortem* analyses revealed lower BDNF levels in the anterior cingulate cortex (ACC) and the caudal brainstem in depressed patients compared to non-depressed individuals [105]. Individuals with the Met allele of the BDNF gene polymorphism (val66met) showed an increased risk for MDD [105]. Therefore, low brain BDNF and the BDNF Met allele might be risk factors for MDD [105]. A significant downregulation of BDNF at the RNA and protein levels was found in the *postmortem* amygdala of female patients with MDD, thus providing evidence in support of low neurotrophic functions in MDD [106]. Blood levels of BDNF were found to be significantly low in MDD patients [107], which was normalized after antidepressant treatment [108]. Several meta-analyses demonstrated that MDD patients have consistently lower peripheral BDNF levels compared to healthy controls and different antidepressant treatments are associated with an increase in BDNF [94, 95, 109, 110]. Since BDNF is correlated with neuroplasticity, these findings suggest that MDD improvement is associated with neuroplasticity [111].

In MDD patients, the reduced expression of GDNF, artemin (ARTN), and NT-3 mRNAs in the peripheral white blood cells of individuals in a depressive state was observed, but not in remissive state. This suggests reduced expression of GDNF, ARTN, and NT-3 mRNAs in MDD is state-dependent [112]. Reduced expression of both GDNF and ARTN in MDD patients has been suggested as possible results of GFR α 1-mediated pathway dysfunction in the pathophysiology of MDD [112]. Elderly patients with MDD showed markedly increased cerebrospinal fluid (CSF) levels of NT-3 compared to healthy controls [113]. Increased levels of NT-3 have been attributed to a decreased level of BDNF as one compensatory mechanism [114]. Clinical studies reported contrasting findings between brain and blood expression of GDNF in MDD [12], such as increased expression of GDNF in the *postmortem* parietal cortex (Michel et al., 2008) and reduced circulating level of GDNF in MDD individuals [115]. Depressive and bipolar disorder patients also showed decreased levels of whole blood GDNF in a remissive state [116]. A meta-analysis revealed that blood GDNF levels are significantly decreased in patients

with MDD compared to control individuals, thereby supporting blood GDNF levels as a biomarker of depression [56]. However, a comparative *postmortem* study found a significant increase in GDNF concentration in the parietal cortex of MDD patients compared to the control group [117].

Increased serum, plasma, and mRNA expression levels of VEGF were found in MDD individuals compared to controls [12, 102, 118, 119]. Lower concentrations of CSF VEGF were found in a clinical sample of patients with treatment-resistant depression compared with matched controls [120]. An association was found between *VEGF* 2578 C/A polymorphism and treatment-resistant depression [121], between C allele and CC genotype of *VEGFA* polymorphism +405G/C and recurrent depressive disorder [122], as well as other polymorphisms and depression [123], suggesting *VEGFA* gene polymorphisms as important risk factors for MDD development. However, Iga et al. (2007) did not find any significant correlation [64]. Clinical studies have reported mixed results related to peripheral levels of VEGF in patients with MDD compared to healthy controls, including higher peripheral levels [123, 124] and unaltered levels [125]. A meta-analysis demonstrated that peripheral VEGF levels were significantly elevated in individuals with MDD when compared to healthy controls, thus supporting the possibility of a role of this mediator as a promising biomarker for MDD [102]. VEGF has been suggested as a potentially trait biomarker for MDD; however considerable inconsistent findings have been reported in MDD patients compared to controls, including higher VEGF levels, unaltered levels, and even lower levels [102].

FGF1 and FGF2, as the most studied ligands of FGF family, have been found to be dysregulated in mood disorders [35, 36]. Postmortem brain analysis in patients with MDD also showed decreased expression of FGF1 and FGF2 in the ACC and dorsolateral PFC [126]. In addition, decreased mRNA expression of FGF2 and increased expression of FGFR1 were found in the hippocampus of depressed patients [127]. Several studies found that increased levels of IGF-1 were significantly associated with depression and impaired treatment response in MDD patients [128–131].

14.7 Conclusions

Based on the neurotrophic hypothesis, MDD is related to aberrant neuroplastic pathways in brain areas involved with emotional and cognitive processing. Atrophy of certain limbic structures in depressed individuals, such as the hippocampus and PFC, has been attributed to decreased levels of neurotrophic factors. Mounting evidence suggests that atrophy and impaired functioning of cortico-limbic regions involved in the pathophysiology of MDD and alterations in neurotrophic factors underlie impaired neuroplasticity, which might be associated with the development of MDD. It has been suggested that disruption of mechanisms involved in cell survival and neural plasticity might be associated with depression and antidepressants could mediate their effects by modulating the neurotrophin signaling pathways

implicated in plasticity and survival and increasing neurogenesis. Circulating levels of neurotrophic factors, particularly reduced levels of BDNF and GDNF, have been suggested as peripheral manifestations of depression.

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Part III
Current Specific Treatments for
Depression

Chapter 15

Clinical Application of Real-Time fMRI-Based Neurofeedback for Depression



Klaus Mathiak and Micha Keller

Abstract Real-time functional magnetic resonance imaging-based neurofeedback (rt-fMRI NF) is a recent technique used to train self-regulation of circumscribed brain areas or networks. For clinical applications in depression, NF training targets brain areas with disturbed activation patterns, such as heightened reactivity of amygdala in response to negative stimuli, in order to normalize the neurophysiology and their behavioral correlates. Recent studies have targeted emotion processing areas such as the amygdala, the salience network, and top-down control areas such as the lateral prefrontal cortex. Different methods of rt-fMRI-based NF in depression, their potential for clinical improvement, and most recent advancements of this technology are discussed considering their role for future clinical applications. Initial findings of randomized controlled trials show promising results. However, for lasting treatment effects, clinical efficiency and optimal target regions, tasks, control conditions, and duration of training need to be established.

Keywords Real-time fMRI neurofeedback · Depression · Emotion regulation · Amygdala

15.1 Introduction

Over the past decade, numerous real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback (NF) approaches have been investigated regarding their potential to improve depressive symptomatology. As localized technique for noninvasive neuromodulation, rt-fMRI NF may offer an alternative or addition to the established treatment regimes. The introduction of rt-fMRI by Cox and colleagues [1] paved the way for its application to NF [2, 3]. Since then large methodological

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developments have enabled the application of rt-fMRI NF using MRI scanners with high field strengths [4] to a wide range of psychiatric disorders [5]. Furthermore, commercial NF applications (e.g., Turbo-BrainVoyager, Brain Innovation) have been available for some time. In rt-fMRI NF, patients train self-regulation of regional brain activation by receiving feedback on changes of the hemodynamic brain signal in real time [6]. In contrast to traditional fMRI studies in which the subject's brain modulation to an external stimulus or behavior is investigated, NF investigates the effect of the subject's voluntary self-regulation of brain activation on behavior. Compared to the more long-standing electroencephalography (EEG) NF approaches, rt-fMRI NF has the advantage of targeting localized cortical as well as subcortical brain areas due to its high spatial resolution enabled by the tomographic data acquisition. However, the fMRI is based on the indirect BOLD (blood-oxygen-level-dependent) effect that has a lower temporal resolution (compared to the millisecond range of EEG). The BOLD signal is measured by localized change in concentration of deoxygenated hemoglobin in the blood. The concentration of deoxygenated hemoglobin depends mainly on blood flow which is regulated according to the local neuronal activity. Its maximal change occurs after about 3–6 s. This must be considered in rt-fMRI studies as the feedback signal will have an inherent delay. Validation of fMRI comes from simultaneous fMRI and electrophysiological recordings that confirm a direct link between BOLD and neural response suggesting that also voluntary regulation of the BOLD response is strictly associated with changes in neural activity and not a direct vascular effect [7].

During online rt-fMRI NF training (Fig. 15.1), the BOLD signal from a circumscribed brain target is measured and presented to the participant in the MRI scanner. The participant is instructed to change this brain signal to learn self-control of the selected target area and the associated cognitive state. The feedback that indicates the degree of regulation success is computed based on the time course of the BOLD signal of single or multiple regions, the difference or correlation of regions or even more complex signals such as the output of a multi-voxel pattern algorithm. Depending on the experimental paradigm, participants may be instructed to up- or downregulate activity in these target areas or networks. To achieve this, participants are usually first provided with instructions to minimize general artifacts such as head movements or changes in respiration [8]. Furthermore, there are several ways to instruct the participant on how to train the regulation of the brain signal, and in all cases the regulation success is rewarded by providing a feedback signal. In many studies no specific strategy is given, and this instrumental learning approach seems to enable the most direct interpretation of the learning process. Alternatively, strategies to train the regulation of the signal may be provided with specific instructions (e.g., autobiographical memory recall, cognitive reappraisal), which usually are directly related to the target network. However, often cognitive effects on the regulation target related to expectation or other information must be considered as well. Frequently, a set of possible strategies usually encompassing imagery may be suggested. Whereas providing participants with a specific strategy is goal directed and provides more time to practice a potentially effective strategy, finding a personal strategy may also be beneficial in some instances. NF presentation of changes in

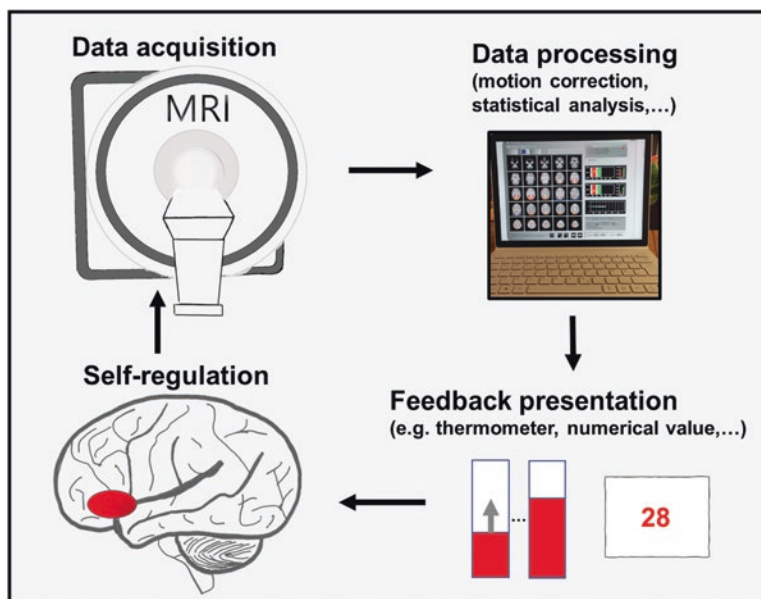


Fig. 15.1 *Real-time fMRI NF setup.* (Self-regulation) Participant in the MRI scanner receives instructions to use cognitive strategies in combination with neurofeedback signal to regulate brain signal. (Data acquisition) Brain activity is measured with fMRI BOLD signal. (Data processing) Online analysis with immediate preprocessing including 3D head motion correction, spatial smoothing, as well as statistical mapping and feedback calculation based, e.g., on contrast between regulate and rest condition. (Feedback presentation) Feedback signal is displayed to the participant either intermittently or continuously depicting, e.g., mean activity of target region. (Adapted from Ref. [3])

target brain activity related to the task can be provided either intermittently or continuously. Intermittent NF is provided at the end of each trial, e.g., as a numerical value or a single outcome on a scale. The provided feedback signal is often based on the difference between task-related activation and a baseline activation in the target region. For instance, this could be the difference between downregulating a target area within the emotion network while seeing a negative stimulus and just viewing a negative stimulus. On the contrary, continuous NF is provided throughout the whole session and is updated after each acquired volume (usually every 2 s). It is typically shown in the form of a curve or a continuously updated scale (often labeled as “thermometer”). Additionally, localized brain activity can be reinforced by the external reward from social feedback such as a continuously updated virtual avatar [9, 10]. Continuous NF offers a better temporal resolution and more information than intermittent NF and may therefore lead to faster learning. However, participants must be aware of the delay in feedback due to the hemodynamic response. Furthermore, continuous NF is inherently a dual task and may act as a distractor that draws the participant’s attention away from the task which may lead to a modulation of brain activity. By providing intermittent feedback, the task and appraisal of

feedback are separated which decreases the cognitive load. Furthermore, intermittent feedback diminishes the effect of the hemodynamic delay.

To investigate whether treatment effects are related to NF itself rather than unspecific non-NF related factors, studies need matched control conditions. In contrast to receiving real feedback from the target region in the experimental group, participants in the control condition may not receive feedback while doing the same task either inside or outside of the scanner. Alternatively, they may receive feedback from another participant (“yoked feedback”) or from an unrelated target region. However, the non-contingency of the feedback may lead to the rejection of otherwise efficient strategies and may support learned helplessness, and thus negative effects may emerge that render the method not suitable as valid control. A consensus points to the direction that the use of various control conditions may be helpful to disentangle the possible confounders [11]. This points out the importance of carefully considering the study design when designing or interpreting a NF study. Further, clinical studies also need to consider comparisons to best practice treatments. So far, fMRI-based NF is investigated by disentangling underlying components in a step-by-step fashion.

Early rt-fMRI NF studies already found effects on participant mood in healthy volunteers such as increasing positive affect in activation compared to baseline blocks [12]. Furthermore, rostral ACC activation during NF was found to be predictive of affect ratings after NF training [13]. However, depending on the target region and the paradigm, no mood change [14, 15] or a blunting of affect [16] may also be observed. Effects of rt-fMRI NF on depression are largely based on operant conditioning. NF brain targets are chosen based on functional and anatomical aberrations in certain psychiatric disorders. The anatomical targets for self-regulation in recent studies involving patients with depression are the amygdala [17, 18], individually defined areas responsive to positive stimuli [19, 20], or areas responsive to negative stimuli [21]. Other studies have investigated NF as a combination treatment following clinical treatment such as cognitive behavioral therapy [22, 23]. An overview of recent rt-fMRI treatment targets and studies in patients with depression are presented in Fig. 15.2 and Table 15.1, respectively, and will be discussed in the next section.

15.2 Real-Time fMRI NF Studies in Depression

NF training of brain activation in depression may be beneficial in several ways. In a deficit-centered approach, parts of neural circuits thought to be involved in the upkeep of dysfunctional cognitive patterns may be targeted. Primary abnormal processes may be hypo- or hyperactivation of specific brain areas or networks such as frontostriatal abnormalities [24], deficient sensory processing in depression [25], or decreased ACC activity in hallucinating compared to non-hallucinating patients with schizophrenia [26]. By training dysfunctional areas or networks to function normally, patients with depression or other psychiatric disorders may have cognitive

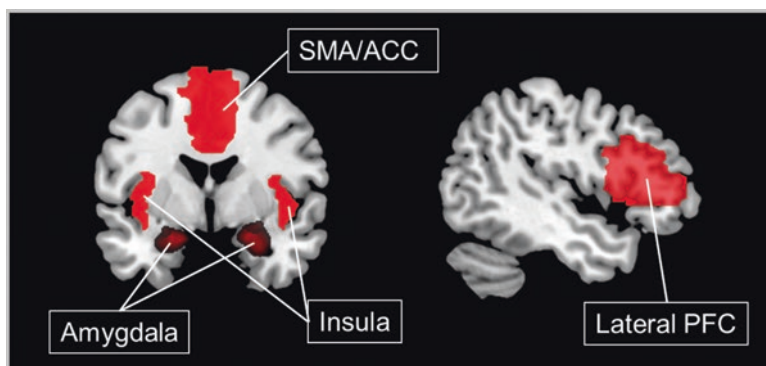


Fig. 15.2 *Potential anatomical treatment targets for rt-fMRI NF in patients with depression.* Structures that have been implicated in the etiology of depression, e.g., amygdala, anterior cingulate cortex (ACC), salience network (bilateral insula and ACC), supplementary motor area (SMA), and lateral prefrontal cortex (PFC). In addition to purely anatomical definitions of target areas, individualized targets resulting from imaging experiments have been applied. As an extension to these one-dimension approaches, multivariate target measures are studied currently

and emotional benefits from gaining control over these brain targets. However, knowledge of the pathophysiology of depression and the neurophysiological mechanisms of symptom change are required that are generalizable to a single patient. For instance, several studies have directly trained areas involved in emotional experience such as the amygdala that is known to be hyperactive or hyperreactive in patients with depression (cf. 18). As a more resource-oriented approach, rt-fMRI NF can target (parts of) functional brain circuits that patients with depression are already using and which support compensatory mechanisms for cognitive processes such as emotion regulation. For example, emotion regulation networks have been well-defined [27] and can also be identified in patients with depression. Therefore, a functional localizer identifies an individualized target region involved in the implementation of emotion regulation strategies such as the lateral prefrontal cortex (IPFC). Training self-regulation of the IPFC by emotion regulation may have a positive effect on patients' ability to downregulate the experience of negative emotions as the upregulation of the IPFC leads to downregulation of hyperresponsive amygdala in response to emotional stimuli with negative valence (cf. 14). Finally, for specific trainings, NF targets can be defined anatomically as well.

Regions that are involved in impaired emotion processing in depression are particularly interesting candidate targets for rt-fMRI NF. Frontostriatal abnormalities have been related to aberrant emotional processing in depression with an attentional bias to negative and away from positive stimuli or events [28]. These emotion processing deficits can be targeted at different processing levels, e.g., neo-, archi-, or subcortical areas. Studies in healthy subjects have shown that self-regulation of numerous brain areas involved in emotion processing is possible [29]. Some studies have successfully trained healthy subjects to control amygdala activity either by upregulating [30, 31] or by downregulating the signal [32–34]. Further, another two

Table 15.1 Real-time fMRI NF studies in patients with depression. Only relevant studies that tested effects of NF exclusively in patients are included

Study	Target region	Control condition	Task	Results	No. of patients with depression
Upregulation of amygdala					
Young et al. (2014)	Left amygdala	Horizontal segment of the intraparietal sulcus	Increase activity using happy autobiographical memories	Regulation of amygdala possible; decreased state anxiety and increased state happiness in experimental group; training effect inversely related to duration of depressive episode	14 (experimental) vs. 7 (control)
Young et al. (2017)	Amygdala	Horizontal segment of the intraparietal sulcus	Increase activity using happy autobiographical memories	Successful upregulation of amygdala; significant decrease of depressive symptoms and increased use of specific AMs in 12 patients from experimental group	19 (experimental) vs. 17 (control)
Upregulation of emotion processing areas					
Linden et al. (2012)	Brain activation while viewing positive pictures (localizer)	No NF (outside the scanner)	Increase activity by using positive mental imagery	Decreased depressive symptoms in experimental group	8 (experimental) vs. 8 (control)
Mehler et al. (2018)	Brain activation while viewing positive pictures NF of emotion areas (localizer)	NF of higher visual brain areas responsive to visual scenes	Increase activity	Decreased depressive symptoms in both groups; self-efficacy rather than regulation success related to clinical improvements → Possible placebo effect.	21 (experimental) vs. 22 (control)

Downregulation of emotion processing areas				
Hamilton et al. (2016)	Node of salience network (SN) with highest response to negative stimuli (localizer)	Yoked feedback from another participant	Decrease activity (e.g., cognitive reappraisal, attentional redirection, imagery, etc.)	Experimental group showed greater decrease of neural and behavioral response to negative stimuli vs. 10 (control) 10 (experimental)
Combination of cognitive behavioral therapy and NF				
Barb et al. (2018)	Left amygdala	Right parietal area	2 days of NF (increase activity to positive autobiographical memories) + followed by 10 weeks of CBT	Experimental group showed higher symptom improvement during first 3 weeks of CBT compared to control group 9 (experimental) vs. 7 (control)
MacDuffie et al. (2018)	ACC (localizer)	No control	Decrease ACC activation by applying cognitive strategies learned during CBT (experimental vs. control strategies – Only experimental strategies used in the scanner)	Stronger NF associated with higher efficacy of experimental strategies 4 weeks later; ratings for unscanned control strategies constant from baseline, scanning session to follow-up 13 (experimental)
(continued)				

Table 15.1 (continued)

Study	Target region	Control condition	Task	Results	No. of patients with depression
Other methodologies					
Zahn et al. (2019)	Connectivity between right superior anterior temporal and subgenual cingulate cortex (ATL-SCC)	Stabilization of previous correlation	Increase ATL-SCC correlation during retrieval of guilt-related events	Increase in ATL-SCC connectivity in guilt relative to indignation in experimental compared to control condition; stable BDI-II ratings; increase in global self-esteem	14 (experimental) vs. 14 (control); (patients in remission)
Zotov et al., (2019) (combined rtfMRI/EEG NF)	Left amygdala, rACC, frontal alpha/beta asymmetry	Sham NF	Increase activity using happy autobiographical memories	Successfully upregulated left amygdala, FAA, and FBA and significant mood improvements	16 (experimental) vs. 8 (control)

relevant structures have been found to respond to fMRI NF: the insula as it is associated with the subjective feelings of emotional states [35–37] and the anterior cingulate cortex (ACC; [13, 38]). In these studies, regulation of the target region was associated with the increase of positive (e.g., happy mental imagery, positive autobiographical memories) or negative (e.g. negative autobiographical memories) emotions as well as a reduction of negative emotions (e.g., cognitive reappraisal, attentional redirection).

Successful control of brain signal in healthy participants is an accepted precondition for the application of rt-fMRI NF in patients with psychiatric disorders. Subsequently to the above findings, studies in depression have focused on training upregulation of emotion processing areas such as amygdala using positive autobiographical memories [17, 18, 39] or upregulation of individualized target regions using positive mental imagery [19, 20, 40], whereas only few studies focused on downregulation of brain areas in response to negative stimuli [21] or a bidirectional approach of up- and downregulating middle prefrontal cortex [41]. Furthermore, more recent studies have tested feasibility of new approaches such as regulating connectivity between regions [42] or moved toward more immersive feedback modalities such as virtual environments [43–45]. In the following subsection, some of these studies will be discussed in more detail (see Table 15.1 for overview of studies).

15.2.1 Upregulation of Amygdala

The amygdala has received most attention for its role in hyperreactive processing of negative or fearful stimuli in depression. However, a few studies have shown an increase in amygdala hemodynamic response to both negative and positive stimuli, indicating that amygdala response may more generally signal salience of emotional stimuli [46]. Furthermore, patients with depression show a hyperactive amygdala BOLD response to negative stimuli and a hypoactive amygdala BOLD response to positive stimuli compared to healthy subjects [47], indicating a dysfunctional emotional reactivity. Interestingly, up to now no study including patients with depression has directly investigated downregulation of amygdala response to negative stimuli. However, Young and colleagues have successfully trained patients with depression to upregulate their amygdala by using happy autobiographical memories (AM; [17, 18]). In their first study [17], mood change in a group of patients with depression who received feedback from the left amygdala was compared to a control group of patients who upregulated an area (intraparietal sulcus) unrelated to AM recall following a single session of NF training. Both groups were able to use positive AM to upregulate the hemodynamic signal in the respective area of interest. However, only patients who trained self-regulation of amygdala response showed a decrease of negative mood and an increase in state happiness. To further investigate clinical importance of these findings, Young et al. [18] conducted a double-blind randomized clinical trial in which upregulation of amygdala compared to upregulation of a

parietal control region was trained for 2 days. Whereas success in upregulating amygdala signal was related to clinical improvements comparable in effect size to those of antidepressant medication or cognitive behavioral therapy, patients in the control group did not improve. Furthermore, amygdala NF training increased resting-state amygdala connectivity with regions involved in self-referential, salience, and reward processing [48]. Interestingly, successful regulation of amygdala was also related to improvement in positive AM recall such as more specific memories and generalized to a decreased amygdala response to negative stimuli [49], indicating that training regulation of BOLD signal in one direction could possibly generalize to an improved control of amygdala response in different situations.

15.2.2 Upregulation of Emotion Processing Areas

Linden and colleagues [19] trained upregulation of emotion processing areas responsive to positive stimuli in treatment-resistant depression. Individualized regions of interest (including vIPFC, insula, and dlPFC) were determined through a localizer run during which patients viewed positive images. The experimental group was trained in the upregulation of a functionally defined region by using positive mental imagery, whereas the control group performed a comparable training without feedback outside of the MRI scanner. Depression ratings decreased significantly in the experimental group, whereas a non-significant increase of depression ratings was observed in the control group. However, as the control imagery group did not receive NF, it was unclear whether the effects were specific to NF of a specific emotion processing area or related to the non-specific reward experience of self-regulation. To follow up on this, Mehler and colleagues [20] trained two groups of patients with depression to upregulate either an area related to emotional processing of positive images (experimental group) or higher visual areas responsive to visual scenes (control group). Interestingly, both groups improved on clinical depression scales. However, self-efficacy (i.e., the perceived ability of self-regulation) rather than regulation success was related to clinical improvements.

15.2.3 Downregulation of Emotion Processing Areas

While many studies have focused on the upregulation of brain areas, one study trained patients with depression to downregulate a salience network node shown to be hyperresponsive to negative stimuli in depression [21]. Whereas patients in the experimental group received real feedback, patients in the control condition received yoked feedback, i.e., feedback from a different participant. The experimental group had a significant decrease of emotional ratings of negative stimuli and in self-relevance ratings of negative adjectives following NF. This underscores the importance of salience network nodes for the pathophysiology of depression.

In a study from our working group, patients with depression were indirectly trained to downregulate an amygdala response by upregulating either the left or the right ventrolateral prefrontal cortex (vlPFC) in a double-blind randomized cross-over design [40]. In order to regulate the vlPFC, subjects were instructed to use cognitive reappraisal strategies to downregulate their emotional response to negative affective stimuli (see Fig. 15.3). Feedback values were provided intermittently based on the difference between reappraising and viewing a negative picture without influencing one’s thoughts. In preliminary analyses, patients with depression were able to upregulate their brain signal from the vlPFC, and the prefrontal activation was related to a subsequent downregulation of amygdala responses. These studies indicate that (indirect) downregulation of areas involved in emotion processing by enhancing top-down control may be clinically effective and could potentially extend the benefits of upregulation training of amygdala with positive stimuli.

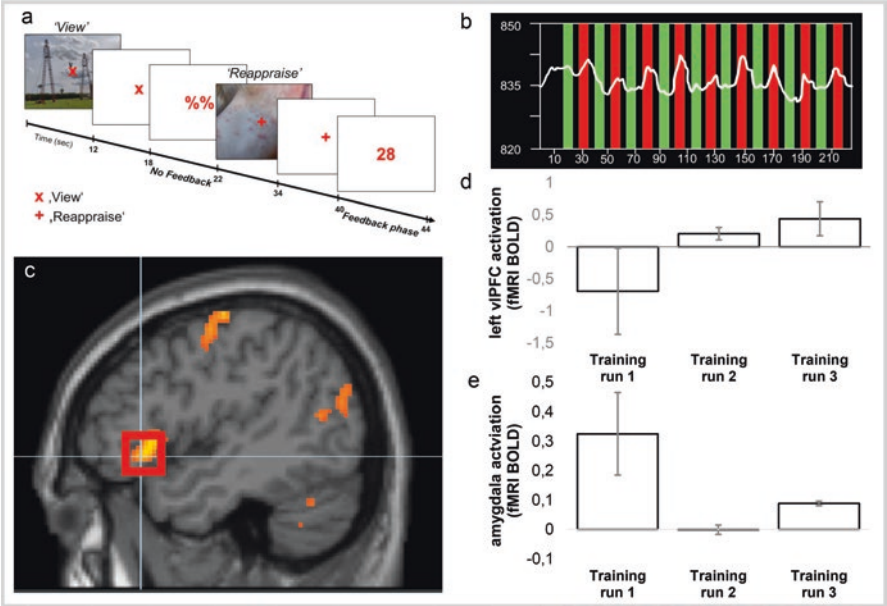


Fig. 15.3 Self-regulation of the left ventrolateral prefrontal cortex (vlPFC) in a representative patient with depression. (a) Cognitive reappraisal paradigm used for rt-fMRI NF training. Participants were instructed to passively view negative pictures during “view” condition and reinterpret the negative content of the pictures during the “reappraise” condition. (b) Example of real-time regulation of left vlPFC during neurofeedback training. Time course shows activation in left vlPFC during view (green) and reappraise (red) conditions. (c) Control over upregulation of vlPFC, i.e., contrast between viewing and reappraising negative picture (regulate – view) shows significant activation in the left vlPFC, the area from which the feedback signal is computed. (d) Self-regulation capability shows a significant increase in vlPFC activation throughout neurofeedback training. (e) At the same time, there is a relative decrease of amygdala activation

15.2.4 Combination of Cognitive Behavioral Therapy and NF

Generalization of cognitive strategies to real-world scenarios is one of the critical challenges of psychotherapy. Some researchers have used NF training to enhance the credibility and availability of previously learned mood regulation strategies [22]. Following cognitive behavioral therapy (CBT), patients suffering from depression were instructed to recollect AM that evoked negative emotions and their most effective cognitive strategies learned during CBT. During rt-fMRI NF training, they were instructed to use them to downregulate ACC activation. Seeing how these subjectively effective strategies influenced their own brain signal increased credibility of strategies learned during CBT, gave patients an understanding of neural processes during emotion regulation, and further guided them in which cognitive strategies were most effective and should be applied in everyday life. In a contrasting preliminary report, Barb and colleagues [23] trained patients in the regulation of either the amygdala (experimental group) or a parietal control region (control group) before 10 weeks of CBT. Patients in the experimental group showed higher depressive symptom improvements within the first 3 weeks of CBT treatment (“sudden gain”). Conceivably, rt-fMRI NF training and CBT treatment may facilitate each other’s effects.

15.2.5 Future Developments of rt-fMRI NF

The field of rt-fMRI NF is continually developing, and more advanced techniques for calculating and delivering the feedback signal are tested, some of which will be discussed here. Certainly, the development of fMRI overlaps with advances in rt-fMRI NF. As fMRI is becoming faster (i.e., faster repetition times and better temporal resolution) and more precise (i.e., higher spatial resolution related to higher field strengths), these advantages will also be applied to NF applications. Seven Tesla NF methods are under development [50, 51] and may eventually enable NF applications on the submillimeter level. Furthermore, rather than simply training the mean activation level of a single region, new NF techniques are, e.g., focusing on training the modulation of functional connectivity (FC) within brain networks [52]. This offers the possibility to directly target the underlying connectivity patterns of psychiatric disorders. In a pilot study, patients with (subclinical) depression successfully learned to reduce the connectivity between hubs of the default mode and the frontoparietal network after 4 days of FC NF training [53]. Furthermore, the decrease of connectivity was associated with improvements in scores on the Hamilton depression rating and Beck Depression Inventory-II. In a different study, patients with remitted depression increased the connectivity between the right superior anterior temporal and the subgenual anterior cingulate cortex which was associated with an increase in global self-esteem [42]. Despite promising preliminary findings, the methodological intricacies of this method such as the sensitivity of FC to respiratory

artifacts [54, 55] have to be carefully considered. Alternatively, patients with depression can train to produce brain patterns associated with healthy emotional brain states using support vector machine algorithms [56]. DecNef is an innovative method based on multivariate analysis to change activity patterns of multiple voxels within a circumscribed target region even in the absence of conscious perception [57]. Neural multi-voxel activity patterns of a targeted mental state are determined, and the participant is asked to train the similarity between the current and target state by receiving a feedback score. Targeting specific activation patterns offers a greater spatial precision compared to the rather coarse mean amplitude of the fMRI signal in a target region. Several studies have shown its potential as an adjunctive treatment for psychiatric disorders [58, 59].

Finally, there is an increasing interest in developing the combination of NF with virtual environment (VE) and virtual reality (VR) applications which have also been applied for alleviating depressive symptomatology [60, 61]. VR/VE is an immersive technology that could increase the ecological validity of rt-fMRI studies as strategies learned throughout the training may be difficult to apply in everyday life. Several studies have demonstrated the feasibility of using rt-fMRI NF in the context of a virtual environment. For instance, Lorenzetti et al. [43] used changes of the color in a virtual environment that successfully guided participants to control the target regions related to feeling either anguish or tenderness. Baqapuri et al. [45] developed a VE using a violent computer game to provide participants with implicit feedback of their SMA activity. They showed that the modulation of movement speed of the avatar by using cognitive strategies to increase SMA activity was feasible. Preliminary results of this paradigm to target lack of motivation in patients with depression resulted in a significant decrease in behavioral apathy scores if participants applied the learned strategies in everyday life [44]. These studies indicate that the application of VE/VR rt-fMRI NF paradigms is feasible and should be further developed. VE/VR NF may combine the best of two worlds as being immersed in a virtual world could make feedback presentation more believable and learned strategies more likely to be applied in similar everyday life situations.

15.3 Methodological Considerations

It is consensus within the rt-fMRI NF community that learning brain self-regulation with NF is possible. Furthermore, NF may be able to remediate or enhance impaired cognitive processes such as emotion regulation in various psychiatric disorders such as depression [29]. However, with respect to possible clinical benefits of brain self-regulation, large randomized controlled studies with long-term follow-up investigations are needed to determine the crucial factors making rt-fMRI NF treatment most effective.

15.3.1 Study Designs to Investigate Clinical Significance of Real-time fMRI NF in Depression

There is large heterogeneity in key methodological parameters such as the target region, experimental paradigm, control conditions and groups, and NF presentation as well as instructions. These differences in methodology and evaluation and presentation of results make it difficult to combine results. Guidelines for reporting results are needed, and attempts have been made to propose common guidelines for designing and conducting clinical and cognitive-behavioral NF studies [62]. Some of these include the preregistration of the study where the experimental procedure and the hypotheses are predefined. A suitable control condition should be chosen, and patients and researchers should be blinded toward the treatment. Thibault et al. [63] suggested that approximately 30% of participants will not learn self-regulation of the brain signal. Thus, studies should not only focus on finding the most effective study design but also on defining markers that identify learners and non-learners to optimize patient selection. For instance, Young and colleagues [18] have shown that targeting patients with depression early in the course of their current depressive episode will make clinical success more likely. Furthermore, as the basic functioning of rt-fMRI NF has been established, well-controlled long-term studies are required to put the clinical effects to the test. It is important to follow up on symptom change as studies have shown symptom improvements for weeks after NF [64].

15.3.2 Placebo Effects

It has been argued that the clinical benefit related to rt-fMRI NF may be due to the reward experience of self-regulation itself rather than the feedback from brain regions implicated in a psychiatric disorder (e.g., [20]). This means that effective self-regulation (as measured by an increase in the NF signal) may be rewarding and subsequently increase mood following the NF training. Furthermore, experimental and control groups are often not matched for reward experience and thus lead to biased effect estimates. For instance, the control group eventually gains less control over the control NF (e.g., sham feedback) as compared to the verum group. However, to our knowledge, there are no other studies that have explicitly investigated placebo effects by using a suitable control regulation condition. This indicates the difficulty of finding suitable control conditions that exclude possible non-specific NF effects. For instance, Young et al. [18] compared regulation success and change of depressive symptomatology using a control region (parietal sulcus) in their well-designed randomized controlled trial. Compared to the experimental group that regulated the amygdala, the control group did not show a significant improvement of mood. However, patients in the control group were less able to regulate their brain signal compared to the experimental group, possibly resulting in a less

intensive reward experience and less improvement of depressive symptomatology. To further clarify the role of placebo effects in rt-fMRI NF, more systematic investigations are needed.

15.3.3 Limitations of rt-fMRI NF

Despite its potential there are certain shortcomings of rt-fMRI NF which limit its usability within the clinical field. First, rt-fMRI NF appears a costly intervention due to the MRI scanning cost and the trained staff needed for operation. Furthermore, NF in the fMRI environment is restricted to people without MRI contraindications. The magnetic waves of the MRI scanner could heat up metal, causing severe harm to these individuals. This means that individuals with metal implants, metal workers, or women during pregnancy cannot receive rt-fMRI NF. Finally, the MRI scanner is a narrow space that may cause anxiety in individuals with claustrophobia which may impair the intervention. It is likely that due to these constraints, rt-fMRI NF will not become a widely applicable treatment. However, using this technology we can gain important information about brain mechanisms in depression. In the long run, research findings should be transferred to a more accessible intervention such as EEG NF. To establish the transfer of findings from fMRI to EEG, several NF studies have done simultaneous EEG and fMRI NF measurements to correlate, for instance, EEG asymmetry with BOLD fMRI signals [39, 65]. Furthermore, the lab of Talma Hendler has already presented the feasibility of using EEG to create an electrical fingerprint (EFP) of the amygdala BOLD activity [66]. Healthy participants in an experimental group (compared to sham NF and no NF) successfully trained the downregulation of the amygdala-EFP and improved in implicit emotion regulation indicating the therapeutic potential of this method [67]. This novel and scalable method is promising as it combines findings from high spatial resolution fMRI with high temporal resolution of EEG which may potentially overcome the shortcomings of fMRI-based NF.

15.4 Current and Future Role of fMRI-Based NF in Depression

Rt-fMRI NF is an important tool in helping patients and researchers to gain more knowledge about the neural and cognitive processes underlying depression. Within the past 20 years, the field has advanced methodologically to develop promising trainings for decreasing symptoms of depression by targeting brain areas involved in processing emotional information (amygdala, insula, prefrontal cortex, or anterior cingulate cortex). The limited number of studies investigating clinical long-term outcomes makes it difficult to state informed conclusions about clinical

effectiveness. However, some studies have shown promising results with effectiveness within range of antidepressant medication or psychotherapeutic treatment. The jury is still out, but it is likely that NF (even in its most effective design) will not be able to completely alleviate symptoms of depression on its own. However, NF may add an important tool to the orchestra of treatments for combating this debilitating disorder.

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Chapter 16

Cognitive Behavioral Therapy and Mindfulness-Based Cognitive Therapy for Depressive Disorders



Sang-Hyuk Lee and Sung Joon Cho

Abstract Recently, the importance of cognitive behavioral therapy (CBT) in the treatment of depression is gradually emerging. Particularly, mindfulness meditation has various approaches related to dialectical behavioral therapy (DBT), acceptance and commitment therapy (ACT), mindfulness-based stress reduction (MBSR), and mindfulness-based cognitive therapy (MBCT), and evidence has been provided that they alleviate depressive symptoms. In particular, as MBCT increases the level of evidence in the treatment of repetitive depressive disorders, guidelines are being recommended to prevent recurrence. Mindfulness may also contribute to improving the patient's symptoms as well as improving the therapeutic relationship with the therapist. For both mindful patients and therapists, positive awareness of internal experiences can be a good way to enrich the mind and overcome depressive disorders.

Keywords Cognitive behavioral therapy · CBT · DBT · ACT · MBCT · Mindfulness · Depression

16.1 Cognitive Behavioral Therapy and Depressive Disorders

Advances in medical science have yielded several treatment options to overcome depressive disorders. Biological treatments include pharmacotherapy, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), deep brain

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stimulation (DBS), vagus nerve stimulation (VNS), phototherapy, and sleep deprivation. Psychotherapy and psychosocial therapy include psychoanalytically oriented therapy, cognitive therapy, behavioral therapy, cognitive behavioral therapy (CBT), interpersonal therapy, and family therapy [1].

There have been numerous studies of the effectiveness of psychotherapy in major depressive disorders. Pharmacotherapy is preferred for patients with moderate or severe depressive disorder because it is faster and more effective, costs less, and has greater accessibility because of the simplicity of its form. However, psychotherapy can be considered primarily for patients with mild to moderate depressive disorder, and the therapeutic effect is maintained even if the treatment is stopped after symptoms improve. Psychotherapy may not be applicable to all depressed patients, but it could be applied to situations where there are serious drug side effects or inability to take medication for reasons such as pregnancy and lactation. In addition, psychotherapeutic approaches could be considered if the patient had previously received psychotherapy and showed a good therapeutic response. In particular, if the patient agrees to psychotherapy, is motivated for his change, and has the characteristics to reflect on and control his problem, application of a psychotherapeutic approach can be reviewed positively [2].

In addition, psychotherapeutic approaches have the features of requiring sufficient support, environment, time, and economic margin. Psychotherapeutic approaches can be particularly useful when psychosocial stress or internal conflict is having a significant impact on the incidence and duration of depression. At present, the best therapeutic effect is achieved when pharmacotherapy and psychotherapy are combined. Recently, in addition to traditional psychodynamic psychotherapy, interpersonal psychotherapy and CBT are known to have the greatest therapeutic effects on depressive disorder [2].

Traditional psychodynamic psychotherapy is the oldest form of psychotherapy and refers to all psychotherapy based on psychodynamic/psychoanalytic theory. The theoretical core hypothesis of psychodynamic psychotherapy is that emotional and distorted defense mechanisms that are unconsciously resolved with an important person contribute to the negative emotions and thoughts that form depressive symptoms. In order to obtain insight, the therapist and the patient explore how conscious/unconscious conflicts are expressed (through transference and countertransference) in the therapeutic relationship at present, find their clues in the past, and go through the process of interpretation and conflict. Psychodynamic psychotherapy has difficulties in widespread use because of the need for long-term treatment and the flaws of standardization. Short-term psychodynamic supportive psychotherapy has been developed to address this problem. Based on psychodynamics, but with a supportive approach, the reduction of symptoms, recovery of social function, and limited alterations of the personality structure are therapeutic goals [3].

Interpersonal psychotherapy emphasizes the patient's current interpersonal relationships and social experience. The treatment also recognizes the patient's attempts to adapt his psychopathology to a constantly changing psychosocial environment. Adaptation to the environment seems to be partly a direct reflection of family

relationships in the early years of life. The therapist approaches depressive disorder as an interpersonal concept and does not assume that interpersonal relationships cause depressive disorder. Regardless of the cause of the depressive disorder, the therapist assumes that the current depressive symptoms appear in an interpersonal context and uses a treatment strategy to help the patient control his or her background. The therapeutic goal of interpersonal psychotherapy is to alleviate the depressive symptoms and to improve the quality and social function of the current interpersonal relationships associated with the depressive symptoms of patients. In psychodynamic psychotherapy, unconscious conflict is the main concern of treatment, whereas interpersonal psychotherapy focuses on interpersonal relationships. On the other hand, CBT, which will be discussed next, differs from interpersonal psychotherapy in that the main concern is to consider and overcome internal problems such as automatic thinking and core beliefs [2, 4, 5].

CBT focuses on the cognitive distortions postulated to be present in major depressive disorders. Such distortions include selective attention to the negative aspects of circumstances and unrealistically morbid inferences about sequences. The patient explores with the therapist which thoughts, beliefs, and interpretations are associated with depression and how they are affected by these factors. In addition, the patient practices how to identify and test their thoughts, beliefs, and interpretations as opposed to depressive symptoms. Finally, learn and practice adaptive skills appropriate to patient's symptoms. CBT does not focus on unconscious conflict, transference and counter-transference, resistance, or interpretation, as in psychodynamic psychotherapy. In CBT, behavioral intervention uses behavioral activation, self-control therapy, social skills training, and problem-solving therapy based on behavioral and social learning theory. Behavioral interventions are particularly helpful for people with depressive disorders with social withdrawal or anhedonia [5, 6].

CBT conceptualizes problems through a cognitive approach and treatment is based on the conceptualized problems. The most important emphasis in the treatment process is case conceptualization, which refers to creating a framework for understanding the client's problems from the perspective of CBT. The concept of CBT is to construct a hypothesis about the process whereby the patient's problem occurs and how it is maintained and to treat the client through this hypothesis. CBT trains patients to identify, evaluate, and correct their dysfunctional thoughts and beliefs. A key mechanism of change in cognitive therapy is disproving self-decentralization and experiential disformation. Decentering is the process of taking a step back from one's problem and looking back on oneself. It promotes decentering through the process of case conceptualization and the process of finding and objectifying dysfunctional thought according to the cognitive model. The patient realizes that when one reacts to a situation, one does not respond to the event itself, but to the event as interpreted through one's schema. Experiential disformation confirms the irrationality of existing dysfunctional schemas as the patient enters a problem situation and has a new experience. If the patient's dysfunctional schema changes first, one will be faced with anxiety and fear, and the experience will allow

one to verify one's dysfunctional schema. CBT emphasizes mutual cooperation and active patient involvement. Collaborative empiricism is important [5].

The treatment effect of CBT for acute phase of depressive disorders has been found to be similar to those of pharmacotherapy, interpersonal psychotherapy, and behavioral therapy. In addition, the results of several clinical studies of CBT showed that a combination of CBT and pharmacotherapy at the same time did not increase the response rate of depressive disorder more than expected. However, since each treatment strategy is complementary, the combination of two treatments can be a very effective treatment strategy for depression [1, 3, 7].

CBT developed naturally as the need for new approaches and awareness of the limitations of conventional psychoanalytic therapy increased. Albert Ellis and Aron T. Beck, trained in psychoanalysis, were skeptical of existing therapies and suggested a new therapeutic approach, CBT. In recent years, CBT has been extensively studied and integrated into clinical applications. In the 1960s, it was mainly applied to patients with depression, and once its effectiveness was proved in this domain, it has been broadened to treat various diseases such as panic disorder, general anxiety disorder, obsessive compulsive disorder, and eating disorder. Since the 2000s, CBT has changed and developed, with another form of treatment such as Mindfulness-Based Cognitive Therapy (MBCT) combining mindfulness meditation and CBT [5].

Recently, MBCT has received much attention as one of various approaches of psychotherapy. MBCT has been developed by presenting scientific certificates based on Oriental vipassana meditation. MBCT has been divided into different categories by different scholars, but it can be divided into two major procedures: focused attention and awareness/open monitoring. MBCT trains additional techniques and improves the techniques so that they can deal more effectively with morbid states such as anxiety and depression. This chapter explores the definition of mindfulness and its techniques and discusses the clinical effects of MBCT and how it is currently presented in depression treatment guidelines [5].

16.2 Mental Habits That Cause Depression

In general, one of the greatest features of cognitive therapy is that it helps to find connections between emotions, thoughts, and behaviors that make up a particular affective disorder. Cognitive therapy not only provides mental guidance to the therapist and patient to understand the clinical condition, but also provides guidance on what is needed for better change based on this understanding. The result is that both the therapist and the patient can use their energy flexibly and creatively to deal with the problem.

The same is true for MBCT. If you are familiar with the exact process of maintaining and recurring depression, this may be useful. However, this method is not simple, because depressive symptoms may not be as severe as they usually appear. In this situation, an understanding of the process of maintaining and recurring depression and an understanding of this general mechanism is needed [5].

A depressed mood is maintained and reappears when the pattern of negative thinking is reactivated. The pattern of negative thinking occurs on its own rather than as a result of intentional selection by the individual. Naturally, all patients do not want this pattern to be maintained and reappear. However, this thinking pattern is automatic in the sense of running along mental traces. Thoughts are more of a matter of “self-moving” minds rather than conscious decisions and choices. In addition, characteristic thoughts, emotions, and physical sensations are integrated as a whole and activated as a package. As the various elements mentioned interact, they reinforce each other through feedback loops and create a whole new set of thoughts, feelings, and body sensations. If left unchecked, this recurring condition develops into more serious and persistent depression [5, 8].

In view of the experience of these depressive symptoms, the “self” seems to be inadequate, worthless, or vulnerable, and negative thoughts seem to accurately reflect reality. Thus, making changes at a deeper level requires more than providing new conceptual information about depressive symptoms, negative thoughts, and recurrence. The therapist must allow the body and mind to repeat and accumulate new experiences and thereby create alternative perspectives [5, 8].

It can be questioned whether the maintenance and relapse of depression is related to the reactivation of mental habits. How does the mind develop these bad habits? Why do the patients have to maintain bad habits that are not very helpful? The reason is simple. The mind is motivated to achieve the actual desired goal. In reality, however, mental strategies used to achieve goals are often very inefficient and often work contrary to their intended purpose. For example, consider a person having trivial troubles with a colleague at work for several days. The person will keep on repeating his thoughts to see why he is upset. Trying to get rid of worries is something that gradually gets lost. In the end, this process returns to “old mental habits [5, 9].”

There is a discrepancy between the cognitive strategy woven in this “old mental habit” and what is needed to change one’s lasting state of mind. Old mental habits make people seem to “think” how to get out of their problems. This includes reflecting on current emotional states, past negative events, and any problems that can arise when there is no change. At the core of rumination is the so-called “discrepancy monitor” engine. When the engine starts running, it finds a mismatch between the current state and the desired state. When a discrepancy is detected, efforts to reduce the discrepancy may be synchronized, but at the same time an undesirable negative mood may be amplified. Attempting to solve a problem by constantly thinking about the inconsistency between the desired state and the present state implies that an individual is in a state that he is trying to escape. Anyone who experiences severe depression will make considerable efforts to prevent further depression and will continue to try despite repeated failures. However, a more proficient response is to let go of the depression and get away from the depressed mood or recurring mind [5].

16.3 Definition of Mindfulness and the Techniques for the Treatment of Depressive Disorder

Mindfulness means intentionally concentrating on what is happening now and being nonjudgmentally aware [10]. Mindfulness is paying attention to the thoughts, emotions, sensations, objects, etc. that are happening in the present, and when the mind wanders in the middle of this task, we have to notice and returns to the present. It is a complex cognitive-emotional task that accepts the thoughts and emotions that come to mind during our every experience nonjudgmentally. “To accept negative perceptions and emotions nonjudgmentally” means we do not automatically respond to the thoughts and emotions as we are used to. The thought that comes to mind is the process of accepting that it is merely a “thought” and not true, and that the emotion is also an “emotion” that one is used to it. Repeating this mindfulness in a familiar process that makes it possible for us to escape acting on “automatic pilot [5].”

Patients with depressive disorders tend to have negative cognition and emotions automatically, even if given neutral stimuli. A depressed individual often reflects on these negative thoughts or feelings (rumination) and tends to cling to them. With MBCT breathing meditation training, patients spend less time concentrating on breathing and have overloads as their mind wanders, resulting in negative associations with biting tails. The therapist then instructs patients to be aware their own ruminations. Patients often struggle with this mindfulness training by criticizing themselves. At this point, the therapist must critically focus on the task of teaching that one’s thoughts are simply “thoughts” that are “not true” and paying attention to the present again. The therapist should also help patients to accept and remain aware of this pattern, reassuring them that this negative association is a natural process [8].

Mindfulness is different from traditional cognitive behavioral therapy (CBT), in which the therapist counters and directly corrects the patient’s distorted cognition. For the first step, the therapist should accept the patient’s automatic association. This also allows patients to rely on their own automatic patterns, resulting in a corrective response. This is a new and powerful aspect. However, it is not easy to understand mindfulness through books, but is a process of learning empirically through mindfulness training.

16.4 Mode of Mind

The mind can be thought of as a collection of components that interact with each other. Each of these elements accepts information from the sensory world or other components of the mind. Each element processes the received information and passes the processed information to other elements. Through the same process, these elements convey more information. We can think of the workings of the mind as a continuous flow and as an exchange of information between elements. If we

look into the mind, we can see some recurring patterns in the interactions between the elements over time. For a while, one pattern dominates, then a change in the internal or external world results in a change, and eventually the same components of the mind that previously interacted in one pattern now act in different states. This interaction prevails for a while until another change occurs and there is a return to the original interaction pattern or changes to another form. Thus, it can be seen that the activity of the mind is constantly changing and repetitive, exhibiting a changing pattern of interactions between its components. Mindfulness training is about teaching people to be more aware of the mode of the mind at every moment and to move away from less useful modes of the mind to more useful ones. Mindfulness training involves recognizing two main modes of mind and learning the skills to move from one to the other [5].

The first is the “doing mode,” which usually happens when seeing something unwanted happening. To be more specific, it appears when one detects a mismatch between what one expects to happen and what one wants or thinks should happen. In this mode, negative emotions occur and habitual mind patterns are activated to reduce the difference between the present or expected state and the desired state.

The second is the “being mode.” The “being mode” can be understood in a direct and empirical way, and in many ways contrasts with the “doing mode.” The “being mode” is not synchronized to achieve specific goals. There is no need to emphasize treatment based on discrepancies without constantly monitoring what you are doing to achieve your goals. Instead, the focus on the mode of existence is to “accept” and “allow” what is there, without feeling the pressure to change it immediately. Instead of roughly addressing where you are in relation to achieving your goals and paying narrow attention to the present, the experience of the “being mode” at any moment can be dealt with deeply, broadly, and abundantly.

The two modes also differ temporally. The “doing mode” needs to be able to calculate future outcomes related to goals, anticipate the outcomes of goal achievements, and demonstrate memories of past problematic or related situations to facilitate goal achievements. Eventually, the “doing mode” often leads to the past or the future, making the experience not real in the “here and now.” On the other hand, the “being mode” allows you to stay fully in the present, devoted only to dealing with instantaneous experiences and to recognizing what is happening.

In the “doing mode,” emotions are often assessed as “good” or “bad” and the mind sets the goal of trying to determine whether each of those emotions should be sustained or stopped. It then embodies emotions as “objects,” with independent and sustained reality. However, in the “doing mode,” these thoughts and feelings are just passing events that arise in the mind, become objects of awareness, and disappear in line with the “decentralized” view at the core of cognitive therapy. The process is characterized by feelings of freedom, freshness, and the development of experiences in new ways.

Note, however, that this does not mean that the “being mode” is a special state in which all activities must be stopped. Both doing and being are modes of the mind and both may or may not involve activity. In a “being mode,” however, if you are

disturbed when you do something, you will have a choice of what to do at that moment, rather than being a source of frustration.

16.5 Programs Based on Mindfulness

There are four recent representative mindfulness meditation programs that are widely used: mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), dialectical behavioral therapy (DBT), and acceptance and commitment therapy (ACT) [11]. These programs are applied in various clinical situations, not only among the general public but also in patients with depressive symptoms.

MBSR was developed as part of an easy-to-learn meditation by Kabat-Zinn in 1990 [12]. Afterward, MBCT was further developed by Segal as a relapse prevention therapy for depressed patients. In particular, MBSR and MBCT help patients to deal with negative thoughts and feelings more effectively and relate to them differently than before. Since then, attempts have been made to apply mindfulness as a part of cognitive behavioral therapy to the treatment of various diseases. Linehan developed DBT, which has been shown to be effective in the treatment of borderline personality disorders [13]. In addition, the main goal of the program is to reduce dangerous behaviors such as suicide attempts. ACT, developed by Hays, is known to increase psychological flexibility and helps to focus on values and acceptance without avoiding unwanted thoughts and feelings [14, 15]. All of these programs differ slightly in their goals and practices, but they have a common root in mindfulness.

MBSR is a mindfulness-based stress management program whose techniques are varied. Raisin meditation, body scans, and focused breathing are typical. Participants move their attention consciously to their physical senses from head to toe through body scans and are encouraged to observe any senses or feelings they feel in the body part they are paying attention to. Likewise, in focused breathing, participants practice the same critical awareness of thoughts that come up naturally as they focus on their breathing [16]. Large-scale randomized controlled studies of the effectiveness of MBSR have been relatively few. The program has been shown to have an effect on depressive symptoms, but the evidence is not strong. Rather, it has been reported that the program may be effectively applied to other psychosomatic diseases, such as psoriasis and cancer [17, 18]. On the other hand, there are reports that there is an association between meditation and psychotic disorders such that meditation seeking in patients with psychotic vulnerabilities stimulated the vulnerability and caused mental disorders [19]. However, there is another report that simple, short, and emphatic meditation is helpful for psychotic vulnerable patients [20].

DBT discourages patients with low functional levels, such as borderline personality disorder, from unconditional avoidance or inefficient responses to emotionally upsetting stimuli [21, 22]. In addition, the therapist uses DBT to train methods for dealing with intense emotions such as self-harm and suicidal thoughts [23].

Mindfulness in the DBT helps patients be “aware” as they are, rather than trying to avoid changing the negative thoughts or feelings they experience. DBT ultimately reduces depression, allowing patients to more objectively observe their own experiences of self-harm or suicidal impulse, thereby reducing risk behaviors [13, 24].

ACT is based on relationship framework theory, derived from functional contextualism. ACT starts with the notion that people’s cognitive styles are only important in the specific context in which they are triggered. The idea is that if we can change that context, the importance of certain perceptions can change. Patients will be able to change or control their behaviors through ACT training. In addition, by understanding the key concepts of values and acceptance, they lead to a way of living based on values and increase their self-preparation through the recognition that life has to pass through various emotions such as pain and anger [25]. Mindfulness in ACT trains patients to better understand the “observing self” that observes their own senses of mind, actions, thoughts, and feelings. The “observing self” introduces the concept of traditional cognitive behavioral therapy to help the patient share thoughts and emotional behaviors about an event [26]. This emphasizes strategies for accepting what is, rather than training for cognitive correction or alternatives that are claimed in traditional cognitive therapy. Through the process, patients will eventually be able to observe a cognition like “I think I don’t deserve to be loved” and describe the emotions involved in the same way [27].

16.6 Effective MBCT Programs for Depressive Symptoms

MBCT is a transformation that applies mindfulness to traditional CBT. Among the various psychological elements of mindfulness, an important element of MBCT is “awareness” of how we perceive and understand events. Mindfulness is a process of changing concentration, such as focused attention and decentralization, that also has cognitive elements. Participants will become “aware” of the pathological factors that come to them after experiencing anxiety or rumination, and learn that “the thought is not true.” To explain “three-minute breathing” as an example, patients first pay attention to breathing and slowly observe nonjudgmentally what thoughts are spreading in their minds and what senses are felt in the body. Once the patients have noticed the experiences, thoughts, and perceptions that are taking place in their minds and bodies, they do not evaluate them but observe them nonjudgmentally and expand their awareness of breathing throughout the body. Repetition of this process is encouraged whenever there is an opportunity in daily life, which can change patients cognitively by improving their ability to recognize how they perceive and react to events [28]. In patients, depressive feelings are usually noticeable, and when they are anxious, vague worries about the future are often prominent [29]. Even in recovered patients with repetitive depressive disorders, rumination can increase as the mood worsens and more negative thoughts develop. Through awareness of the process and changing the cognition associated with it, rumination is reduced, serving to prevent recurrence [5].

A meta-analysis of randomized control studies on MBCT conducted in the United Kingdom, Canada, Australia, Belgium, and the Netherlands found that compared to general depressive disorder treatment, MBCT significantly reduced the risk of relapse or relapse of depressive disorder for 60 weeks. It has also been reported that MBCT reduces the risk of relapse in depressive disorders compared to antidepressant therapy, which is the mainstream approach. These results did not differ by gender, age, or education level, and the effect was similar regardless of the meditation leader. The therapeutic effect of MBCT on the relapse or risk of relapse of depressive disorders was greater in patients with higher levels of depression measured at the start of the study. This suggests that MBCT is particularly useful for patients with severe depression. There were mentions of side effects, but none were due to MBCT.

16.7 Recent Depressive Disorder Treatment Guidelines and MBCT

As various studies of CBT have been conducted in the treatment of depressive disorder, treatment guidelines have changed. Representative guidelines addressing this issue include the Canadian Network for Mood and Anxiety Treatments, a guideline for the treatment of adult depressive disorders, published in Canada, established in 2009, and revised in 2016 [30]. Compared with previous generations of guidelines, MBCT was considered the primary treatment to be considered in maintenance therapy in psychiatric treatment of depressive disorders in addition to CBT. In addition, this guideline suggests MBCT as an additional approach that can be considered as a secondary treatment in the treatment of acute phase of depressive disorder. MBCT has been widely applied in patients who do not respond to treatment of residual depressive symptoms and early phase depression after treatment; it has a significant effect and has been shown to be effective in treating heterogeneous situations, such as when depressive symptoms are present or in remission. This study, the Canadian Network for Mood and Anxiety Treatments, conducted a systematic literature search focused on meta-analysis and question and answer formats. The guideline is based on the quality of evidence and the consensus from clinical practitioners and is considered to constitute valid recommendations.

MBCT is also mentioned in the adult depression treatment and management recommendations revised in 2017 by the National Institute for Health and Care Excellence (NICE). In particular, MBCT is emphasized in patients at high risk of relapse of depressive disorder. First, MBCT is recommended as a psychotherapy along with medication in patients who have recovered from severe depression but have a high risk of relapse (history of three or more recurrences) and are on medication, in addition suggesting that if patients discontinue treatment, it may help to reduce the risk of recurrence through MBCT. MBCT can also be considered when treatment is less effective; it is proposed as one of the psychotherapeutic modalities for patients with depression who have been treated for more than 12 weeks with a

combination of medication and psychotherapy but who have not shown an adequate response. NICE also presented appropriate MBCT sessions and follow-up observations, such that the program should be provided in a group of up to 15 participants, with sessions followed by 2 h per week for 8 weeks and four follow-up sessions for 12 months after treatment.

16.8 Biological Mechanisms of Mindfulness

Many studies have been done on the biological mechanism of meditation, among which a brain imaging approach to mindfulness is being actively pursued [31]. Studies of various parts of the brain are being conducted omnidirectionally. Among these studies are many related to the anterior cingulate cortex [32–34]. This area explains how mindfulness is related to changes in “the ability to pay attention.” First, a cross-sectional study reported activity of the anterior cingulate cortex during meditation while waiting for unpleasant stimuli [35]. Other longitudinal studies also reported greater activity of the anterior cingulate cortex in the meditation group [36]. More specifically, structural changes in the anterior cingulate cortex have been reported after MBCT in patients with panic disorder [37].

Research has also been conducted on the areas of the brain associated with the “awareness” of mindfulness. The main concept regarding the prediction of this area is the default mode network (DMN) in terms of looking at oneself [38]. This concept has been in the spotlight recently, and changes in the posterior cingulate cortex and prefrontal cortex are expected [39]. First, in a cross-sectional study, a change in the functional connectivity of the posterior cingulate cortex was observed in the group who performed meditation [40, 41]. In another longitudinal study, an increase in the function of the right posterior cingulate cortex was observed in a meditation relaxation training group [36]. In another longitudinal study, changes in prefrontal cortex activity were observed in a group of meditation trainees [42, 43]. In addition, other longitudinal and cross-sectional studies have reported that the insula, which are deeply related to DMN, are regulated in relation to mindfulness [36, 44, 45].

Since mindfulness affects emotional control, studies have also been conducted of related brain areas. First of all, the anterior cingulate cortex and prefrontal cortex mentioned above are thought to be the brain areas related to emotional regulation, and in which there have been reports of various changes. Next, the limbic system is also known to play a major role in emotion processing. In one longitudinal study, there was a report that the amygdala showed decreased activity in a group with mindfulness training in the direction of less severe changes in emotion and less anxiety [46, 47].

The mechanism for inducing such changes in brain structure is not yet clear. One possible mechanism is that changes in the sympathetic nervous system and hypothalamus-pituitary-adrenal axis through stress control affect the brain [48]. In addition, estimates of the likelihood that neuronal proteins, such as brain-derived neurotrophic factor, influenced synaptic changes in the brain have been carefully considered [49, 50].

16.9 MBCT in Other Mental Illness

MBCT is designed to prevent the recurrence of depressive episodes in patients with chronic recurrent depressive disorder. Since then, several studies have reported significant improvement in depressive disorder as well as generalized anxiety disorder [51, 52]. Studies in patients with traumatic experience have shown that the mindfulness-based therapies described above have significant effects, but many studies have not yet been conducted involving MBCT. According to a preliminary study comparing the effects of short-term group MBCT on war-related posttraumatic stress disorder patients, the symptoms of posttraumatic stress disorder decreased. MBCT has been reported to be particularly effective in reducing avoidance and cognitive-related symptoms [53]. This is in line with the fact that, like other mindfulness meditation therapies like MBSR, it reduces the avoidance of unwanted negative emotions or experiences. In addition, mindfulness training was found to significantly reduce self-criticism or perceived perception of the world by focusing on positive experiences and critical acceptance.

Recently, MBCT has been suggested as an important psychological treatment for panic disorder. MBCT studies in patients with panic disorder have shown that MBCT not only reduces anxiety and panic symptoms but also anxiety sensitivity [54, 55]. Mindfulness training helps to deal with worrying about the future, catastrophes, and disaster and thus can effectively deal with anxiety and panic symptoms and reduce the “intolerance of uncertainty” and increase endurance [56]. “Intolerance of uncertainty” is defined as a negative response at the emotional, cognitive, and behavioral level resulting from uncertainty and negative beliefs implied by it [57]. Although the concept of “intolerance of uncertainty” originated from generalized anxiety disorder, it was known to play an important role in the diagnosis and treatment of panic disorder, and thus could be reduced by MBCT. On the other hand, according to a study of the treatment effect of MBCT for panic disorder patients, comorbid personality disorder and anxiety sensitivity appear to be factors influencing the effect of MBCT treatment [58].

16.10 The Eight-Session Program

The MBCT program usually consists of eight sessions. When conducting a program for depressed patients, they have the following key goals: First, learn techniques to prevent depression from recurring. Second, help them become more aware of their physical senses, feelings, and thoughts at each moment. Third, develop ways to relate to different senses, thoughts, and feelings, and to accept and recognize specially unwanted feelings and thoughts rather than automatic, programmed routines that sustain one’s problems. Fourth, help the patient respond most skillfully to unpleasant thoughts, feelings, or situations [5].

The structure of MBCT program sessions is as follows. The first half of the session focuses on learning how to focus attention. We learn how little we pay attention in our daily lives. Patients then learn how to notice how quickly the mind moves, identify the wandering mind, and return it to focus. At this time, parallel content is to pay attention to each part of the body and the breathing. In conclusion, patients learn how to notice how negative thoughts and feelings are caused by the wandering mind and to pay attention to the different parts of the body and the breathing. Next, patients learn how to notice how negative thoughts and feelings are caused by the wandering mind. Through this process, MBCT can be used to improve sensitivity to mood changes. Later sessions then deal with mood swings. In MBCT, the therapist emphasizes that whenever negative thoughts and emotions arise, they should be allowed to just stay there before moving on to a proficient response using a special strategy. Patients have to train themselves to be fully aware of their thoughts and feelings, and then focus on their breathing for a few minutes and extend it throughout their body. Finally, participants become more aware of the unique warning signs that depression is recurring and develop specific action plans when this happens.

At the beginning of each session, the basic theme and curriculum of the session are presented, and participant handouts in the MBCT study are used at the end of each session. Later classes can be organized according to the situation. The number of participants will depend on the facilities available. Jon Kabat-Zinn has taught groups with 30 or more students and points out that too few classes can be a problem because it is too easy to enter the “treatment” form from the “class” form.

When the MBCT program comprises eight sessions, it is organized as follows.

Session 1: Automatic Pilot

Session 2: Dealing with Obstacles

Session 3: Mindful Breath

Session 4: Stay in the Present

Session 5: Accepting/Allowing

Session 6: Thoughts Are Not True

Episode 7: How Can I Care for Myself?

Each session will be taught involving meditation such as raisin meditation, body scan meditation, breathing meditation, right seat meditation, walking meditation, and 3 min of breathing. To learn this process effectively, the patient needs to complete assignments such as thought sheets, pleasant event sheets, objectionable event sheets, meditation exercises, and reviews.

16.11 Conclusions

As mentioned above, mindfulness meditation has various approaches related to DBT, ACT, MBSR, and MBCT, and evidence has been provided that they alleviate depressive symptoms. In particular, as MBCT increases the level of evidence in the treatment of repetitive depressive disorders, guidelines are being recommended to

prevent recurrence. Mindfulness may also contribute to improving the patient's symptoms as well as improving the therapeutic relationship with the therapist. For both mindful patients and therapists, positive awareness of internal experiences can be a good way to enrich the mind and overcome depressive disorder.

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Chapter 17

Acceptance and Commitment Therapy for Major Depressive Disorder: Insights into a New Generation of Face-to-Face Treatment and Digital Self-Help Approaches



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Abstract Major depressive disorder (MDD) represents a key contributor to the global burden of mental illness given its relatively high lifetime prevalence, frequent comorbidity, and disability rates. Evidence-based treatment options for depression include pharmacotherapy and psychotherapy, such as cognitive behavioral therapy (CBT). Beyond traditional CBT, over 15 years ago, Hayes proclaimed a new generation of contextualistic and process-orientated so-called third wave of CBT interventions, including acceptance and commitment therapy (ACT). Using mindfulness and acceptance as well as commitment and behavior change processes, the transdiagnostic ACT approach aims to increase psychological flexibility as universal mechanism of behavior change and to build a value-driven orientation in life. ACT for MDD can be provided as either stand-alone individual, group, or self-help formats (e.g., apps) or combined with other approaches like behavioral activation. To date, a steadily growing empirical support from outcome and process research

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suggests the efficacy of ACT, which appears to work specifically through the six proposed core processes involved in psychological flexibility, such as defusion. In view of an ongoing interest of clinicians in “third-wave” CBTs and the important role of clients’ preferences in providing therapy choices that work, the purpose of this chapter is to give a brief overview on the application of ACT in the treatment of MDD in adults.

Keywords Depression · Cognitive behavioral therapy · Acceptance and commitment therapy · eHealth · DSM-V

17.1 Introduction

Major depressive disorder (MDD) represents a tremendous contributor to the global burden of mental illness [1, 2]. In the USA, MDD has a lifetime prevalence of 20.6% and is associated with a high risk of chronicity as well as comorbidity, especially with generalized anxiety disorder (odds ratio of 5.7) [3]. Furthermore, depression is associated with increased mortality (higher overall relative risk of 1.8) [4]. There are various effective pharmacological and psychological therapies that can be recommended as stand-alone, combined, or sequential treatments for MDD in adults [5, 6]. For mild depressive symptoms, low-intensity psychotherapy is a first-line treatment choice, while for at least moderate acute depressive episodes, medication therapy, preferably in combination with psychotherapy, should be prescribed [7, 8]. However, pharmacotherapy can be associated with side effects and treatment discontinuation [9], which can be challenging in the prevention of recurrent or management of chronic forms of MDD [10]. Also, current evidence challenges antidepressant treatment recommendations [11]. Furthermore, negative attitudes against pharmacotherapy among some patients suffering from depression may make it necessary to also focus on evidence-based psychological treatments [9]. Overall, research indicates that a mismatch between patients’ treatment preference (pharmacotherapy vs. psychotherapy) and the subsequent treatment strategy for depression can be associated with poorer engagement and higher attrition rates (e.g., [12]). Among the psychotherapeutic approaches, cognitive behavioral therapy (CBT) is the most commonly applied and represents the best researched psychological gold-standard intervention for depressive disorders [13, 14].

According to a meta-analysis of 92 studies with 6,937 individuals by Cuijpers et al. [15], about two-third (62%) of patients no longer met the criteria for MDD diagnosis after psychotherapy (e.g., CBT and interpersonal psychotherapy, IPT), but many also improved in control conditions (43%) and care as usual (CAU; 48%), so that the additional, specific benefit psychotherapy accounted for decreased to 14%. Similarly noteworthy appears the fact that more than one-third of depressed patients (38%) in the included studies did not meaningfully improve after psychotherapy. Another issue in MDD management concerns the often recurrent or even

chronic course of depressive disorders, found among up to half of cases [16]. As a rule of thumb, it is estimated that about one-third of patients remit from depression, while one-third suffer from a recurrent form and the remaining one-third are chronically depressed [17]. Moreover, a meta-analysis [18] indicated that 29% of responders to CBT relapsed within 1 year after treatment (and 54% within 2 years). Therefore, it appears worthwhile to identify further effective psychological prevention and treatment approaches that may fit individual needs as well as preferences of more patients in order to provide more choices besides traditional psychotherapy protocols of, for instance, CBT and IPT. It is also important to establish efficient prevention strategies for preventing relapse and recurrence in MDD [19].

Over the past two decades, an increasing interest among clinicians, patients, and the public in mindfulness- and acceptance-based treatment and self-help options could be observed [20]. Among this newer generation of CBT-related approaches, acceptance and commitment therapy (ACT) has been proposed to add a contextual perspective to behavioral and cognitive treatment of mental health problems like depression [21]. In this sense, the acronym “ACT” stands for A = accept thoughts (and be present), C = choose values (toward a valued direction), and T = take action, which lead to moving toward the important directions and toward psychological flexibility [22].

Hence, this chapter aims to provide a pragmatic overview on the application of ACT in the treatment of MDD in adults.

17.2 A Short Journey from “Second-Wave” CBT to ACT

Over 15 years ago, in 2004, Hayes [23] suggested using the metaphor of waves to classify three paradigmatic shifts in CBT: while the “first wave” of CBT was behavioral therapy focusing on learning principles to change overt behavior, the “second wave” established new methods and concepts that put emphasis on maladaptive thinking patterns [23, 24]. The core strategy of cognitive approaches for mental disorders is to identify, challenge, and change maladaptive cognitions [25]. In CBT for depression, Becks’ cognitive triad (about the world, the self, and the future; [26]) is a centerpiece. Simply said, the therapeutic principles of CBT target the closely connected triangle of behavior, thoughts, and feelings [27]. In ACT, struggling with cognitive fusion is the central clinically relevant issue, when overt behavior like actions and covert behavior like attention or both lead to psychological inflexibility [28].

The advances of “second wave” of CBT for evidence-based psychotherapy were tremendous, but a weakness was that too little attention was paid to the empirical investigation of underlying mechanisms of change in terms of the processes involved in behavior change [29]. This was a starting point for experimental, behavioral, and philosophical analyses that resulted in a variety of process-based contextual treatment approaches representing the “third wave” of CBT. In contrast to “second-wave” CBTs, approaches like ACT focus on the function of thoughts (process and

effects of human language) and not in their specific content [29]. This remark is important, since the same type of action can lead to either positive or negative effects, depending on its function. For example, when the function or purpose of playing video games is not relaxation or joy but experiential avoidance in terms of an escape from painful cognitions, it can become problematic on the long run.

The “third wave” of CBT includes diverse approaches beyond ACT [30], such as mindfulness-based cognitive therapy [31], dialectical behavioral therapy [32], and metacognitive therapy [33]. “Third-wave” therapies are proposed to address contextual change and the function (over form) of cognitions in terms of one’s association with thoughts and feelings (and their impact on one’s life) by promoting the momentary awareness and acceptance of thoughts or feelings [21, 34]. Behavioral treatments of the “third wave” of CBT have a scope on the cultivation of new skills such as mindfulness, compassion, detachment, and acceptance [23]. While traditional CBT distinguishes between behaviors, emotions, and thoughts, ACT understands cognitions (thoughts and feelings) as private events and behavior as everything a person thinks or does [28, 35]. In ACT, *the content of specific thoughts* shall not be changed (as opposed to traditional CBT), since this represents a problematic attempt of control. Instead, ACT tries to change the function (i.e., perspective) of an unwanted thought, for instance, by accepting it. ACT assumes that the suppression of unwanted inner experiences results in the opposite of what the client desires. Consequently, ACT aims to help clients to reduce the power of painful cognitions (acceptance), while performing actions toward building a values-guided, meaningful life (commitment) [28].

ACT is said to belong to a family of CBT interventions [23, 36] but can also be placed within the contextual behavioral sciences (CBS) [37]. More specifically, ACT is not only a therapeutic principle or orientation but is also grounded in a process-focused approach that theoretically and empirically tests which and how behavioral and cognitive therapeutic procedures work [37]. Clinicians trained in ACT include, for instance, psychotherapists or psychiatrists, psychologists, mental health counselors, or social workers. According to Hayes [38], in early 2019, there were more than 2,000 studies on ACT published since 1986, which involve over 280 randomized controlled trials (RCTs; with approximately 33,000 participants) for a broad range of syndromes, mental health, and behavioral outcomes, and about 60 studies on process research on moderating and mediating effects of principles that are involved in increasing psychological flexibility.

17.3 Theoretical Underpinnings of ACT

Acceptance and commitment therapy (ACT; said as one word “act”) [23] was developed in the mid-1980s and has become well-known in the therapeutic community since the 1990s through publications by its founder Steven C. Hayes and his co-founders Kirk Strosahl and Kelly G. Wilson (c.f., [39]). ACT is conceptualized as a transdiagnostic approach to increase psychological flexibility [40]. ACT

pragmatically connects with Buddhist concepts and practice in acknowledging the ubiquity of human suffering and relating it to the constructs of mindfulness, valued action, and the transcendent self [41]. More precisely, ACT differentiates between primary (e.g., depressive symptoms) and secondary suffering (e.g., avoidance behavior, rumination). Consequently, ACT provides a counterpole to the “healthy normality,” suggesting you are only normal when you are well [42]. In addition, ACT is rooted in the pragmatic philosophy called functional contextualism and the comprehensive relational frame theory (RFT; [43]) that integrates human language into a complex behavioral analytic framework. RFT explains why experiential avoidance and cognitive fusion are not only ubiquitous and normal but can also become harmful as both can create psychological inflexibility [40].

According to ACT/RTF, humans learn to relate stimuli (e.g., as “opposite,” “bigger”) under arbitrary contextual control and to transfer these relations toward new objects that are formally related in the same way (e.g., relating “fox,” “rabbit,” and “squirrel” to the concept of “animal”) [40]. This makes it possible for humans to derive decisions and overt behavior to new situations. This kind of relational learning is apparently normal, but cognitive fusion can also lead toward rigid behavior patterns and experiential avoidance [22]. Cognitive fusion includes an excessive reliance on rules about possibilities in one’s life, including a verbal control over behavior (taking negative thoughts literally) [37]. To be more precise, the ability to form relational networks can be destructive in terms of creating psychopathology: in depressive terms, “worthless” might become related to “job performance” or any kind of related domains. Therefore, a number of situations linked to achievement may cause questioning one’s self-worth. Often, depressed people aim to get rid of, control, or suppress these thoughts (in terms of experiential avoidance), which reinforces their negative impact (paradoxically) even more. In ACT, cognitive fusion as relational learning mechanism and experiential avoidance as a behavioral outcome are seen as major issues for psychological flexibility, increasing the risk of psychopathology [37]. Psychological flexibility is defined by Hayes et al. [30] as “the ability to contact the present moment more fully as a human being, and to change or persist in behavior when doing so serves valued ends” ([30], p. 7). Psychological flexibility is also the base for the therapeutic stance throughout the therapy concerning the client, the therapist, and their relationship [44].

17.4 Therapeutic Aims and Strategies in ACT for Depression

ACT follows a bottom-up, inductive approach to analyze how cognitive processes produce psychological inflexibility and proposes that the symptoms of a client have the function to keep them away from engagement in valued domains of everyday life (e.g., related to family or work) [37].

Following the ACT approach, not the depressive symptoms (Textbox 17.1), have a huge impact on one’s life. In ACT it is assumed that the struggle to live with

depressive symptoms by unsuccessfully attempting to control them makes depression a problem for a value-driven life [23, 45].

Textbox 17.1: Depressive Symptoms: Diagnostic Criteria for Major Depressive Disorder in the DSM 5 [46]

A. Five or more symptoms present during the same 2-week period; at least one of the symptoms has to be (1) or (2):

1. *Depressed mood (nearly all days, most of the day)*
2. *Diminished interest or pleasure (nearly all days, during most of the day and activities)*
3. *Significant weight loss or gain (more than 5% in 1 month); decreased or increased appetite*
4. *Insomnia or hypersomnia*
5. *Psychomotoric agitation or retardation*
6. *Fatigue or loss of energy*
7. *Feelings of worthlessness or excessive or inappropriate feelings of guilt*
8. *Recurrent thoughts of death, suicidal ideation, plan for committing suicide, or suicide attempt*

The symptoms...

- B. ... cause significant distress or impairment in areas of functioning (social, occupational, or other).
- C. ... are not attributable to physiological effects of a substance or a medical condition.
- D. ... are not better explained by another mental disorder (e.g., schizoaffective disorder).
- E. There has never been a manic or hypomanic episode.

Increasing psychological flexibility can be obtained by implementing six core principles in ACT (Fig. 17.1) that lead toward specific techniques [37]. There is support from process research for the positive effects of psychological flexibility increased by ACT, working through its proposed core principles across outcomes [47, 48]. All six core principles are interrelated and do not follow a sequential order [29]. Different types of mindfulness exercises can be applied across the four principles of acceptance, defusion, self as context, and contact with the present moment. In addition, defusion exercises represent an integral key part of different principles, including acceptance and self as context.

ACT is characterized by a vivid therapeutic process that uses plenty of metaphors [49]. Besides metaphors and experiential exercises, ACT also uses paradox exercises with many examples (e.g., “just relax” or “try to be spontaneous now”) to make the contradictions of human language and its effects apparent ([29], p. 312). For therapists, there are several resources, including an ACT therapy skills-training manual by Louma et al. [50] and a book for ACT newbies called *ACT Made Simple*

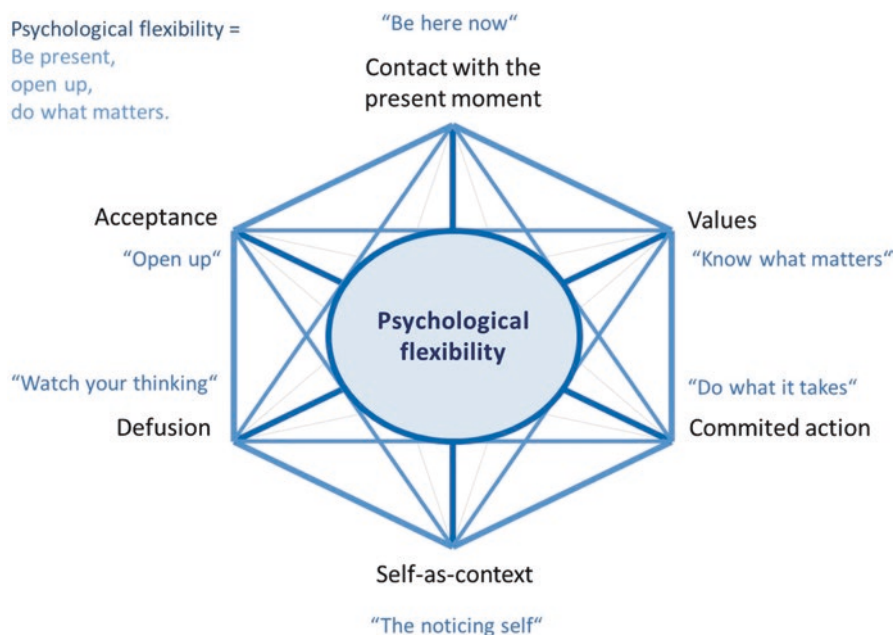


Fig. 17.1 Psychological flexibility and the six core principles of ACT, adapted from an ACT/RFT model of health and treatment processes by Hayes et al. ([37], p. 25) and by Harris ([28], p. 6)

by Harris [28]. Furthermore, the clinicians' guide *ACT for Depression* by Zettle [51] helps therapists to structure interventions step-by-step using techniques of acceptance- and value-based behavior change. The opposite of the six core principles of psychological flexibility (Fig. 17.1) can be summarized in an ACT model of psychopathology (Fig. 17.2) and then be applied to depressive symptoms (Textbox 17.1, [46]).

17.4.1 Acceptance

In the ACT model of psychopathology, the opposite of acceptance is experiential avoidance of the so-called private events [37]. Initially, clients reflect on their attempts to control (e.g., ignore, suppress, battle) unwanted private experiences related to depression and may experience a state of "creative hopelessness" if strategies failed to improve their well-being. Acceptance then is promoted as an active engagement or willingness, which should not to be confused with "giving up" or passively enduring negative conditions. In that way, ACT does not advocate accepting all kinds of unwanted thoughts or feelings but of those that cannot be controlled and which are keeping the client moving away from a value-driven life (in terms of the so-called "unworkable" behaviors). ACT may support clients to find

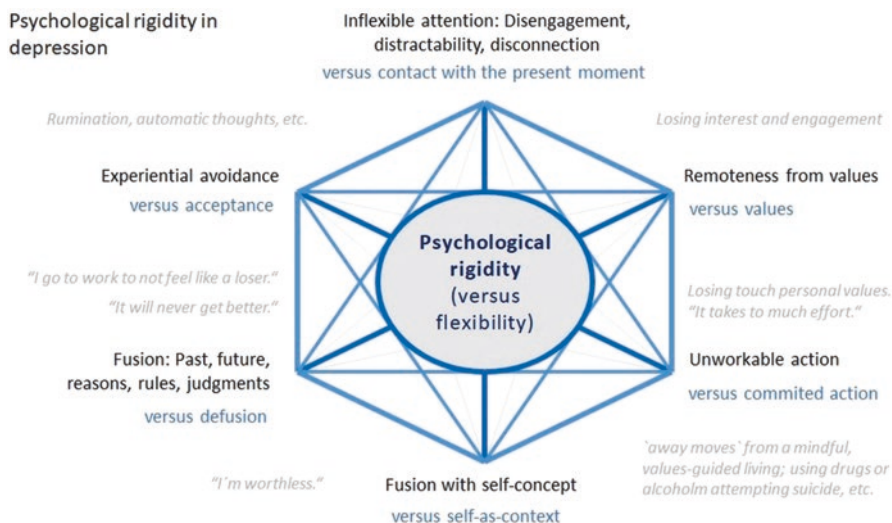


Fig. 17.2 Psychological rigidity in depression: an ACT model of psychopathology adapted, modified, and extended from Harris ([28], p. 33)

ways to accept discomfort in situations of performance or achievement in the short term, while moving toward behaviors that are in line with personal values. It may also mean to accept sleepless nights, rather than forcing one-self to find sleep. In other words, trying to control unwanted thoughts or feelings can work paradoxically (“the harder you try, the worse it gets”). In ACT, suitable metaphors for the client can be developed with the therapist, based on examples that can be referred to whenever the client talks about unworkable behaviors [29]. A prominent example for a metaphor is called “tug of war with a monster.” Another example involves the monsters on the sideway of the client’s valued path, which cannot be avoided or controlled – in terms of depression, acceptance may mean to take them with you on your journey.

17.4.2 Defusion

In depression, experiential avoidance and cognitive fusion usually go hand in hand [28]. In ACT, the normal ability of cognitive fusion is considered as the main issue for psychological flexibility and thus a key target as well as starting point for working on depressive symptoms. Often, depressed individuals are merging with their feelings and thoughts. Fusion with a negative self-concept then may manifest as negative, globally self-referential thoughts, self-criticism, excessive worries, and rumination (e.g., “I will never get any better,” “therapy won’t work,” “I am a loser,” etc.) that can become associated with severe depressed mood [28]. Applying techniques related to the principle *defusion* may help clients with stepping back and

lowering the impact of these unwanted thoughts by mindfully noticing thinking as it occurs (e.g., “I am having the that...I am worthless”) without evaluation, judgment, or unhelpful or rigid regulatory functions. Labeling the thinking process helps clients to create defusion (or deliteralization) and a distance between the client and the client’s thought [37]. There are seemingly endless possibilities for defusion exercises, which may include singing thoughts aloud.

17.4.3 Contact with the Present Moment

Skills to increase the *contact with the present moment* are often trained through mindfulness exercises (e.g., focused attention) that help clients with MDD to actually notice their needs in the “here and now” rather than brooding over the conceptualized past and experiencing related feelings (e.g., guilt, disappointment, or shame) or worries regarding the future. It also helps to create an understanding for personal needs and emotions (self-knowledge) [37] and thus also modify attention biases in depression [52]; contact with the present moment is thus essential to break the cycle of automatic negative thoughts and rumination [53]. A brief informal technique to foster mindfulness skills is “notice X” (e.g., “pay attention to X” for 10 s), whereas “X” can be, for instance, sensory perceptions [28]. Other mindful exercises are more formal like the “body scan,” whereas their selection should depend on the preferences and needs of the client. Therapists should also consider that the word “mindfulness” can have negative connotations for clients or that it is confused with meditation, Buddhism, or relaxation techniques, which are not a part or scope of ACT. Therefore, Harris suggests that ACT therapists may avoid ambiguous or vague terms like “mindfulness” with most clients and rather use terms leading to the specific skills or aims of the exercise in daily life [28].

17.4.4 Self as Context

The principle *self as context* creates a distance between the burdensome depressed thoughts and the self (e.g., “I’m worthless”). In ACT, the client is said to be in charge of these thoughts and feelings. Exercises may focus on modifications of the language of a thought or the pace and tone of the inner voice. The aim is to break the rigid attachment to the conceptualized self [37]. Other exercises put their emphasis more on feelings, for instance, by using the weather or sky as metaphors. Mindfulness exercises can be applied to train the skill of decentralization (similar to distancing in CBT), acceptance, increased exposure to cognitions and feelings, and greater self-awareness [54]. When clients are encouraged to notice inner experiences, therapists may ask them who is noticing that. The chessboard metaphor can help to understand the distinction between the chessboard (the client as whole) and chessboard pieces (specific thoughts of the client) [29].

17.4.5 *Values*

Depressed clients regularly suffer from hopelessness and loss of interest. Applying the principle *values*, the client is asked to clarify and choose important values that give an orientation for daily actions. In ACT terms, values serve as a lighthouse in daily life that help to circumnavigate around cliffs such as daily hassles and struggles without getting lost in a storm [37]. Homework assignments are often used to help the client step-by-step in clarifying values (e.g., being a reliable partner or parent), differentiate present values from feelings as well as directions from (future-orientated) goals, and to identify a discrepancy between the compass point and the degree of actual movement toward it [29]. This creates momentum for behavioral change. “Ten years from now, looking back” or “the video of your mistakenly held funeral” are examples for potential exercises on values (cf., [28], pp. 218–219).

17.4.6 *Committed Action*

Depression is often associated with loss of energy and fatigue. In ACT, value clarification and committed action are important processes to produce clinically relevant improvements in depression [55]. Applying the principle *committed action* may mean to motivate the client to engage in some activities which are in the direction of their clarified values, such as opening up to significant others although this may at first cause discomfort. Opposed to committed action is inaction, impulsivity, or avoidant persistence [37]. In ACT, unworkable behaviors differ from workable behavior not through the action per se but through their function or purpose. There are several ways to foster committed action, such as linking goals to values and “SMART” goal setting [28].

17.5 Settings and Delivery Modes of ACT for Depression

ACT for depression is most commonly delivered in a face-to-face individual or group setting, but the treatment can also be supported using self-help formats like bibliotherapy and digital interventions [45], including mHealth apps [56] and Web-based programs [57]. ACT does not follow a linear approach to work on psychological flexibility and can thus start at any of the six core processes (Fig. 17.1). In addition, the length of ACT is not fixed: the number of sessions depends on the client’s individual needs, and so ACT can be delivered over a longer period or as a brief therapy with few sessions [28].

17.5.1 Individual Setting

ACT delivered in the individual setting can focus on specific symptoms, such as repetitive negative thinking [58], or on specific populations with depression, such as suicidal patients [59], transdiagnostic samples [60, 61], or older residents (age 63–97) in a long-term care facility [62]. Furthermore, ACT can serve as an early intervention for depressive symptoms [63] or subclinical depression [64].

Zettle's [51] clinician's guide *ACT for Depression* provides therapists with information on the ACT view of depression and gives a lot of material and techniques adopting the core principles of ACT, such as a 12-session ACT sample treatment protocol that helps to implement ACT in clinical practice.

ACT for Depression (ACT-D) is another 12-week treatment manual (Textbox 17.2) by Walser et al. [65] that has been shown to be effective in increasing therapist competence and reducing depressive symptoms in veterans [66, 67]. ACT-D can be also expanded from 12 to 16 sessions [65].

Textbox 17.2: The 12 Sessions of Acceptance and Commitment Therapy for Depression (ACT-D) [65]

- Session 1: Commitment to therapy and assessment
- Session 2: Values assessment
- Session 3: Creative hopelessness
- Session 4: Control as the problem
- Sessions 5/6: Willingness: building acceptance, defusing language (part I and II)
- Sessions 7/8: Self as context (part I and II)
- Sessions 9/10: Values (part I and II)
- Session 11: Committed action
- Session 12: Termination

17.5.2 Group Setting

Several ACT group interventions have been manualized [68], either as transdiagnostic (e.g., [69]) or disorder-specific programs [70]. ACT group programs for depression can focus on specific populations like treatment-resistant clients [71] or women with perinatal depressive symptoms (e.g., 4-session group ACT [72]), to name only a few.

ACT may also be combined with CBT or CT group treatment (e.g., [73]). Moreover, different studies that compared the efficacy of CT and ACT found equivalent effects on depression but different mechanisms of change (e.g., [60, 74]).

17.5.3 Self-Help Formats and Digital ACT Programs

There are also several ways to apply ACT to self-help for MDD. For instance, Kirk Strosahl and Patricia J. Robinson [75] developed a mindfulness and acceptance self-help workbook for people with depression. Another well-known self-help book called *The Happiness Trap: How to Stop Struggling and Start Living: A Guide to ACT* by Russ Harris [76] deals with struggle in general and depressive symptoms in particular; it also serves as the framework for a commercially available 8-week online intervention (<https://thehappinesstrap.com>) and the associated “ACT Companion” app (<http://www.actcompanion.com>). Besides these tools, several other acceptance- and mindfulness-based apps have been developed [77], such as the “ACT Daily” app [56], and a variety of Web-based ACT interventions for different mental health outcomes [57, 78], including depression [79–81].

17.5.4 Combining ACT with Behavioral Action in Self-Help Programs

In the (self-help) treatment of depression, a combination of ACT and behavioral activation (BA), another CBT-related technique that helps patients to reactivate pleasurable and rewarding activities, represents another promising approach. Distancing and decentralizing (e.g., from brooding) and BA appear to have profound effects when used in ACT for depression [51]. ACT and BA share some components and intervention strategies but differ in some points, for instance, in their conceptualization of avoidance: in ACT, experiential avoidance is under verbal control, while BA puts more emphasis on nonverbal processes [82]. An example for a digital self-help program is described by Calbring et al. [83] who developed and tested an 8-week Internet-based BA program, including components of ACT with minimal therapist guidance (i.e., weekly written feedback), a workbook, interactive online components, and a CD-ROM for mindfulness and acceptance exercises.

17.6 Research on ACT for Depression

Since 1986, there is a steadily growing number of studies on the efficacy of ACT for a broad range of conditions (outcome research) and mediation analysis on mechanisms of action (process research) [38]. Although ACT is conceptualized as a unified model of behavior change [38], it is interesting to note that the first ACT studies were conducted with depressed patients [45].

Overall, several systematic reviews and meta-analyses including ACT across mental health outcomes and delivery modes have derived partly divergent conclusions regarding the current strength of evidence for ACT, especially in comparison

to the longer-established “second-wave” CBT. Another issue is that most review articles have investigated ACT together with several other “third-wave” treatments for a variety of mental health outcomes. Hence, we will here scope on the findings for ACT for depression, as far as applicable.

17.6.1 Outcome Research on ACT

First of all, several systematic reviews and meta-analyses on RCTs showed a significant effect favoring ACT (e.g., [30, 84–86]) over control conditions (e.g., wait-list control (WLC), CAU or treatment as usual (TAU), or psychological placebos), mainly with overall moderate effect sizes across comparisons. Moreover, in a recent meta-analysis of 68 studies (4,729 participants), Ong et al. [87] showed that the weighted mean dropout rates in ACT intervention conditions of 16.0% were equivalent to other (non-ACT) psychological treatments (15.8%), which did neither vary by client characteristics nor study quality. However, publications on ACT regularly mention substantial methodological limitations as well as a need for more high-quality RCTs controlling for therapy-unspecific effects with psychological placebo [88]. There is also a lack of research that is capable of identifying whether or under which conditions ACT may be equally (non-inferiority trials) or more effective (superiority trials) than other active treatments like CT [84]. While some reviews found a superiority of ACT compared to other CBT-related treatments (e.g., [30, 89]), other identified no significant difference (e.g., [90, 91]). Accordingly, there is an ongoing controversy debating the strength of evidence for ACT for depression and for ACT compared to “second-wave” CBTs, which will be next illustrated with noticeable, selected examples.

17.6.1.1 Reviews on Third-Wave CBTs Including ACT for Depression

In 2008, Öst [85] published a meta-analysis of “third-wave” CBTs, including 13 ACT trials, according to which ACT results in moderate overall mean effect size of 0.68. Nevertheless, compared to CBT, Öst acknowledged a less stringent research methodology of ACT studies for depression and other outcomes. This meta-analysis has been criticized by Gaudiano [92] due to an unbalanced matching of ACT with CBT studies, for not considering the different stages of clinical testing, and the insufficient consideration of funding (i.e., grants of at least 150,000 US dollars were found in 77% of CBT studies versus 8% of ACT studies). In 2014, Öst [90] published an updated meta-analysis of 60 RCTs on ACT for psychiatric disorders, somatic disorders, and stress at work. This meta-analysis indicated a small overall mean effect size across all comparisons of 0.42 and no significant difference to CBT (effect size of 0.16). Öst concluded that the decrease from a moderate effect size compared to the prior meta-analysis from 2008 [85] was to some part based on the heterogeneity of comparisons (e.g., studies on somatic disorders yielded higher

effect sizes than those for psychiatric disorders). Regarding depression (2 RCTs), Öst [90] reported that ACT was significantly more effective than the control condition and is probably effective in depression. This meta-analysis was again criticized by, for instance, Atkins et al. [93] who conducted a reexamination and questioned the reproducibility of the findings.

In 2012, Klainin-Yobas et al. [94] conducted a meta-analysis of 39 studies on mindfulness-based interventions on depressive symptoms in people with mental disorders and found a large effect size for acceptance-based behavior therapy ($d=1.33$), which was, however, lower than for exposure-based CT ($d=2.09$) and MBSR ($d=1.92$).

17.6.1.2 Reviews on the Efficacy of ACT for Depression

In a systematic review and meta-analysis of 16 studies, Ruiz [89] found favorable effects of ACT versus CBT for primary outcomes ($g=0.40$), while a nonsignificant (positive) trend for ACT was obtained in depression at posttreatment ($g=0.27$). Compared to CBT, ACT showed a greater influence on its supposed process of change ($g=0.38$), a finding Ruiz concluded based on the results from mediation analyses reported in nine studies. However, this meta-analysis has also been criticized by, for instance, Öst [90] and Zettle [45] for the heterogeneity of comparisons.

Due the fact that systematic reviews and meta-analyses have evaluated the efficacy of ACT for a broad range of outcomes, Hacker et al. [95] conducted a meta-analysis for depression and anxiety and found a moderate effect size for depression in the cumulative meta-analysis. Using more elaborated sequential meta-analysis techniques, however, the authors found insufficient evidence for the moderate efficacy for ACT for depression when compared to active control conditions.

Twohig and Levin [96] reviewed 36 RCTs on ACT for depression and anxiety (published between 1986 and 2016), of which 17 RCTs targeted ACT for depressive disorders. Their qualitative synthesis of evidence suggests the efficacy of ACT in reducing depressive symptoms compared to WLC in seven RCTs ($d=0.32$, $d=1.18$) and to TAU in four out of five RCTs ($d=0.38$, $d=1.45$). In five RCTs that compared ACT with CT/CBT, four RCTs showed ACT to be comparably effective relative to CT/CBT, while one RCT found greater improvements in depressive symptoms in ACT compared to CT.

In a recent meta-analysis of 18 RCTs on ACT for depression, Bai et al. [97] demonstrated that ACT significantly reduced depressive symptoms compared to control conditions, with a standardized mean difference of 0.59 (95% CI [0.38, 0.81]). The subgroup analysis revealed a significant difference between ACT and control conditions at posttreatment and the 3-month follow-up as well as in samples with participants with mild depression and in healthy adult populations.

17.6.1.3 Reviews on Digital Self-Help ACT for Depression and Other Outcomes

Despite the existence of effective treatments for depression, only few of those affected by depression receive such treatments due to several structural and attitudinal barriers [98]. Therefore, additional prevention and treatment options such as digital self-help ACT programs are promising, highly scalable, and low-threshold tools [99].

Empirical evidence indicates the efficacy of ACT when provided as self-help format, albeit with mainly small effect sizes across meta-analyses. For instance, Cavanagh et al. [100] performed a systematic review and meta-analysis of 15 RCTs on “third-wave” interventions, including 7 RCTs on ACT, and showed that mindfulness- and acceptance-based components in self-help interventions produced a significant beneficial impact on depression with a small effect ($g=-0.37$) compared to control conditions. Moreover, Spijkermans et al. [78] conducted a meta-analysis of 15 RCTs on Web-based mindfulness-based interventions, in which 8 of the 17 comparisons examined MBSR, 2 MBCT, and 5 ACT. For depression (12 comparisons), a significant, small effect was observed ($g=0.29$), and no significant differences between subgroups such as intervention approach, populations, or provision of guidance were found.

A meta-analysis by Brown et al. [57] of ten RCTs on ACT for different mental health outcomes (published between 2012 and 2016) also indicated the effectiveness of Web-based delivery format for the management of depression (small effect size of $g=0.24$). In another systematic review and meta-analysis of 13 RCTs on self-help ACT for different outcomes, French et al. [101] concluded that ACT produced small effects on depression ($g=0.34$), that psychological flexibility is probably a moderator of depression outcomes in ACT, and that a higher degree of therapist support may improve clinical outcomes.

Finally, Sierra et al. [102] conducted a systematic review of nine RCTs and meta-analysis of six RCTs on Web-based “third-wave” interventions for depression (versus WLC or TAU), the latter indicating medium to large effect sizes (weighted effect size of $d=0.61$). Of these six RCTs, two RCTs focused on Web-based ACT, and another RCT implemented combined Web-based versions of ACT and BA.

Taken together, the current evidence base suggests that ACT can be effectively delivered as (digital) self-help format for the management of depressive symptoms. However, as a general limitation of the research on Web-based ACT for depression, Zettle [45] noted a lack of active control conditions (e.g., psychological placebo) to control for unspecific effects, which is especially important to consider when self-help ACT is combined with BA or CT/CBT components.

17.6.2 *Process Research on ACT*

Process research in ACT is considered as an important complement to outcome research [38]. In a recent systematic review of 12 contemporary mediation studies, Stockton et al. [103] found a consistency with the psychological flexibility model of ACT. A number of studies have also investigated whether ACT increases psychological flexibility and by these means help reduce depressive symptoms (e.g., [45]).

In the aforementioned review by Twohig and Levin [96], 11 out of the 17 RCTs targeting ACT for depression investigated processes of change. The authors found that in three RCTs ACT improved psychological flexibility relative to WLC ($d=0.50$, $d=0.67$), in three RCTs relative to TAU ($d=0.64$, $d=0.76$), and in one RCT relative to a placebo condition (expressive writing with $d=0.43$ vs. ACT with $d=0.77$). In addition, two out of four RCTs found a benefit of ACT in improving psychological flexibility compared to CT/CBT, while the remaining two RCTs found equal improvements between ACT and CT/CBT outcomes. Moreover, mediation analysis demonstrated that changes in psychological flexibility mediated the influence of ACT on depression relative to WLC in three RCTs, while one RCT identified a mediating effect of defusion on the influence of ACT versus CT on depression outcomes.

As an implication, Zettle [45] recommended the extension of component analyses in ACT research using multiple mediation analysis that may also include improvements in quality in life and daily functioning in depression and to track changes in outcomes more accurately (e.g., session by session).

To conclude, there is a lot of movement in the ACT research literature. An up-to-date list of published papers on ACT can be found on the website of the Association for Contextual Behavioral Science (https://contextualscience.org/state_of_the_act_evidence).

17.7 **Conclusions**

ACT provides a theory-led framework for clinicians in the individual or group treatment of MDD that leaves room for therapeutic flexibility and creativity. Moreover, digital ACT interventions represent promising tools for self-help purposes and for therapist-guided support. To date, there is steadily growing empirical support from outcome and process research for the efficacy of ACT in preventing and treating depressive symptoms through the proposed processes specific to the psychological flexibility model and across different delivery modes [45]. Given the issues of non-response rates and the risk of chronic courses in depressive disorders, the observed growing interest in “third-wave” CBTs appears not surprising. Hence, health professionals may feel encouraged to find out whether or under which circumstances ACT may work for them in clinical practice in order to provide their clients with more choices within the family of CBT interventions.

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Chapter 18

Current Updates on Newer Forms of Transcranial Magnetic Stimulation in Major Depression



Chih-Ming Cheng, Cheng-Ta Li, and Shih-Jen Tsai

Abstract Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved technique for treating medication-resistant depression. Conventional rTMS includes high frequency (HF) to left dorsolateral prefrontal cortex (DLPFC) and low frequency to right DLPFC. However, not all depressed patients could benefit from standard rTMS protocols. Meta-analytical evidence indicated that there was an average response rate of 29.3% for patients receiving the most commonly adopted HF rTMS to the left DLPFC. Hence, newer forms of rTMS paradigms are warranted to improve antidepressant response and remission rate in patients with depression, especially those who are refractory to adequate antidepressant trials. In the current chapter, we review newer forms of rTMS paradigms and the content will cover standard theta burst stimulation (TBS), prolonged iTBS (piTBS), accelerated rTMS (aTMS), deep TMS (dTMS), priming TMS (pTMS), synchronized TMS (sTMS), and magnetic seizure therapy (MST).

Keywords Repetitive transcranial magnetic stimulation (rTMS) · Prolonged intermittent theta burst stimulation TBS (piTBS) · Accelerated rTMS (aTMS) ·

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Deep TMS (dTMS) · Priming TMS (pTMS) · Synchronized TMS (sTMS) ·
Magnetic seizure therapy (MST)

18.1 Background

Repetitive transcranial magnetic stimulation (rTMS) has been approved by the U.S. Food and Drug Administration (FDA) for treating medication-resistant depression in 2008. The antidepressant efficacy of high-frequency (HF, e.g., 10 Hz, Fig. 18.1a) rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) has been widely supported by a number of large international studies [1–3]. Not only

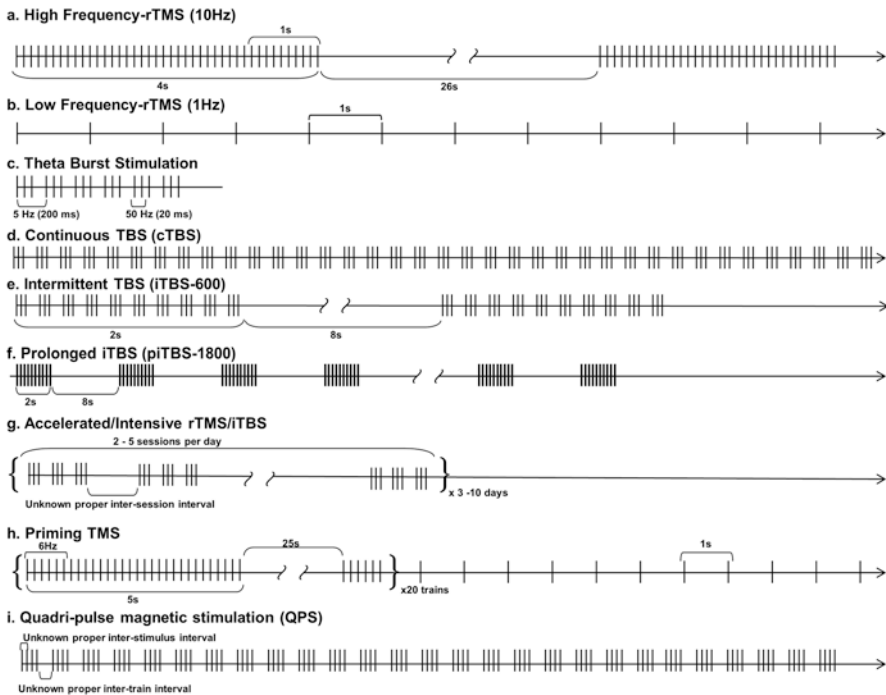


Fig. 18.1 Newer forms of transcranial magnetic stimulation. (a) High frequency-rTMS: 3000 pulses/session; (b) low frequency-rTMS: usually 900 pulses/session, but no consensus pulse numbers; (c) Theta Burst Stimulation (TBS): bursts of three 50 Hz pulses (or 20 Hz) at 5 Hz intervals; (d) continuous TBS (cTBS): either 300 pulses or 600 pulses without any interruption; (e) intermittent TBS (iTBS): 2-second train of bursts every 10 s, standard dose: 600 pulses/session; (f) prolonged iTBS (piTBS): three times longer than standard iTBS, 1800 pulses/session; (g) accelerated/intensive rTMS/iTBS: usually given 2–5 sessions a day with proper inter-session interval, treated for 3–10 days; (h) priming TMS: priming 20 trains of 6 Hz rTMS followed by 1 Hz 900 pulses/session; (i) quadri-pulse magnetic stimulation (QPS): four equal TMS pulses at proper inter-stimulus interval and proper inter-train interval

HF to the left DLPFC, low-frequency (LF) rTMS to the right DLPFC also has evidence to support its antidepressant efficacy [4] (Fig. 18.1b). Moreover, beyond the DLPFC, dorsomedial prefrontal cortex (DMPFC) is recognized to be another potential stimulation site for depressed patients, that one study demonstrated the antidepressant efficacy after 10 Hz rTMS stimulation at this area [5]. Even so, not all depressed patients could benefit from standard rTMS intervention. For example, Berlim et al. reviewed 29 randomized controlled trials (RCTs) and found an average response rate of 29.3% for subjects receiving HF-rTMS in a meta-analysis [6]. Hence, newer forms of rTMS paradigms are warranted to improve antidepressant response and remission rate in patients with depression, especially those who are refractory to adequate antidepressant trials. In the current chapter, we review newer forms of rTMS paradigms.

18.2 Other TMS Modalities Beyond Conventional RTMS Protocols

18.2.1 *Theta-Burst Stimulation*

18.2.1.1 Standard Versus Prolonged TBS Protocols

Theta-burst stimulation (TBS, Fig. 18.1c) is a patterned form of magnetic pulses that demonstrates more rapid and longer effects on synaptic plasticity than traditional rTMS protocols. The standard TBS protocol is 3-pulse 50-Hz bursts given every 200 ms (at 5 Hz) and an intensity of 80% active motor threshold (aMT) [7]. Experiments on the motor cortex have revealed that intermittent theta-burst stimulation (iTBS) consistently increases cortical excitability, whereas continuous theta-burst stimulation (cTBS) decreases cortical excitability [8]. Huang et al. proposed standard TBS protocols which include cTBS (either 300 pulses or 600 pulses without any interruption, Fig. 18.1d) and iTBS (2-s train of bursts every 10 s, 600 pulses, Fig. 18.1e) [7, 9, 10].

The earliest case series showed the first promising therapeutic potential of iTBS delivered to left DLPFC. Five out of seven depressed patients responded and three out of seven patients achieved remission [11]. Afterwards, a preliminary open-label add-on study ($N = 33$) provided the evidence of antidepressant efficacy after 2-week treatment of the left prefrontal iTBS (1200 pulses) and right prefrontal cTBS (1200, 1800, and 3600 pulses) in patients with medication-resistant depression [12]. Another pilot randomized sham-controlled study ($N = 32$) further showed the antidepressant efficacy after 6-week bilateral prefrontal TBS treatment (600 pulses cTBS in the right DLPFC and 600 pulses iTBS in the left DLPFC) [13].

Prolonged iTBS (piTBS, Fig. 18.1f) adopts pulses three times longer than standard iTBS, that is, using 1800 pulses each session instead of 600 pulses. Li et al. first proposed this protocol under the consideration that TBS aftereffects are primarily

based on the total stimulation pulses [7] and iTBS-1200 pulses have been proven as suboptimal efficacy (cTBS-3600 > cTBS-1800 > cTBS-1200 > iTBS-1200) [12].

In 2014, Li et al. conducted a randomized, double-blind, sham-controlled study first to investigate the antidepressant efficacy of piTBS for refractory depression. This 2-week add-on prefrontal TBS study had four study arms (Group A = cTBS 1800 pulse/sessions at right DLPFC; Group B = piTBS 1800 pulses at left DLPFC; Group C = bilateral prefrontal TBS = cTBS at right and piTBS at left DLPFC; Group D = sham TBS) and this study observed that piTBS and bilateral TBS had significantly better antidepressant effect than cTBS and sham group. The response rates were 40% in the piTBS and 66.7% in the bilateral TBS [14]. Overall, piTBS is a promising and well-tolerated protocol for the treatment of depression without time-consuming. No seizure, mania-switching, or other severe adverse events were found in the series of piTBS trials [14, 15].

Berlim et al. conducted a meta-analysis of five TBS RCTs ($N = 221$) and concluded active TBS is significantly more effective than sham TBS in the treatment of refractory depression (pooled response rates = 35.6% vs. 17.5%, respectively, $p = 0.005$). In the subgroup analyses, patients who received left-sided iTBS and bilateral cTBS/iTBS showed a significantly greater mood improvement and higher response rates than sham TBS, but cTBS alone showed no difference from sham TBS [16].

Recently, Li et al. conducted another large randomized, double-blind, sham-controlled study, confirming that piTBS monotherapy is much more effective in treating recurrent depression than sham stimulation, with the response rate of 45.7% and the remission rate of 25.7%, over a 2-week intervention. For these benefited from piTBS, 75% responders and 77.8% remitters maintained the antidepressant efficacy at least 3 months after piTBS intervention. In addition, the authors further observed that those who achieved at least 20% improvement at the first week indicated the antidepressant responses at the end of piTBS treatment (area under the curve, $AUC = 0.827$; $p < 0.001$) [15]. Compared with standard rTMS protocol for 4–6 weeks, a 2-week piTBS monotherapy demonstrated the similar antidepressant efficacy within shorter treatment duration [17]. Notably, piTBS for 2 weeks also demonstrated an unexpected clinical improvement in the first week for patients with posttraumatic stress disorder [18].

18.2.1.2 The Comparison Between TBS and Conventional rTMS

A network meta-analysis established the relative antidepressant efficacy between different modalities of rTMS and demonstrated TBS was more effective than sham stimulation, with a 2.54-fold better response rate. No significant difference between TBS and other rTMS modalities (i.e., HF-rTMS, LF-rTMS, bilateral rTMS) was found [19]. Mutz et al. recently reviewed 113 trials of nonsurgical brain stimulation for acute treatment of adult major depressive episode ($N = 6750$). The result conducted by a network meta-analysis further showed iTBS (OR = 3.20, 1.45–7.08)

and bilateral TBS (OR = 4.44, 1.47–13.41) were associated with higher response than sham treatment, but not cTBS (OR = 1.03, 0.29–3.60). Regarding antidepressant efficacy between different rTMS modalities, cTBS revealed significantly lower response rate than bilateral rTMS (OR = 0.21, 0.06–0.79); however, there was no important difference between other TBS protocols (iTBS, and bilateral TBS) and conventional rTMS (HF-rTMS, LF-rTMS, and bilateral rTMS). No differences between three TBS treatments and sham stimulation were found for all-cause discontinuation [20].

Blumberger et al. performed the first open-label, multicenter, randomized, non-inferiority trial (THREE-D study, $N = 414$) to directly compare the antidepressant efficacy over left DLPFC between U.S. FDA-approved standard HF-rTMS (120% resting motor threshold, rMT, 3000 pulses per session; total duration of 37.5 min) and iTBS (120% rMT, 600 pulses per session; total duration of 3 min and 9 s). The treatment course was a 4–6-week daily stimulation session on weekdays. As a result, they found add-on iTBS was noninferior to add-on 10 Hz rTMS in reducing depressive symptoms, including clinician-rated and self-reported measures, response rate, and remission rate. The mean scores of Hamilton Depression Rating Scale-17 items (HDRS-17) improved from 23.5 to 13.4 in the 10 Hz rTMS group and improved from 23.6 to 13.4 in the iTBS group. The response rates and remission rates were 47% and 27% in the rTMS group, and 49% and 32% in the iTBS group. Dropout rates of two groups showed no differences [17]. The most common adverse event in both groups was headache. This trial facilitates the current treatment strategy for refractory depression that 3-min iTBS protocol served noninferior effect to the standard 37.5-min 10 Hz rTMS protocol with similar side effects. About the impact of prior failed experience of adequate antidepressant treatment on the efficacy of iTBS, the researchers found patients with three or more prior treatment failure exhibited a lower remission rate following 4–6 weeks iTBS treatment, compared with those with two or fewer failed trials (17.3% vs. 29.4%, respectively, $p = 0.03$). The different antidepressant classes did not show the influence on the remission rates [21].

It is worth noting that the researchers used the stimulation intensity of 120% rMT in the TBS protocol, instead of the standard iTBS protocol of 80% aMT [7]. Although current guidelines recommend using 100–120% rMT as the stimulation intensity for conventional rTMS protocol, it is still uncertain if iTBS would have similar neurophysiological effect in higher stimulation intensity as originally reported by Huang et al. [7]. TBS pulses are composed of high-frequency bursts (50 Hz), so the risk of seizure should be carefully monitored. This trial provided the safety evidence of delivering iTBS with 120% rMT without reducing tolerability. In regard to the medical cost, compared with 10 Hz rTMS, iTBS demonstrated shorter stimulation duration and higher treatment capacity, which convert to a significant cost-savings per patient (USD \$1108 for iTBS vs. \$1844 for 10 Hz rTMS) and per remission (\$3695 for iTBS vs. \$6146 for 10 Hz rTMS) [22].

In the first randomized sham-controlled trial, Li et al. reported that piTBS monotherapy for 2 weeks was as effective as rTMS monotherapy in treating recurrent depression [15]. Compared with the iTBS-600 pulses protocol for 4–6 weeks, a

2-week piTBS monotherapy demonstrated similar antidepressant efficacy within shorter treatment duration [17].

18.2.2 TBS with Adjusted Burst Frequency

Some reports used burst frequency other than 50 Hz. For example, TBS with 20 Hz (TBS-20 Hz) was investigated and researchers reported its promising antidepressant efficacy in a case series ($N = 4$), which included the same burst frequency of 5 Hz, but each burst was composed of three 20 Hz pulses, rather than 50 Hz. The stimulation intensity was 90–95% rMT. In this case series, four treatment-refractory depressed patients, who failed to remit after 38.3 sessions of TBS-50 Hz, remitted after mean 39.8 sessions of TBS-20 Hz [23]. The same study team further conducted a retrospective chart review and examined 58 primarily treatment-resistant depressed patients. Bilateral neuro-navigated TBS-20 Hz consisted of cTBS 3600–4800 pulses over the right DLPFC and then iTBS 4950 pulses over the left DLPFC. Patients were treated 5 days a week until remission, financial constraints, or plateaued improvement for two consecutive weeks. In this study, 79% of patients had a history of failed response to three or more adequate antidepressant trials in two different classes. Five patients failed to respond to standard rTMS, and three patients failed to electroconvulsive therapy. As a result, 72% of patients remitted, and 83% of patients responded. Remitters showed an 81% decrease in average Beck Depression Inventory–II (BDI-II) score from 35.2 to 6.6, and nonremitter showed a 24% decrease from 40.8 to 31.3. The average treatment period for remission was 7.3 weeks. In addition, the authors also found the potential continuous improvement if the treatment course were extended (cumulative interim remission rates: 26% at 6 weeks and 60% at 12 weeks). No severe adverse events were reported [24].

Overall, it remains unclear about the neurophysiological changes after TBS-20 Hz. However, these results showed the TBS-20 Hz might exhibit different treatment efficacy from TBS-50 Hz. In addition, TBS-20 Hz theoretically may have lower seizure risk than TBS-50 Hz. Based on the potentially significant higher remission rates, larger RCTs are warranted for bilateral neuronavigated TBS-20 Hz. On the other hand, evidence showed TBS-30 Hz may have similar changes of motor evoked potential (MEP) amplitudes over motor cortex with TBS-50 Hz; however, no study examined its efficacy in depressed patients [25].

18.2.3 Accelerated and Intensive rTMS/iTBS

rTMS has been proven to have meaningful clinical benefits in the treatment of depression, and the utilization of rTMS is growing in clinical practice worldwide. However, the time-consuming standard rTMS protocol (daily treatment for 37.5-min stimulation, 5 times per week over 4–6 weeks) is to some extent a challenge for

clinical service and patients. Daily transportation burden and interrupted life for patients with a full-time job were other practical limitations to hinder the clinical feasibility of conventional rTMS [26]. To overcome this issue, several “compressed” protocols, which were called intensive, accelerated, or spaced TMS/TBS protocol, have been investigated the safety and viability (Fig. 18.1g). These compressed protocols applied multiple rTMS/TBS treatment sessions daily (2–5 sessions) for several days (2–6 days) or in a short period of time (10 days) that overall numbers of treatment sessions are similar to the standard rTMS course [26, 27]. The difference between intensive and accelerated treatment is the former focusing on providing same clinical response as full course of standard rTMS protocol in fewer treatment days but the latter focusing on providing more request for the rapidity of response [26]. Beyond the “general” intensive or accelerated protocols, a case series reported a more aggressive protocol, named spaced iTBS, as threefold standard iTBS (piTBS, 1800 pulses each session) applying 10 sessions per day for five consecutive days [28]. In the case series of six participants, spaced iTBS protocol (90% rMT, piTBS 1800 pulses/session, 10 sessions/day, 50-min intersession interval, 90,000 total pulses for 5 days) was applied to the left DLPFC by neuronavigation and revealed a dramatically mean 76% reduction in HDRS-17 score from 28.8 to 7.0 at final treatment session. Five out of six patients responded and four out of six patients remitted at the final session. However, at the 4-week follow-up visit, no patients met responder criteria anymore. No major adverse events or significant decreasing cognitive function was observed. This is the first preliminary study to deliver such a high quantity of iTBS pulses to a human brain in 1 day [28].

These special protocols could be given by conventional HF-rTMS or iTBS. TBS can provide the same or greater neurophysiological response and noninferior clinical efficacy as standard rTMS in considerably shorter treatment duration [17]. Hence compared with conventional HF-rTMS, TBS is a more ideal tool to apply with accelerated/intensive assignment. In clinical practice, performing multiple TMS sessions per day in a patient is a severe challenge for a treatment agency that may disrupt the current treatment arrangement, because other patients are still scheduled to treat one session daily.

Sonmez et al. reviewed four open-label trials and four active arms of RCTs demonstrated a cumulative effect size of 1.27 for the efficacy of accelerated TMS. However, focusing on the antidepressant response in RCTs, accelerated TMS applied to the left DLPFC did not show a significant difference with the sham group (OR = 3.12, 0.98–9.97, $p = 0.054$) [27]. A recent network meta-analysis also revealed no statistically significant differences in response rates between accelerated TMS and sham (OR = 2.03, 0.64–6.40) [20]. Besides antidepressant efficacy, accelerated TMS is expected to have a role in reducing acutely suicidal ideation because standard rTMS presents slow time-to-response and electroconvulsive therapy is considered to have potential cognitive side effects. Among the limited studies, reducing intensity of suicidal ideation following the accelerated TMS intervention was found, but unfortunately this benefit demonstrated no difference with sham group or with active standard rTMS group [26, 29, 30]. However, it is too early to conclude the efficacy of intensive or accelerated TMS due to the greatly

small sample size, few studies, and a variety of parameters in existing accelerated TMS studies.

Recently, Fitzgerald et al. in a pilot RCT compared an intensive iTBS intervention to the U.S. FDA approval HF-rTMS protocol. Intensive iTBS protocol (600 pulses/session, 3 sessions/day, 15-min intersession interval) was composed of (1) Week 1: three sessions per day over 3 days; (2) Week 2: three sessions per day over 2 days; and (3) Weeks 3 and 4: three sessions only for 1 day per week, consolidation phase. The result demonstrated intensive iTBS had similar efficacy and rapidity of response in the treatment of depression with HF-rTMS standard protocol [26].

The optimal dosing strategy for accelerated TMS/TBS remains unknown and more studies are needed to evaluate the neurophysiological influences and clinical impact of different intersession intervals, number of session per day, and other stimulation parameters. Especially about the intersession intervals, the current studies used a variety of time intervals such as 15 min, 30 min, 50 min, 60 min, or 120 min, which needs further investigation for the optimal time interval between TBS sessions. In the limited literature, intersession time intervals may greatly influence the TBS effect on the motor cortical excitability and the long-term potentiation [31–33]. Additionally, lacks of adequate follow-up assessment and blinding technique (the difficulty to mask single vs multiple sessions per day) also need more efforts to overcome. Overall, these existing accelerated and intensive TMS/TBS studies provide the preliminary evidence for reducing depressive symptoms with safety, feasibility, and tolerability. Further studies are required to establish evidence of the therapeutic equivalence, superiority, or more rapid response of accelerated TMS versus US FDA-approval HF-rTMS protocol [27].

18.2.3.1 Safety of TBS

Rachid et al. reviewed the safety of TBS in the treatment of psychiatric disorders and found no major adverse events (e.g., seizure or mania-shifting) were reported when using TBS, except for mild headaches, dizziness, nausea, and discomfort at the stimulation site [34]. There were also no reported adverse concerns regarding hearing and speech perception when receiving TBS [35]. However, TBS pulses are composed of high-frequency bursts, the risk of seizure should be carefully monitored, and the predisposing factors for seizure should be evaluated appropriately. Two cases reported seizure induction in healthy participants. Oberman et al. reported a 33-year-old healthy man had seizure occurrence following about 50 trains (150 pulses) cTBS over the primary motor cortex at an intensity of 100% rMT (approximately equal to 120% aMT) with a figure of eight coil [36]. Lenoir et al. reported one case with generalized epileptic seizure (25-year-old healthy woman) and one with suspected partial epileptic seizure (23-year-old healthy man) during 100 trains (300 pulses) cTBS over the right operculo-insular cortex at an intensity of 80% rMT, with an angled double-cone coil [37]. Not like rTMS guideline for stimulation parameters [38], safety guidelines for TBS have not yet been established.

18.2.3.2 Current Challenge and Future Direction

According to the results from the THREE-D trial, iTBS has received the U.S. FDA approval and the Conformité Européenne (CE) mark for use in treatment-resistant depression since 2018. Although the iTBS protocol of 600 pulses once a day at the intensity of 120% rMT for 4–6 weeks is confirmed to have the noninferior antidepressant efficacy as the conventional HF-rTMS, the optimal treatment protocol for refractory depression is yet to be determined. To date, heterogeneity of TBS stimulation parameters makes a little confusion when directly moving iTBS into clinical utility, such as stimulation intensity (80–100% aMT or 80–120% rMT), course durations (10–30 sessions), and total treatment pulses (12,000–72,000 pulses). Chen in a review article mentioned that sub-threshold iTBS intensity (e.g., 75–90% rMT) may have a better therapeutic efficacy [9]. In fact, TBS using sub-threshold intensity could have different mechanisms, which involve GABAergic and glutamatergic neurotransmissions, from conventional rTMS using supra-threshold intensity [39]. Neuronavigated rTMS for coil localization has been believed to express better antidepressant efficacy than targeting by “5-cm rule” as the result of its precisely locating targets. But recently Li et al. argued this notion that he found MRI navigation method did not yield better clinical benefit than the “5-cm rule” method [15]. Like the experience to confirm rTMS antidepressant efficacy, further large, multi-site, sham-controlled studies are warranted to have a definite conclusion for the antidepressant efficacy of iTBS and its therapeutic role for depression in neurostimulation field [9].

Furthermore, researchers are still keeping investigating antidepressant effects of the different iTBS protocols, such as prolonged iTBS (piTBS), bilateralTBS-20 Hz, and accelerated or intensive TBS. It takes more studies to see which one is more effective in treating depression.

18.2.4 Deep TMS (dTMS)

Deep TMS (dTMS) received U.S. FDA clearance in 2013 in treating treatment-resistant depression based on promising results in a double-blind RCT conducted by Levkovitz et al. [40]. By using specific coil configuration (Helmet-like H-coil), dTMS can stimulate deeper and larger brain volumes than conventional HF-rTMS. However, a systematic review and network meta-analysis, which included only one RCT for dTMS, showed no difference in response and remission between dTMS and sham therapy [41]. In another recent network meta-analysis including two RCTs for dTMS, a pairwise meta-analysis showed a slightly significant response in the dTMS group than the sham group and still showed no difference between dTMS and sham in the network meta-analysis [20]. In recent 2 years, two new RCTs for dTMS have been published [42–44]. To address this efficacy analysis gap, Chu and the colleagues updated the meta-analysis for dTMS efficacy in patients with treatment-resistant depression and found dTMS showed

significantly higher pooled response than the sham group. Notably, in the subgroup analysis the authors observed only studies with concomitant dTMS and antidepressant medications showed the better efficacy than sham, but dTMS alone did not [44]. These inconsistent results need more RCTs to confirm the dTMS efficacy in the real world.

18.2.5 Priming Transcranial Magnetic Stimulation (pTMS)

As a variation of low-frequency TMS, priming transcranial magnetic stimulation (pTMS, Fig. 18.1h) is a specific protocol to perform a brief period of low-intensity high-frequency TMS (“priming stimulation”) firstly, followed by main treatment of low-frequency right-sided DLPFC rTMS. For example, 6-Hz priming stimulation at 90% rMT enlarges the 1-Hz rTMS-related cortical suppression in the motor cortex [45]. Subsequently Fitzgerald and the colleagues in an RCT confirmed the better antidepressant efficacy in the priming 1-Hz right-sided rTMS group than 1-Hz right-sided rTMS alone group [46]. In recent network meta-analyses, pTMS showed a higher antidepressant response than cTBS [20]. Especially, pTMS demonstrated lower drop-out rates than sham stimulation [20, 41]. Recently, similar but not the totally same concept was conducted in a TBS study targeted the primary motor cortex. In this study, iTBS session applied 10 min after a priming cTBS session (cTBS+iTBS) and showed larger MEP change than iTBS after a priming sham session (sham+iTBS) [47]. To date, only a few RCTs have been conducted for pTMS [46, 48] and it warrants further investigation.

Another method is to perform specific cognitive tasks before TMS stimulation that may enhance the antidepressant efficacy of rTMS. For example, Li et al. carried out a 2-week double-blind, randomized, sham-controlled trial and observed that patients receiving a computerized rostral anterior cingulate cortex-engaging cognitive task (RECT) followed by active HF rTMS had a greater reduction in depression score and higher response and remission rate, compared to sham cognitive task with active rTMS and RECT with sham rTMS (the mean HDRS-17 decrease = −52.1% vs. −39.6% vs. −18.6%, respectively) [49].

18.2.6 Magnetic Seizure Therapy (MST)

Magnetic seizure therapy (MST) induces a generalized seizure by using magnetic fields. Compared with electroconvulsive therapy (ECT), MST stimulates more focal brain regions and induces a seizure in more superficial cortex regions that may cause less impact on deeper brain structures, such as the hippocampus [50, 51]. In a recent systematic review study, the pairwise meta-analysis showed no different antidepressant response between MST and ECT, and the network meta-analysis evidenced the preliminary better response of MST than sham therapy. A limited number

of MST studies, relatively small samples, and no sham comparison may confound the results in the network meta-analysis [20].

On the other hand, MST studies usually adopted the conventional protocol with high frequency (100 Hz) to stimulate the vertex. Recently one study pointed out the potentially different MST efficacies at different frequencies (conventional high frequency of 100 Hz, moderate of 50-60 Hz, low of 25 Hz) and different stimulation sites (conventional vertex vs. prefrontal cortex). Longer MST courses may be associated with higher remission rates [52]. Additionally, they also found a significant decrease in suicidal ideation following MST intervention [53]. Now a randomized double-blind trial with a noninferiority design is carrying out to compare the antidepressant efficacy and cognitive adverse effects between MST and ECT ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03191058): NCT03191058).

18.2.7 Synchronized Transcranial Magnetic Stimulation (sTMS)

Synchronized transcranial magnetic stimulation (sTMS) is to use rotating spherical neodymium magnets placed along the midline of the scalp to deliver low-field sinusoidal waveform stimulation, which synchronized to an individual's alpha EEG frequency [20, 54]. Following the brain's natural resonance at the individual's alpha frequency, sTMS is believed to achieve antidepressant efficacy by using lower energy than conventional HF-rTMS intensity [55] and may have fewer undesired adverse effects. Reanalyzing per-protocol sample ($N = 120$) from the Leuchter et al.'s study [54], the same study team found sTMS may provide more benefits in patients whose baseline had greater depression severity and higher anxiety than sham sTMS did [56]. In a recent network meta-analysis study, sTMS could not provide more efficacy than sham for treating depression, but the limited number of included studies may confound the result. Also, the drop-out rate of sTMS did not show the difference from other TMS modalities and sham therapy [20]. Further investigations including more RCTs and head-to-head comparison studies with other TMS modalities are warranted.

Recently, a study team tried to integrate the concept of synchronized individual's alpha EEG wave into conventional HF-rTMS protocol [57, 58]. In their preliminary single-session crossover trial, they found alpha-synchronized rTMS over left DLPFC could reduce resting alpha activity in the left DLPFC, but nonalpha-synchronized rTMS protocols could not [57], in patients with antidepressant-resistant depression. Frontal alpha power is reported to be associated with the depressive symptomatology and antidepressant response [59, 60]. The therapeutic potential of repeated alpha-synchronized rTMS needs more investigation.

18.2.8 Quadri-Pulse Magnetic Stimulation (QPS) and Quadri-Pulse TBS

The other patterned stimulation protocols except TBS is the quadri-pulse magnetic stimulation (QPS, Fig. 18.1i) and quadri-pulse TBS, which consisted of repeated trains of four pulse bursts and it is believed to have less variable neurophysiological effects on cortical excitability in normal subjects. However, these protocols have not yet been studied in depressed patients [61–63].

18.3 Concomitant Therapy with TMS

rTMS might enhance the response of some antidepressant medications [64] and those patients with concomitant antidepressant medications exhibit a better response following rTMS treatment than those without medication (47.8% vs. 36.6%, $p < 0.005$) [9, 65]. However, some psychotropic drugs (e.g., hypnotics, anxiolytics, and mood stabilizers) may have a negative impact on the antidepressant results of brain stimulation. So, more studies are warranted to investigate such issues.

Apart from concomitant antidepressant medications, in order to achieve a higher likelihood of antidepressant efficacy, standard rTMS protocols (daily session, about 30 min, 5 days a week for 4–6 weeks) provide lots of room to combine other evidence-based treatment modalities, which can be performed before or after or simultaneously with TMS session.

For example, Mania et al. in their open-label case report demonstrated the 100% response rate and 50% remission rate in six patients following standard H-coil rTMS protocol with simultaneous bright light therapy (given for 20 min). These six patients failed to respond to at least four antidepressant medications and psychotherapy. As a result, after combination therapy, the mean HDRS-17 scores were decreased from 28.3 at baseline to 5.8 at the end of the study. Bright light therapy is easy to use with almost no additional side effects [66].

Another example in a large naturalistic open-label study ($N = 196$) demonstrated the clinical efficacy of simultaneous rTMS and psychotherapy in depressed patients. rTMS was applied over left DLPFC (10 Hz, 110–120% rMT, 5 s-on and 30s off, 1500 pulses per sessions) or right DLPFC (1 Hz, 110–120% rMT, 1200 pulses per session) or both sequentially (1 HZ for 1000 pulses first and then 10 Hz for 1500 pulses). Psychotherapy for a period of 45 min each session is mainly provided as the cognitive-behavioral therapy (little cases of schema therapy or Eye Movement Desensitization and Reprocessing, EMDR). In the first 20 min, patients received psychotherapy plus rTMS therapy and then only psychotherapy was continued until 45 min. The total number of mean combined treatment was 20.9 sessions, but the session numbers per week and the total number of sessions were varied for each patient. As a result, the response rate was 66.3% and remission rate was 56.0%. The mean BDI-II score decreased from 31.3 at baseline to 14.1 at last visit. The outcomes of rTMS plus psychotherapy were clinically meaningful and provided

another treatment combination for those suffering from undesirable antidepressant side effects. Future RCTs are required to direct comparison between either therapy alone and combined rTMS with psychotherapy to replicate the promising outcomes [67].

18.4 Conclusion

Beyond psychotherapy and pharmacotherapies, noninvasive neurostimulation techniques such as rTMS are the tertiary wave to treat major depressive disorder. In decades, many studies have provided the evidence to confirm antidepressant efficacy and safety profiles of standard rTMS applied to the left DLPFC. The latest CANMAT treatment guideline for major depressive disorder considers rTMS as the first-line recommendation for depressed patients with at least an inadequate response to one antidepressant trial [68]. However, some patients still could not achieve good responses after rTMS intervention and higher levels of treatment resistance were associated with worse clinical responses to rTMS [15]. In addition, the conventional rTMS protocols restricted its generalizability and treatment capacity due to its longer session lengths (37.5 min). The rTMS effects on acute suicidal thoughts were also limited. These clinical issues trigger the need for more optimal protocols of TMS modality.

In this chapter, we update newer forms of rTMS in major depression, including standard iTBS, piTBS, accelerated rTMS/iTBS, deep TMS, priming TMS, synchronized TMS, and magnetic seizure therapy. Furthermore, identifying reliable indicators for early rTMS response, such as patients' characteristics or neurophysiological results, could help the selection of appropriate stimulation protocols and modalities. For example, the changes of depression scores after 1-week piTBS intervention could predict the final antidepressant response [15]. Another example is the baseline cortical inhibition ability that could be used to identify who could alleviate more suicidal ideation after MST intervention [69]. Future studies are still needed to replicate and determine the most optimal cutoff value.

In the near future, as the clinical effects and reliable predictors are getting clearer, we also need to investigate the underlying mechanisms of each rTMS/TBS protocol and provide the possibility for approaching precise medicine.

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Chapter 19

Well-being Therapy in Depressive Disorders



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Abstract A specific brief psychotherapeutic intervention aimed at empowering psychological well-being, the so-called Well-Being Therapy (WBT), has been manualized in 2016 by Giovanni Fava and has shown to be effective in randomized controlled trials. WBT is based on the multidimensional model of psychological well-being developed by Marie Jahoda which encompasses environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, positive relations with others, and balance of psychic forces. WBT aims at promoting the achievement of an optimal-balanced functioning between the dimensions of psychological well-being, and such a balance is subsumed under the rubric of euthymia. There are evidences that WBT may be a suited clinical approach for second- or third-line treatment of depressive disorders with particular reference to decreasing vulnerability to relapse and modulating psychological well-being and mood. It has been also proposed a role of WBT in depressive disorders in clinical conditions such as treatment resistance, loss of antidepressant clinical efficacy, persistent post-withdrawal disorders, trauma exposure, and medical disease comorbidity. The present chapter provides an overview of the possible applications of WBT as treatment of depressive disorders.

Keywords Well-being therapy · WBT · Depression · Depressive symptom · Psychological well-being · Psychotherapy · Resilience

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19.1 Well-being Therapy: Conceptual Issues

For decades, mental health research has been dramatically weighted on the side of psychological dysfunction, and health has been equated with the absence of illness rather than the presence of wellness [1]. However, already in 1954, Parloff et al. [2] proposed that the goals of psychotherapy were not necessarily the reduction of symptoms but increased personal comfort and effectiveness. Similarly, Jahoda [3] criticized the concept of mental health as absence of disease suggesting that it could be more fruitful to tackle the concept of mental health in its positive connotation. Thus, she proposed a model of psychological well-being identifying six criteria for positive mental health: autonomy (i.e. regulation of behaviour from within); environmental mastery; satisfactory interactions with other people and the milieu; the individual's style and degree of growth, development, or self-actualization; the attitudes of an individual towards his/her own self (i.e. self-perception/acceptance), and the individual's balance and integration of psychic forces [3]. In the same period, also the World Health Organization pointed out that health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity [4].

As a consequence of a distress-oriented literature, for a long time, an effective treatment had been viewed only as able to reduce symptoms which have become the main target of psychotherapeutic strategies [5, 6]. Well-being and distress were considered as mutually exclusive, i.e. well-being resulted from removal of distress. Nowadays, on the contrary, there is evidence that not necessarily high distress is linked to impaired psychological well-being and different association between well-being and distress may occur [7]. Some individuals might have high levels of both ill-being and well-being, while others might have psychological disorders and low psychological well-being, and further individuals might have no psychological disorders and high psychological well-being [8]. Although treatment aimed at reducing distress and bringing subjects out of negative functioning is still recommended, interventions which promote a progression towards the restoration of positive functioning and well-being are also effective [6]. In this vein, in the last two decades, a number of converging developments have paved the clinical ground for an appraisal of the role of well-being in mental health, especially in affective disorders [5, 6]. Carol Ryff [9] elaborated five of the six dimensions of positive functioning proposed by Jahoda [3] and introduced a tool for their assessment, the psychological well-being scales [10]. The mentioned psychological dimensions were further refined by Fava, as summed up in Table 19.1 [11]. In addition, Fava introduced in 1999 [5] a well-being-oriented psychotherapeutic strategy, the Well-Being Therapy (WBT), which is based on the model of psychological well-being developed by Marie Jahoda in 1958 [3] and which has been recently [6] manualized.

Table 19.1 Dimensions of psychological well-being according to Ryff's model [9] as adapted by Fava et al. [11]

Dimensions	Optimal level
Environmental mastery	The subject has a sense of mastery and competence in managing the environment. Makes effective use of surrounding opportunities. Is able to create or choose contexts suitable to personal needs and values.
Personal growth	The subject has a feeling of continued development. Has a sense of realizing own potential. Sees improvement in self and behaviour over time.
Purpose in life	The subject has goals in life and a sense of directedness. Feels there is meaning to present and past life. Holds beliefs that give life purpose.
Autonomy	The subject is self-determining and independent. Is able to resist to social pressures. Evaluates self by personal standards.
Self-acceptance	The subject has a positive attitude towards the self. Accepts his good and bad qualities. Feels positive about past life.
Positive relations with others	The subject has warm and trusting relationships with others. Capable of strong empathy affection and intimacy. Understands give and take of human relationships.

Table 19.2 Main phases of well-being therapy [6]

Phase	Aims
Initial sessions	Check-up and self-monitoring of episodes of well-being, mastery, and pleasure tasks
Intermediate sessions	Identification of thoughts and beliefs leading to premature interruption of well-being
Final sessions	Discussion and modification of dysfunctional beliefs according to the well-being dimensions

19.1.1 *Well-being Therapy: The Structure*

WBT is a manualized, short-term psychotherapeutic strategy which emphasizes self-observation, with the use of a structured diary, homework, and interaction between patients and therapists [6]. The initial phase is concerned with self-observation of psychological well-being. Once the instances of well-being are properly recognized, the patient is encouraged to identify thoughts, beliefs, and behaviours leading to premature interruption of well-being (intermediate phase). The final phase involves cognitive restructuring of dysfunctional dimensions of psychological well-being and meeting the challenge that optimal experiences may entail [6]. The main phases of WBT are summarized in Table 19.2.

Although initially WBT aimed at increasing psychological well-being, its goal was subsequently refined in the achievement of a state of euthymia, the Jahoda's

sixth dimension [3, 6]. Indeed, in 2016, Fava and Bech [12] defined euthymia as a state characterized by the following features: (a) lack of mood disturbances that can be subsumed under diagnostic rubrics; if the subject has a prior history of mood disorder, he should be in full remission; if sadness, anxiety, or irritable mood are experienced, they tend to be short-lived, related to specific situations, and do not significantly affect everyday life; (b) the subject feels cheerful, calm, active, and interested in things, and sleep is refreshing or restorative; (c) the subject displays balance and integration of psychic forces (flexibility), a unifying outlook on life which guides actions and feelings to shape the future accordingly, and resistance to stress (resilience and anxiety or frustration tolerance) [12]. Euthymia is not only a generic advice of avoiding excesses and extremes, but it is how the individual adjusts the psychological dimensions of well-being to changing needs [12]. The psychological dimensions of well-being can compensate each other.

WBT aims at promoting the achievement of an optimal-balanced functioning between dimensions of psychological well-being [6, 12, 13]. Table 19.3 depicts the low/high levels as well as the optimal levels for the dimensions described by Fava [6]. Thus, for instance, subjects with balanced levels of environmental mastery have a sense of competence in managing the environment, make good use of surrounding opportunities, and are able to choose what is more suitable to personal needs. Subjects with impaired level of environmental mastery feel difficulties in managing everyday affairs, feel unable to improve things around, and are unaware of opportunities, while those who have excessive level of environmental mastery may look for difficult situations to be handled, are unable to savour positive emotions and leisure time, and are too engaged in work or family activities and often others constantly ask for their help, which results in feeling of being exploited and overwhelmed by requests [6].

WBT may be used as the only therapeutic strategy or in sequential combination with other psychotherapeutic strategies [6], such as cognitive behaviour therapy (CBT) [14].

19.1.2 Well-being Therapy and Positive Psychology Interventions

WBT is not a positive psychology intervention since it presents different features which are here summed up: patients are encouraged to identify episodes of well-being and set them into a situational context by monitoring episode of psychological well-being in a diary; patients are encouraged to identify automatic thoughts and beliefs leading to premature interruption of well-being, as performed in cognitive therapy [14], but the trigger for self-observation is different, being based on well-being instead of distress; the therapist reinforces and encourages activities that are likely to elicit well-being and optimal experiences by behavioural exposure and encourages cognitive restructuring using specific psychological well-being

Table 19.3 Optimal balanced level of psychological well-being [6]

Psychological well-being dimensions	Low level	Optimal-balanced level	High level
Environmental mastery	The subject has/feels difficulties in managing everyday affairs, feels unable to change or improve surrounding context, is unaware of surrounding opportunities, and lacks sense of control over external world	The subject has a sense of mastery and competence in managing the environment, controls external activities, makes effective use of surrounding opportunities, and is able to create or choose contexts suitable to personal needs and values	The subject looks for difficult situations to be handled, is unable to savour positive emotions and leisure time, and is too engaged in work or family activities
Personal growth	The subject has a sense of being stuck, lacks sense of improvement over time, and feels bored and uninterested in life	The subject has a feeling of continued development, sees self as growing and expanding, is open to new experiences, has a sense of realizing own potential, and sees improvement in self and behaviour over time	The subject is unable to elaborate past negative experiences, forgets or does not give enough emphasis to past negative experiences, cultivates benign illusions that clash with reality, and sets unrealistic standards for their performances
Purpose in life	The subject lacks a sense of meaning in life, has few goals or aims, lacks the sense of direction, and has an impaired level of purpose in life	The subject has goals in life and a sense of directedness, feels there is meaning to present and past life, holds beliefs that give life purposes, and has aims and objectives for living	The subject has unrealistic and excessive expectations and hopes; he is constantly dissatisfied with performance and is unable to recognize failures
Autonomy	The subject is over-concerned with the expectations and evaluation of others, relies on judgement of others to make important decisions, and conforms to social pressures to think or act in certain ways	The subject is self-determining and independent, can resist to social pressures, regulates behaviour from within, and evaluates self by personal standards	The subject is unable to get along with other people, work in team, and learn from others. He spends time and energy fighting for his opinions and rights, relies only on himself for solving problems, and is unable to ask for advices or help

(continued)

Table 19.3 (continued)

Psychological well-being dimensions	Low level	Optimal-balanced level	High level
Self-acceptance	The subject feels dissatisfied with self, is disappointed with what has occurred in past life, is troubled about certain personal qualities, and wishes to be different than what he is	The subject has a positive attitude towards the self, accepts his good and bad qualities, and feels positive about past life	The person has difficulties in admitting own mistakes and attribute problems to others' faults and deficiencies
Positive relations with others	The subject has few, close, trusting relationships with others; finds it difficult to be warm, open, and concerned about other; is isolated and frustrated in interpersonal relationships; and is not willing to make compromises to sustain important ties with others	The subject has warm and trusting relationships with others, is concerned about the welfare of others, is capable of strong empathy affection and intimacy, and is appropriate in human relationships	The subject sacrifices his needs and well-being for those of others. Low self-esteem and low sense of worth may lead to excessive willingness to forgive obvious offenses

dimensions. Therefore, the patient becomes able to readily identify moments of well-being, is aware of interruptions to well-being feelings (interfering thoughts and/or behaviours), uses cognitive behavioural techniques to address these interruptions, and pursues optimal experiences. In addition, the patient is not encouraged to pursue the highest possible levels in psychological well-being in all dimensions, as reported in most positive interventions [15], but to obtain a balanced functioning subsumed under the rubric of euthymia [12]. WBT assumes that the optimal-balanced well-being represents the real psychological well-being (see also Table 19.3) and is different from patient to patient, according to factors such as personality traits, social roles, and cultural and social contexts [6].

19.2 Staging in Depressive Disorders

Notwithstanding the long tradition of staging in medicine, psychiatry and clinical psychology had for a long time neglected staging as a model to classify the development of mental disorders [16]. This neglect has paralleled the reliance on cross-sectional descriptions instead of longitudinal study of prodromes, acute phase of the disorder, and residual symptoms [17]. As a result, traditionally, the acute phase of psychiatric disorders has been considered the main target of psychotherapeutic efforts, while subclinical symptomatology was viewed as devoid of substantial

clinical interest. However, psychiatry disorders are not static, sharply defined disorders with separate aetiologies and courses, but are syndromes which develop across stages. Evidence has substantiated how the majority of patients with affective disorders displays residual symptoms upon successful treatment of their illness and residual symptoms entail prognostic value in the entire range of affective disorders [16].

Moving from a cross-sectional to a longitudinal view of the development of mental diseases, Fava and Kellner for the first time in 1993 [17] introduced the clinimetric concept of staging as a clinical tool to enhance the diagnostic and treatment procedure in psychiatry. Staging was refined in 2013 by Cosci and Fava [16] and nowadays allows to know the degree of progression of a disease. Staging distinguishes prodromes (i.e. early symptoms and signs that differ from the acute clinical phase) and residual symptoms (i.e. persistent symptoms and signs despite apparent remission or recovery) [17]. Prodromal and residual symptoms may be associated, since as the illness remits, it progressively recapitulates, although in reverse order according to the so-called rollback phenomenon [18]. Some prodromes may be overshadowed by the acute phase of a disorder but persist as residual symptoms and progress to become prodromes of the following episode of illness (relapse). Staging identifies four steps for development of a psychiatry disorder: the prodromal phase, which refers to the time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness (stage 1), the acute phase (stage 2), attenuated symptoms (e.g. residual symptoms) (stage 3) which might be due to partial persistence of the disease or to a worsening of a pre-existing abnormal personality trait, and finally, the chronic phase (stage 4) [16].

When staging is applied to unipolar depression, the prodromal phase (stage 1) is characterized by no depressive symptoms (with mild functional change or decline) or by mood symptoms [16]. Anxiety and irritability appear to dominate the clinical picture of the prodromal phase; other symptoms that can characterize the stage 1 are anhedonia, initial and delayed insomnia, depressed mood, guilt, anorexia, fatigue, and impaired activities [16]. Prodromes may increase the risk of the occurrence of major depression, are quite similar to residual symptoms, and can be the front door of the relapse [16]. At stage 2, subjects present a major depressive episode [16]. Then, residual symptoms may occur at stage 3. Cosci and Fava [16] described three types of residual symptoms: no depressive symptoms (i.e. sleep disturbances, generalized anxiety, irritability, anorexia, impaired libido), mood symptoms (i.e. depressed mood, guilt, hopelessness), and dysthymia. Residual phase may mirror the prodromal phase [19] since almost 70% of residual symptoms are present in the prodromal phase of the illness [17]. Residual symptoms were found to be predictors of relapse/recurrence, despite apparent recovery [16]; high relapse rates have been observed in depressed patients with residual symptoms compared with those without residual symptoms (76% vs 25%) [20]. In addition, patients with residual symptoms relapse three times faster than those without such symptoms and mainly in the 4 months after remission [20]. Stage 4 is characterized by recurrent depression or double depression [16, 20]. Recurrence is defined as a new major depressive episode after recovery, i.e. after at least 6 months without meeting full diagnostic

criteria for a major depressive episode [20]. It was estimated that approximately eight out of ten subjects experiencing a major depressive disorder have one or more further lifetime episodes (i.e. a recurrent major depressive disorder) [20]. Finally, at stage 5, subjects present chronic major depression [16]. It has been shown that one out of four patients with non-chronic major depressive disorder progresses to a chronic disorder, while half of the patients with a chronic major depressive disorder remain chronic during a 4-year follow-up [16, 20].

Overall staging defines the extent of the progression of depressive disorders across different stages and defines where a person is currently along the continuum of the course of the illness [16].

Staging has some interesting clinical applications. First, it allows clinicians to apply a stage-specific intervention. A sequential treatment of depression, i.e. use of pharmacotherapy for the acute episode (stage 2) followed by psychotherapy addressed to its residual phase (stage 3) [20], has been developed and was found to yield long-term benefits [16, 20]. In addition, cognitive behavioural therapy [14] seems suitable for all phases, and WBT [6] is suitable for the residual phase (Stage 3) of depression. Second, staging allows clinicians to assess past and potential resistance to treatment in depressive disorders [16, 20]. It is well-known that it is quite different to treat a patient with a major depressive episode who displayed a positive response to previous therapeutic trials or a patient who failed to respond to various adequate trials, including one involving augmentation/combination [21]. A staging method for assessing treatment resistance and clinical deterioration during psychotherapy of depression has been proposed [16, 20].

19.3 Psychological Well-being in Depressive Disorders

An association between impairments in psychological well-being and depression has been described [7, 10, 22–25]. Negative correlations were found between the six dimensions of PWB scores [10] and depression both in non-clinical samples [10, 22, 23] and in subjects in remission from a mental illness [7, 24]. Nierenberg et al. [25] observed that in subjects currently suffering from depression, mean standardized PWB scores were extremely low for the dimension of environmental mastery and for the dimension of self-acceptance (two standard deviations below the population mean), low for the dimensions of purposes in life and positive relations with others (one standard deviation below the mean), but within the normal range for the dimensions of personal growth and autonomy. In a case-control study, Edmondson and MacLeod [26] observed that depressed subjects scored significantly lower than non-clinical controls on all six dimensions of PWB [10], with environmental mastery and self-acceptance showing the greatest deficit.

Some areas where psychological well-being is likely to play an important role in depression have been outlined. In addition, it has been assumed that well-being may contribute to the onset of depression and affect its clinical outcome (e.g. more severe symptoms, higher rate of relapse, impaired recovery) [5, 6, 27]. Recently it was also

proposed that the role of well-being in depression could be extended to other clinical issues such as treatment resistance, loss of clinical efficacy of antidepressants, persistent post-withdrawal symptoms, empowerment of resilience, and management of medical disease comorbidity [28, 29].

Some evidences suggested that impairments in psychological well-being may be a substantial risk factor for the onset of depression [27, 30]. In a large cohort study of 5566 subjects who completed a survey at two time points (i.e. aged 51–56 at time 1 and 63–67 at time 2), subjects with lower scores on PWB were over 7 times more likely to be depressed 10 years later than those with no impairment in PWB dimensions [27]. Those with low PWB were at risk of being depressed regardless of whether PWB was assessed as a global construct or separately as self-acceptance, autonomy, purpose in life, positive relationships with others, environmental mastery, and personal growth [27]. Interestingly, Wood and Joseph [27] showed that individuals with low PWB had greater risk to be depressed in the future than those with non-impaired PWB, independently from prior levels of depression, personality, demographics, and medical conditions. These findings were confirmed by Grant et al. [30] who showed that in a cohort of 11,621 individuals set to begin medical internship, lower well-being was prospectively associated with depressive symptoms even after accounting for neuroticism, early childhood environment, gender, and baseline depressive symptom scores.

There has been increasing awareness that the challenge of treatment of depression seems to be the prevention of relapse more than the attainment of recovery [29]. Ramana et al. [31] explored the course of depression with respect to remission and relapse in a 2-year prospective study and found that remission was rapid with 70% of patients remitting with pharmacological treatment within 6 months and only 6% failing to do so by 15 months; however, 40% relapsed over the first 10 months. Some evidence suggested that impairments in psychological well-being may be associated with recurrence of depression [7, 27, 32]. Rafanelli et al. [7] found impairments in psychological well-being in 20 remitted patients with mood or anxiety disorders compared to healthy controls. This finding was replicated in Risch et al. [32] who evaluated PWB in remitted depressed patients compared to healthy controls and acutely depressed patients. Both remitted depressed (recurrent depression; with complete remission over 8 weeks) and acutely depressed patients showed significantly lower scores on each PWB scale than controls, while remitted depressed and acutely depressed patients did not differ significantly in scores of PWB scales except for the dimension of self-acceptance, on which acutely depressed patients showed a significantly lower score than remitted depressed patients. Thus, even when recurrent depressed patients remitted for at least 2 months, impairments of PWB such as self-acceptance or relationship to others may persist [32]. The lack of significant differences on PWB between remitted depressed and acutely depressed patients supports the possible role of psychological well-being as risk factor for depressive recurrence [32].

Assessing psychological well-being may add important practical utility for preventing depression and recurrence; thus, efforts to increase psychological

well-being may be effective in protecting individuals from depression and may aid in decreasing the overall healthcare costs associated with this disorder [27, 29, 30].

19.3.1 Psychological Well-being and Recovery

The term recovery derives from the Latin ‘recuperare’ that connotes the act of regaining or returning towards a normal or usual state of health [11, 33]. To date there is lack of consensus about the use of this term, and often clinicians and researchers in clinical psychiatry confound response to treatment with full recovery [33]. This implies that some basic issues are neglected that may demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same psychiatric diagnosis [11, 33, 34]. One of such basic issues concerns psychological well-being. Ryff and Singer [1] remarked that the absence of well-being creates conditions of vulnerability to possible future adversities and that the route to recovery lies not exclusively in alleviating the negative but in engendering the positive. The balance between positive and negative effects and its biological counterparts may carry considerable weight on the complex regulation underlying long-term outcome of affective disorders [7, 23]. In drug trials, subscales describing well-being were found to be more sensitive or as sensitive to drug effects than subscales assessing symptoms [11, 33, 34]. Moreover, in a survey on factors identified by depressed outpatients as important in determining their remission, the most frequently judged as such was the presence of features of positive mental health, such as optimism and self-confidence; a return to one’s usual, normal self; and a return to the usual level of functioning [35].

Ill-being (e.g. depressive symptoms, major depressive disorder) and well-being are independent and interrelated dimensions [7, 35, 36]. This means that some individuals might have high levels of both ill-being and well-being, whereas others might have major psychological disorders and poor psychological well-being, and further individuals might have no major psychological disorders and high psychological well-being [29]. If psychological well-being is incorporated in the definition of recovery, interventions that bring the person out of negative functioning do not have a full recovery but the achievement of a neutral position [29]. A full recovery can be reached via interventions that facilitate progress towards restoration or enhancement of psychological well-being [3] as well as towards patients’ feelings of well-being which can be equated to a premorbid state [11, 33, 34].

The need to include well-being in the definition of recovery is further supported by the fact that well-being may enhance psychotherapeutic strategy (i.e. Well-Being Therapy) with a significant reduction in residual symptoms in patients with affective disorders [29]. A substantial residual symptomatology (i.e. anxiety, irritability, interpersonal problems) was found to characterize the majority of depressed patients who successfully responded to pharmacological or psychological therapies [11, 33, 34]. According to the sequential model of depression [20], in patients with affective disorders remitted upon drug treatment, the sequential administration of two

psychotherapeutic strategies, e.g. CBT followed by WBT directed towards residual symptoms, may yield long-term benefits [11, 33, 34]. Fava et al. [29] pointed out that WBT targeting euthymia may address specific features that may be associated with depressive illness and that hinder recovery concern with the occurrence of mental pain and its relationship with suicidal ideations [29]. WBT working on dimensions such as purpose in life may counteract suicidal behaviour, since there is strong evidence that the way people think about their future holds the key for understanding their suicidal thinking [38]. Moreover, although it should be tested with appropriate controlled studies, WBT may have a potential function in decreasing the experience of mental pain [6, 28] that many suicidal patients may present with [37, 38].

Reference to well-being appears to be unavoidable for recovery [11]. In a recent study, Guidi et al. [39] observed a heterogeneous clinical population in primary care and found that euthymia was lower in patients with DSM-5 diagnosis of mood disorders [40] and/or DCPR diagnosis of demoralization [41] compared to those without such diagnoses. They also found that euthymia was negatively correlated with mental pain and affective symptoms, and positively correlated with well-being [40].

A multidimensional redefinition of recovery including well-being was already proposed in 2007 [11] (Table 19.4) and has been more recently refined based on the concept of euthymia [12]. Recovery is nowadays conceptualized as a condition characterized by the absence of affective disorders and by the presence of psychological flexibility and resistance to stress [12].

Ryff's [9] psychological dimensions may be adequate to assess recovery [11] as well as other self-rating scales such as the Euthymia Scale [12] and the 5-item World Health Organization Well-Being (WHO-5) Index [42]. The Euthymia Scale [12] is a 10-item self-report scale which incorporates Jahoda's conceptualization of euthymia [3] (i.e. the individual balance among psychic forces leading to high levels of resilience and frustration tolerance). The 5-item World Health Organization Well-Being (WHO-5) Index [42] is a widely used 5-item self-report index which measures of psychological well-being and assesses depression. Carozzino et al. [43] conducted a clinimetric analysis of the Euthymia Scale and found a two-dimensional structure (i.e. psychological flexibility and well-being); in addition, the scale

Table 19.4 Definition of recovery

Recovery from a major depressive episode occurs when:
The patient remains in full remission despite discontinuation of treatment (whether pharmacological or psychotherapeutic).
If subclinical or subsyndromal symptoms are present, they do not interfere with everyday life and social adjustment to a considerable degree.
The patient reports psychological well-being in at least one of the six areas according to the Ryff's model [9].
Normalization of altered biological markers in the acute phase of illness (if available) should have occurred.

Adapted from Ref. [11]

presented a satisfactory incremental contribution to the prediction of well-being and neuroticism over and above the WHO-5 Index [43].

19.4 Well-being Therapy as Treatment of Depressive Disorders

WBT must be conceived as a therapeutic tool to be incorporated in a therapeutic plan. WBT may be more suitable for second- or third-line treatments than as first-line treatment of an acute phase depressive disorder [6]. WBT was not conceived to be used in every patient who meets specific diagnostic criteria [6], but it should follow clinical reasoning and case formulation facilitated by using macro-analysis, micro-analysis [21, 44], and staging [16]. In depressive disorders there are some areas where WBT is likely to play an important role.

19.4.1 Recurrent Depression

Preliminary findings from clinical trials suggested that the sequential combination of CBT and WBT in recurrent depression may result in a decreased rate of relapse [45–48]. In 1998, Fava et al. [45] conducted the first study aimed at testing the effectiveness of the sequential combination CBT/WBT in recurrent depression. Forty patients with recurrent major depression (i.e. defined as the occurrence of 3 or more episodes of unipolar depression, with the immediately preceding episode being no more than 2.5 years before the onset of the current episode) were randomly assigned to either CBT package including WBT or clinical management (i.e. reviewing the clinical status of the patient and providing the patient with support and advice, if necessary). In both groups, antidepressants were tapered and discontinued. The group that received CBT and WBT had significantly lower levels of residual symptoms after drug discontinuation in comparison with the clinical management group. CBT and WBT resulted in a significantly lower relapse rate (25%) at 2-year follow-up than the clinical management (80%) [45]. At 6-year follow-up [46], the relapse rate was 40% in those who received CBT and WBT and 90% in those assigned to clinical management; moreover, the group treated with CBT and WBT had a significantly lower number of recurrences when multiple relapses were taken into account. At 6-year follow-up, more than half of the patients treated with CBT and WBT were symptom and drug free [46].

In 2013, Stangier et al. [47] run a multicentre trial on 180 patients with 3 or more lifetime episodes of major depression randomly assigned to an experimental condition (i.e. combination of CBT, WBT, and mindfulness-based cognitive therapy) or a control condition (i.e. manualized psychoeducation). At 1-year follow-up, relapse

was less likely in patients with five or more episodes of depression than in those assigned to the control condition [47].

CBT and WBT combination was found effective in reducing the risk of relapse also in a sample of 144 children and adolescents with major depression [48].

From the available studies [45–48], it is not clear whether WBT was a specific effective ingredient and what was the mechanism decreasing the likelihood of relapse. A dismantling study that was performed in generalized anxiety disorder [49] suggested that an increased level of recovery could be obtained with the addition of WBT to CBT. Patients were randomly assigned to eight sessions of CBT or to the sequential administration of CBT followed by four sessions of WBT; although both treatments were associated with a significant reduction of anxiety, significant advantages of the CBT/WBT sequential combination over CBT were observed both in terms of symptom reduction and psychological well-being improvement [49]. An increase in psychological well-being occurred with CBT only, but not to the degree that took place with WBT, suggesting a specific mechanism of action for WBT [29, 49].

Finally, a study run in Iran [50] on 40 high school and university students randomly assigned to CBT or WBT suggested that WBT promoted a decrease of depressive symptom severity more than CBT [50].

19.4.2 Mood Modulation

WBT was applied to treatment of cyclothymic disorder [51]. Sixty-two patients with cyclothymic disorder were randomly assigned to the sequential combination of CBT and WBT or clinical management (i.e. reviewing the patient's clinical status and providing the patient with support and advice, if necessary, according to a structured protocol). At post-treatment, significant difference was found in outcome measures (i.e. subclinical symptoms of mood disorders, symptoms of mania, reactivity to social environment, persistence of both cyclothymic disorder, and DSM comorbidity) with greater improvements in the CBT/WBT group compared to clinical management [51]. The therapeutic gains were maintained at 1- and 2-year follow-ups [51].

These findings suggested that WBT may address both polarities of mood swings and is geared to a state of euthymia [12, 29].

Whether WBT target of euthymia decreases vulnerability to relapse in bipolar spectrum disorders with particular reference to the occurrence of hypomania among depressive episodes would be an important area that deserves specific studies [29].

19.4.3 Treatment-Resistant Depression

Despite substantial advances in treatment and management strategies for major depressive disorders, approximately less than 70% of patients responded to first-line antidepressant treatment or psychotherapy [20, 52, 53]. The large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness study, including 4000 adults, showed that only one third of patients achieved remission following an initial antidepressant trial, while up to a third of patients in the STAR*D study did not reach remission despite multiple antidepressant trials [54].

In two studies, WBT was applied to patients with depressive disorder who displayed treatment resistance [55, 56]. The first study involved a 53-year-old woman with major depression and one previous depressive episode 10 years earlier that was refractory to pharmacological treatment and was successfully treated with the sequential combination of CBT and WBT [55]. At the early stage of treatment, the patient was treated with desipramine up to 200 mg per day, which improved both depressive and anxious symptoms; after 3 months of treatment, desipramine was tapered and discontinued. However, 3 months later, the patient developed depressive symptoms, and the medication that was given the first time (i.e. desipramine) did not show to be any more effective. After some pharmacological attempts, the sequential combination of CBT and WBT was administered, and the patient got better and stayed well reporting that she did not relapse at 12-year follow-up [55].

The second study involved two cases [56]. In the first case, WBT was administered to a 42-year-old married male with recurrent depression that, after pharmacological treatment (i.e. selective serotonin reuptake inhibitor antidepressant) and CBT, did not fully recover showing lower functioning (e.g. he still felt unable to resume work full time, visit friends, and practice sport). WBT was introduced and medication was maintained. At the end of the treatment, the patient felt more self-confident and fully recovered, showed good global functioning, became more active, resumed playing football and working full time, and remained well at 6-month follow-up [56]. In the second case, WBT was administered to a 28-year-old female with a diagnosis of dysthymic disorder according to the DSM-IV-TR [57]. After CBT, the patient recovered partially, but, although the symptoms became less severe, she still had depressive symptoms. WBT was administered as only treatment. At the end of the psychotherapy, there were no more depressive symptoms; the patient became happier with her body and dressed fashionably; some of her friends became close friends. At 6-month follow-up, she was still well; showing a global good functioning; she had received an employment contract and started a romantic relationship [56].

Although further large studies are needed to corroborate these findings, these case reports suggest that WBT may be of particular value in patients who failed to respond to standard pharmacological and/or psychotherapeutic treatments of depression [29]. The possible role of WBT as therapeutic approach to overcome treatment resistance is further supported by findings showing that WBT provides a viable alternative when standard cognitive techniques based on monitoring distress

do not yield any improvement or even cause symptomatic worsening in panic disorder [58], obsessive-compulsive disorder [6], and anorexia nervosa [59].

19.4.4 Loss of Clinical Efficacy of Antidepressants

Loss of efficacy of antidepressants in long-term treatment of depression is a common and vexing problem which increases with prolonging of treatment duration [60]. The return of depressive symptoms during maintenance of antidepressant treatment was found to occur in 9–57% of patients [61]. Several pharmacological strategies, such as increase or decrease in dose, drug augmentation, or switching to a different drug, have been suggested for addressing such loss of efficacy [29, 62]. However, the literature suggests flat dose-response curves for many antidepressant drugs [61].

In 2002, Fava et al. [63] explored the feasibility of a sequential combination of CBT and WBT to be proposed in case of loss of clinical effect of long-term antidepressant therapy. Ten patients with recurrent depression who relapsed while taking antidepressants were randomly assigned to dose increase and clinical management (i.e. reviewing the patient's clinical status and providing the patient with support and advice, if necessary) or to a sequential combination of CBT and WBT and maintenance of the antidepressant drug at the same dose [63]. Four out of five patients responded to a larger dose, but all relapsed on that dose by 1-year follow-up; four out of five patients responded to psychotherapy, and only one relapsed at 1-year follow-up. These findings suggested that WBT may counteract the loss of clinical effects during long-term antidepressant treatments [29]; WBT may restore and maintain remission with antidepressant drugs when response fails or is about to fail [29]. However, investigations on large samples are needed to confirm these preliminary findings.

19.4.5 Withdrawal After Reduction or Discontinuation of Antidepressants

Discontinuation of antidepressant drugs represents a major clinical challenge [64–66]. Psychotropic drug treatments, particularly after long-term use, might cause or precipitate adverse effects on the course, characteristics, and responsiveness of an illness that do not necessarily subside with discontinuation of the drug or of modifying responsiveness to subsequent treatments [67, 68]. In 2015, Chouinard and Chouinard [64] proposed a comprehensive classification of SSRI/SNRI withdrawal, later refined by Cosci and Chouinard [69], according to which they identified three different syndromes: new withdrawal symptoms (i.e. symptoms which were not present before the beginning of the SSRI/SNRI treatment as well as before

reduction or discontinuation of the drug), rebound withdrawal (i.e. return of symptoms, but a greater intensity, which were present before the beginning of the SSRI/SNRI treatment but were not present before reduction or discontinuation of the drug), and persistent post-withdrawal disorders (i.e. return of symptoms which were present before the beginning of the SSRI/SNRI treatment but were not present before reduction or discontinuation of the drug or of the return of the original illness with additional symptoms or appearance of symptoms related to emerging new mental disorders). Withdrawal symptoms may constitute an iatrogenic comorbidity that might be persistent and not limited to a short phase [67, 68] and might affect the course of illness as well as the response to subsequent treatments [67].

As pointed out by Fava et al. [29], discontinuation of antidepressants is feasible when psychotherapy is provided and may yield enduring results. A protocol based on the sequential combination of CBT and WBT has been tested in three cases with persistent post-withdrawal disorder following antidepressant discontinuation [70]. This protocol was based on the following steps: explanatory therapy including symptom interpretation according to the oppositional model of tolerance, individualized CBT (i.e. monitoring of emergent symptoms in a diary followed by cognitive restructuring and lifestyle modifications, teaching techniques of decreasing abnormal reactivity related to social environment as stressful situations related to the level of arousal increased by drug withdrawal), and WBT (see Table 19.5) [70].

The first case is a 45-year-old man treated with paroxetine 20 mg at bedtime for major depressive disorder for 12 years. After he started paroxetine, he developed pathological gambling. He switched paroxetine to fluvoxamine (50 mg at bedtime) without tapering paroxetine. Thereafter, the patient developed withdrawal symptoms (i.e. aggressiveness towards his partner, impulsiveness, electric sensations to the face, visual problems, sleep difficulties, and severe generalized anxiety) which lasted more than 2 months. A sequential combination of CBT and WBT was

Table 19.5 Components of sequential CBT/WBT for persistent withdrawal disorders induced by antidepressant reduction or discontinuation

1	The protocol is of 6–16 weekly 1-hour sessions and consists of explanatory therapy, which includes providing accurate information on withdrawal, repeated reassurance, and teaching the physiological principles underlying withdrawal phenomena. For example, the patient is told: ‘It is quite frequent to have these symptoms after antidepressant discontinuation’
2	Monitoring of emergent symptoms in a diary according to the cognitive behavioural model, followed by cognitive restructuring consisting of alternative interpretations of patient thoughts about his symptoms
3	Homework exposure for avoidance patterns. For example, ‘without my drops, I cannot go out with friends’
4	Lifestyle modifications: Avoidance of alcohol, increased physical exercise, limited caffeine consumption, and no change in cigarette smoking habits
5	Techniques of decreasing abnormal reactivity to the social environment, consisting in learning ways to cope with stressful situations related to the level of arousal increased by drug withdrawal
6	Teaching Well-Being Therapy. For example, ‘life exists after antidepressants’

Adapted from Ref. [68]

proposed. After 3 months, gambling stopped with improvement in withdrawal-induced disorders. The patient started to remember events that had happened during paroxetine treatment, and fluvoxamine was then slowly tapered in a period of 8 weeks and successfully discontinued. CBT/WBT lasted 6 months; at 1-year follow-up, the patient was in remission and drug free [70]. Similarly, a sequential combination of CBT and WBT produced a reduction on persistent post-withdrawal symptoms in the two cases with a diagnosis of panic disorder with agoraphobia and anxious depression [70].

Overall, three cases here reported provide preliminary evidences of the usefulness of a sequential combination of CBT/WBT to persistent paroxetine post-withdrawal disorders [70]. These findings should be interpreted with caution since symptoms may have disappeared spontaneously, even though the clinical evolution would suggest unlikelihood of spontaneous remission [70]. Future investigations on large samples are needed.

19.4.6 Resilience Increase and Trauma Overcome

The role of resilience as a protective factor is clear as well as the role of stress as pathogenic factor for depression [71–73]. Higher levels of resilience were found in those without depression compared with depressed patients and were found associated with less depressive symptom severity and an increased odds of not being depressed than depressed [71, 74, 75].

The exposure to trauma and stressful life events is consistently associated with increased odds of being depressed than not depressed, as well as with severe depressive symptoms and poor treatment outcome than to positive response to treatment [74–78]. Moreover, major depressive disorder is often comorbid with post-traumatic stress disorder (PTSD) [79]. Thus, treatments allowing to increase resilience and overcome trauma in subjects with depressive disorders appear to be a mandatory [71, 75].

Ryff et al. [80] defined resilience as the capacity to maintain or recover high well-being in the face of life adversity. Looking for the presence of wellness following adversity comprises a more demanding and rigorous conception of resilience than the avoidance of illness or negative behavioural outcomes, the usual gold standards. Examples are provided by life histories of women regaining high well-being following depression [81] and the ability to sustain psychological well-being during serious or chronic illness [82].

Some evidence suggests that WBT could be a suited intervention to increase resilience and overcoming trauma exposure [6].

First, WBT was found effective in promoting recovery and preventing relapse in individuals with mood disorders [6, 29]. This may be explained by two distinct clinical phenomena. First, an increase in psychological well-being, as a protective effect in terms of vulnerability to chronic and acute life stresses [83] has been observed as well as a certain degree of inverse correlation between positive and

negative affects [7, 23] which implies that changes in well-being may induce a decrease in distress and vice versa [84]. Second, there is evidence of effectiveness of WBT alone or in sequential combination with exposure as treatment of PTSD, with the central trauma being discussed only in the initial history taking session [85] and later underlining an alternative way to overcome the trauma and develop resilience [6]. Traumatic experiences let people avoid associated cues in everyday life, that is, after a car accident, they may stop driving. WBT encouragement to transfer experiences, that is, to make a recognition of the similarities between problems handled successfully in the past and those which are likely to come, resembles exposure homework and showed to be helpful [85]. Third, research on the neurobiological correlates of resilience has disclosed how different neural circuits (i.e. reward, fear conditioning and extinction, social behaviour) may involve the same brain structures, particularly the amygdala, the nucleus accumbens, and the medial prefrontal cortex [86]. Reconsolidation is a process in which old, reactivated memories undergo consolidation: each time a traumatic memory is retrieved; it is integrated into an ongoing perceptual and emotional experience, which involves N-methyl-D-aspartate and β -adrenergic receptors and requires cyclic adenosine monophosphate response element binding protein induction [87]. Singer et al. [86] suggested that WBT may stimulate dendrite networks in the hippocampus and induce spine retraction in the basolateral amygdala (a site of storage for memories of fearful or stressful experiences), leading to a weakening of distress and traumatic memories. Fourth, traumatic experiences can give rise to positive transformations, subsumed under the rubric of post-traumatic growth [88, 89]. Positive changes can be observed in self-concept (e.g. new evaluation of one's strength and resilience), appreciation of new possibilities in life, social relations, hierarchy of values and priorities, and spiritual growth. WBT may be uniquely suited for facilitating the process of post-traumatic growth [6].

Although it should be tested with appropriate controlled studies, it may be assumed that in patients with depressive disorders exposed to trauma or stressful life events, WBT may have a potential function to increase resilience and overcoming trauma exposure.

19.4.7 Improvement in Patients with Depressive Disorders and Concurrent Medical Disease

There is ample evidence demonstrating a strong association between depression and medical disease [90–92]. Depression was consistently reported in Cushing's syndrome, hypothyroidism, hyperparathyroidism, pancreatic and lung cancer, myocardial infarction, Wilson's disease, AIDS, and migraine [90–92]. As pointed out by Cosci et al. [90], medical disease should be considered in the diagnostic workup of patients who present with depression, particularly when they appear to be refractory to standard psychiatric treatments. Affective symptoms due to a medical illness tend

not to fully respond to antidepressants, even when properly administered, but rather to the proper treatment of the underlying medical disorder [90].

Recent studies provided preliminary evidences of the usefulness of WBT in the setting of medical disease [6]. A randomized controlled trial to evaluate the efficacy of CBT plus WBT in improving depression and reducing cardiac risk in depressed/demoralized acute coronary syndrome (ACS) patients compared to clinical management (CM) has been recently concluded [93]. One-hundred patients with depressive disorders and/or demoralization with or without type A behaviour, 1 month after a first ACS episode, were randomized to CBT/WBT or CM group. Both psychological and cardiac data up to 36 months after baseline were collected. CBT plus WBT was associated to both fast decrease of depressive symptomatology severity at the end of the treatment and significant improvement of biomarkers (i.e. platelet count, HDL, d-dimer). The two groups showed similar frequencies of adverse cardiac events, while relapses in CBT/WBT group were predicted by older age and higher global cardiac risk, whereas relapses in CM were predicted by depression in comorbidity with type A behaviour. These preliminary findings suggested the clinical utility of a sequential combination of CBT/WBT approach on the psychological and biological parameters of cardiac risk [93].

Preliminary findings also rise from a single case of migraine patient [94], which is part of an ongoing randomized controlled trial [95]. WBT was applied to an 18-year-old woman with a diagnosis of chronic migraine. At baseline, the patient reported 54 migraine attacks in the previous 15 days; low levels of autonomy, environmental mastery, and self-acceptance; high levels of personal growth, positive relations with others, and purpose in life as measured by the PWB scales [96]; and moderate psychological distress as measured by the Psychosocial Index [97]. At the end of WBT, the patient had 18 migraine attacks in the previous 15 days, an increase of autonomy and self-acceptance, and a decrease of psychological distress.

Although it should be tested with appropriate controlled studies, it may be assumed that in patients with depressive disorders, WBT may also have a potential function to counteract the limitations and challenges induced by the co-occurrence of medical disease.

19.5 Conclusions

WBT assumes that impairments in well-being may vary from illness to illness, from patient to patient, and even from one episode to another of the same illness in the same patient [7]. The pursuit of euthymia [12] can be achieved with a personalized approach that characterizes the treatment protocol requiring a comprehensive initial evaluation [98]. The role of WBT in depressive disorders is broader than that originally assumed, that is, decreasing the risk of relapse in the residual phase. WBT in depressive disorders may be a suited clinical approach that may allow clinicians to reduce treatment resistance, overcome the loss of clinical efficacy of antidepressant drugs, manage persistent post-withdrawal disorders after antidepressant drugs

reduction or discontinuation, increase resilience, overcome trauma exposure, and counteract the limitations and challenges induced by the co-occurrence of medical disease.

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Chapter 20

Current Research on Complementary and Alternative Medicine (CAM) in the Treatment of Major Depressive Disorder: An Evidence-Based Review



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Abstract Complementary and alternative medicine (CAM) encompasses a wide range of different *non-mainstream* therapies that have been increasingly used for treatment or adjunctive treatment of various ailments with mood disorders and “depressive difficulties” being two of the commonly CAM (self-)medicated conditions. We focus specifically on clinically diagnosed (in line with the standard criteria) depressive disorders, primarily major depressive disorder (MDD), and overview evidence of efficacy/safety of a range of CAM modalities addressing exclusively randomized controlled trials (RCTs) and systematic reviews/meta-analyses of RCTs. The list of addressed CAM interventions is not exhaustive: due to space limitation, addressed are interventions with at least a few conducted RCTs in the specific clinical conditions. We try to provide numerical and meaningful data as much as it is possible and to (a) indicate situations in which the reported data/estimates might have been “too enthusiastic” and (b) warn about heterogeneity of results that, together with other possible limitations (various biases and imprecision), results in uncertainty about the effects.

Keywords Complementary and alternative medicine · Depressive disorders · Major depressive disorder · Randomized controlled trials · Systematic reviews/meta-analyses · Evidence-based medicine

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20.1 Introduction

In this chapter we attempt to provide an overview of evidence about efficacy/safety of complementary and alternative medicine (CAM) interventions in the treatment of depressive disorders (unipolar; predominantly MDD), i.e., *clinical depression* diagnosed in line with standard diagnostic criteria. Evidence pertaining to other situations in which people may experience depressive difficulties [e.g., exercise for depressive difficulties in pregnant women not diagnosed with any depressive disorder [1]] is omitted. This might not be in line with the concept of *complementary and integrative health* that implies the use of CAM as a part of a holistic approach, but settings where depression is the only or the primary disorder are more appropriate for detecting the potential of CAM procedures for its treatment. In a recent Springer's edition [2], we addressed the same topic but in the setting of anxiety disorders. Certain introductory comments need to be repeated. Here, the main points are somewhat rephrased – see previous text for further considerations [3].

Conventionally, CAM depicts “therapies that lie outside the spectrum of traditional, science-based clinical medicine and surgery” [4]. This appears to be a simple definition. Still, it touches the essence of contemporary (*mainstream*) medicine – an art or a science? This is not a purely academic dilemma as it is in the roots of the theoretical and epistemological basis of medicine [for in-depth discussion, see [5]]. The point seems to be particularly relevant regarding psychiatry [e.g., see [6]], and it reflects on the definition of CAM, as well – in general or specifically in psychiatry. We opt for the view [5, 7] that makes a distinction between (*bio*)*medical science(s)* and *medicine* – the latter defined as an art, but scientifically-based art, rational, whose knowledge base derives from science [5, 7]. Medicine has evolved from a prescientific art to a scientific art largely due to the advent of (bio)medical sciences [5]. It has seen treatments that were at one time considered *unscientific* and then became *mainstream* just to be eventually abandoned [8]. The *science-based* nature of such interventions is largely related to understanding of underlying biology of (expected) benefits. Still, even for a number of *mainstream* psychiatric treatments, a lot is unknown about their mechanisms. Does this make them *unscientific*? CAM can hence be depicted as “any non-mainstream practice” aimed at achieving a beneficial health outcome with not always sharp and fixed boundaries vs. *mainstream* [9]. Reasons for defining a treatment as CAM are not only scientific but also political, social, and conceptual [10]. Actually, the focus should be [8] on the contrast between *beliefs* and *evidence*, i.e., between practicing the art of scientific vs. “pre-scientific” medicine (psychiatry) [5, 7]. The paradigm of evidence-based medicine (EBM) requires critical assessment of evidence, where *scientific evidence* means empirical observations in humans and *quality evidence* means empirical observations that leave little uncertainty (consistent, direct, unbiased, precise) about the direction and size of the effect of an intervention – and may be applied regardless of how incomplete is our understanding of the underlying mechanisms. More than 100 different CAM practices are utilized in the general population [11, 12]. While some can be easily classified as those for which there is no reason to expect efficacy in any

indication [or could be promptly defined as charlatanism [8]], potential of many has been recognized, just as the need for their evaluation in the EBM sense [4, 8, 9]. In psychiatry, interventions that would have been considered *heavily alternative* not more than 10–15 years ago are “on their way” to become *evidence-supported* [8]. Many are addressed in this book, and many are embraced in professional guidelines on depressive disorders (e.g., [13–17]).

Mood disorders are a common reason for CAM self-medication in the general population [18]. A survey [19] across 25 countries worldwide showed that around 4.5% of people suffering from mood disorders used CAM treatments within the past 12 months – alone (i.e., *alternative* aspect of CAM) or combined with conventional treatment (*complementary* aspect of CAM). Moreover, overall proportion of CAM users was 11.7% among those seeing a mental health specialist and 14.6% among those with severe disorders and seeing a mental health specialist. We assume that every practicing psychiatrist commonly sees such patients and has built his/her own rational-empirical framework to practice the art for the benefit of each individual patient and, in this context, to choose between encouraging, discouraging, discussing or not commenting on, or offering some of the treatment options that currently fall into the “CAM category.” Here, we attempt to overview evidence that would support general claims, i.e., estimates about treatment effects that are likely to be accurate, i.e., “closer to the truth” about the therapeutic potential of such treatments – just as it is done for the *mainstream* interventions. Considering the plethora of publications, a selection had to be made, so this overview is far from exhaustive. We searched PubMed/Medline, Cochrane databases, and Google Scholar for systematic reviews of RCTs pertaining to treatment of depression and professional guidelines on the topic published between 2000 and January 31, 2020, and selected those reporting on the use of CAM. A treatment was considered as CAM if (i) declared as such in the guidelines or by the study authors or (ii) it fell into the CAM categories (e.g., see 9 or [20] for generally accepted classifications). Where indicated by the systematic reviews, we further searched individual RCTs. We provided numerical data when we deemed it informative to support claims about treatment (non)effects. Others can be found in the cited literature. We attempted to evaluate the level of (un)certainty about the effects suggested for individual treatments applying reasoning elaborated in Table 20.1. Finally, we did not address otherwise “mainstream” interventions, like nonsteroidal anti-inflammatory drugs, statins, modafinil, N-acetyl cysteine, minocycline, pioglitazone, transcutaneous variations of the vagus nerve stimulation, or modalities of deep brain stimulation, each clinically evaluated in depressive disorders to a certain extent – for a pragmatic reason of space limitation and for a conceptual reason: these undertakings can be viewed as a part of the “drug/treatment repurposing” efforts.

Table 20.1 Key elements in reasoning in evaluation of quality of RCTs and meta-analyses of RCTs and of (un)certainty about utility of CAM for treatment of depressive disorders [modified from the chapter on the use of CAM in anxiety disorders [3]]^a

Individual RCTs	
Patient sample	Sampling procedure. Effects observed in single-center samples are at a higher risk of being by chance (sampling variation) than the effects in multicenter samples. Even with the same inclusion-exclusion criteria, single-center samples are less likely to fully represent the population. Size. Small samples (vs. large) are less likely to fully represent the population; observed effects are more likely to be inflated and/or by chance and fragile
Control treatments	Representing “idea of treatment.” Placebo or adequate sham interventions are likely to transfer the “same idea of treatment” or “expectation” as the tested intervention. No-treatment control may inflate the treatment effect (e.g., due to negative expectations). Waiting list control may introduce selection bias (trial may include only patients “susceptible” to CAM effect) combined with inflation of treatment effect (negative expectation in the “waiting list” group). Active treatment. Superiority to otherwise known effective treatments supports efficacy, but size of the effect cannot be estimated. “Lack of difference” vs. otherwise known effective treatments is not a proof of efficacy. For example, the experience with mainstream pharmacological (and approved) treatments in depressive disorders has been that (i) patients on placebo commonly provide high response rates and (ii) in 1/3 to 1/2 of the trials, active treatments cannot be distinguished from placebo (see [21]). Hence (i) demonstration of efficacy through non-inferiority vs. a known active treatment would need to come in a trial including placebo, where superiority of the reference vs. placebo would need to be first demonstrated; (ii) under such circumstances, non-inferiority margins are difficult or impossible to predefine; and (iii) in such a setting, superiority vs. placebo is proof of efficacy; hence non-inferiority is superfluous (see [21]). Superiority to treatments not otherwise confirmed as not harmful does not unambiguously support efficacy. In order to gain regulatory approval, <i>mainstream</i> pharmacological treatments are required to be tested in RCTs including placebo [at least short term, e.g., 6 weeks, with an option for deteriorating patients to be withdrawn from the trial and provided with the standard therapy (see [21])]
Treatment assignment	Randomization and concealment of the randomization sequence are expected to ascertain balance between groups regarding potential confounders/effect modifiers and to prevent selection bias (arising from knowledge or anticipation of the subsequent treatment). Some findings might indicate that this process has failed, e.g., excessive similarity between groups that is not likely to be by chance, a marked imbalance in group sizes (compared to the intended ratio), excessive baseline differences between groups not likely to be by chance, or imbalance in likely confounders/effect modifiers or baseline values of the outcome measures. However, such signs are difficult to assess in small trials (how to estimate “deviation” from chance?), and small but relevant imbalances might be undetected. Hence, one has to rely upon what was reported by the authors. Although this might sound prejudiced, we consider that sponsored trials (e.g., professional societies, institutes, industry) are less likely to be flawed in this respect simply due to the fact that they are more likely to be more scrutinized during the planning and conductance phase

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Trial/ treatment duration	Regulatory requirements for <i>mainstream</i> pharmacological treatments consider 6–8-week trials to be “short-term” trials and include also “long-term” trials (typically up to 6 months – to demonstrate maintenance of effect/prevention of relapse after an acute episode) (see [21]). Treatment (pharmacological or psychological) of depressive disorders, however (in particular of MDD), is a long-term process, and efficacy may become apparent only after longer periods of treatment and/or may vary in time. Exclusively short-term trials do not unambiguously support a claim related to successful management of depression in line with professional recommendations and also do not unambiguously exclude possible efficacy
Outcome measures	<i>Mainstream</i> treatments are expected to provide benefits in terms of reduction of severity of symptoms (adequate symptom scales) and a benefit in terms of proportions of subjects experiencing: (a) clinically relevant response; (b) remission; or (c) relapse [21]
Detection of outcomes (beyond blinding)	Validated scales with known psychometric properties are likely to accurately quantify depression. For detection (ascertainment) of outcomes in trials of <i>mainstream</i> treatments, clinician-implemented tools are recommended (see [21]) – like 17-item Hamilton Depression Rating Scale or Montgomery-Asberg Scale, and investigators are expected to be trained in their implementation. Inexperienced assessors/assessors being trained through evaluation of the study subjects and unequally trained assessors may introduce bias. Also, clinical global impression on improvement (CGI-improvement) needs to be evaluated
Blinding of patients	Considering the nature of the condition (depressive disorder) and the fact that its quantification includes subjective patient reporting, when patients are aware of their assigned treatment, effects could easily be overestimated (e.g., unequal “expectation” vs. no-treatment/waiting list, recognizable sham procedure) but also underestimated (e.g., vs. established <i>mainstream</i> treatment). Reporting of adverse events may also be biased
Blinding of investigators/ assessors	Investigators/carers aware of the assigned patient treatments may introduce performance bias. Considering the judgment component in outcome assessment, assessors aware of the assigned patient treatment may introduce detection bias
Treatments that cannot be adequately blinded	While for biologically based therapies (e.g., herbal preparations, nutraceuticals) provision of adequate placebos is feasible allowing for blinding of both patients and carers/outcome assessors, adequate sham procedures (and, consequently, blinding) might be more difficult to achieve for various other CAMs. This, however, does not mean that this is impossible, i.e., that it is not possible to achieve a fair level of reduction of risk of various biases potentially arising from the patient/carer/outcome assessor’s awareness about the assigned treatments. Some sham procedures might be reasonable enough as to allow for the blinding of patients (but not carers/assessors). Separating the roles of carers/treatment providers/outcome assessors would then allow that carers/assessors are also blinded. Sometimes, it might be uncertain whether the sham procedure conveys only the “idea of treatment” or whether it actually might be effective, which would generate “control treatment bias” and underestimate or completely blur the effect of treatment. Factorial or incomplete factorial designs could be useful in such situations, including, for example, <i>mainstream</i> pharmacological treatments and respective placebos, resulting in multiarm trials

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Attrition and related issues	Efficacy analysis based exclusively on patients who complete the trial “as planned” (i.e., <i>per</i> protocol, PP) tends to inflate the treatment effect. Hence, tests of inequality should be based on all randomized (intent-to-treat, ITT) patients or, what appears more reasonable in the case of RCTs in depressive disorders, all randomized patients who are evaluated at baseline and have received at least one “dose” of the assigned treatment. PP would be applicable for non-inferiority trials, but in depressive disorders, as mentioned, non-inferiority is a questionable concept. Eventually, a test of non-inferiority should follow after a test of inequality (expected superiority) of a reference (presumed) active treatment vs. placebo/sham (and would also be based on the ITT data). Considering the nature of the disease and expected several weeks needed to observe a treatment effect, the outcome measures are based on “difference in symptoms after a period of treatment vs. baseline,” thus requiring some form of data imputation for patients who drop out of the trial (for any reason) to preserve the ITT principle. There is no ideal imputation method. Fixed data imputation (e.g., LOCF) however is commonly used in this type of trials. Imbalance in the rate of attrition or in reasons for attrition may introduce bias. Even if the reasons are comparable for the evaluated and control treatment, when attrition is high (i.e., a considerable amount of data needs to be imputed) – the estimates of treatment – control differences are of questionable accuracy
Assessment of safety	Ascertainment of adverse events. Adequate methods for ascertainment of adverse events in a trial are essential in order to make any claims about their (non)occurrence. All patients receiving at least “one dose” of a treatment should be considered. Reporting. Reports not explicitly stating a lack of a particular adverse event are uninformative
Data analysis	Baseline values of a certain measure have a great impact on the value of this measure taken at a certain later time point. Regardless of an apparent balance between groups in respect to baseline severity of symptoms, outcome measures based on “change from baseline” (actual score, change in score vs. baseline, or proportion of responders or remitters) need to be adjusted for the baseline value. Randomization is expected to achieve a balance in confounders/moderators. However, even when there are no obvious imbalances between groups in characteristics that may affect the outcome, such characteristics should be considered in data analysis, particularly in smaller trials
Treatment effect estimates across trials (pooled estimates, meta-analysis)	
High risk of bias trials	To get an accurate estimate of a true effect, estimation should be based on unbiased observations. High risk of bias trials are likely largely inaccurate; hence pooling data from such trials makes little sense – it may only increase “precision in inaccuracy” and thus be misleading. Even if a pooled effect is similar to a pooled effect across low risk of bias trials, it still makes no sense since we do not know what the estimates would be in such trials (patient samples) had they been better protected from various biases
Clinical homogeneity	Effects pooled across clinically inhomogeneous trials (e.g., different patient characteristics; different doses or e.g., acupuncture points or type of exercise; different duration) make little sense even if results are “statistically homogeneous” (particularly when the number of trials is limited) as they provide different information – they pertain to different patient (sub)populations and/or different modalities of one same therapeutic principle

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	Showing similar effects in different clinical settings (e.g., different patient characteristics, trial duration) is a different thing and is more informative about robustness of the effect than showing “lack of statistical heterogeneity” across a limited set of trials – with a limited number of trials, formal tests or measures of heterogeneity/inconsistency can be underpowered/imprecise, hence not reliable
Statistical heterogeneity and inconsistency	Whether or not to generate pooled estimates - and how to interpret them - across trials with heterogeneous treatment effects is a delicate issue. By using the <i>fixed-effect</i> approach, pooled estimates are likely to be inaccurate, that is, the confidence intervals will be narrower than they should (i.e., standard error of the estimate would be unrealistically low, and hence the estimate might be falsely flagged as “significant”). Moreover, the idea is conceptually wrong: pooled effect tends to present something that might not exist – a single true effect. The <i>random-effect</i> method(s) will account for the between- study variance but would not “resolve it.” The produced estimate is difficult to interpret, and it is commonly interpreted for what it is not – i.e., in the sense of prediction (see [22]). In fact, it is the estimate of the mean of the (presumed) different effects in the population: if the random-effect CIs differ from zero, this does not necessarily mean that the population of effects does not also contain “effects not different from zero” or some other, larger effects; if not different from zero, it does not mean that there are no “different from zero” effects. The best indicator of heterogeneity of effects and measure that needs to be reported with each random-effect meta-analysis is prediction intervals (see [22]) as they incorporate a measure of the extent of heterogeneity and illustrate the range of the distribution of the population of effects. In fact, if meta-regression is not possible (and it requires a substantial number of trials) that would identify effect moderators, i.e., subsets of trials each estimating one of the effects from the “population of effects” (e.g., in younger and in older; after 6 or 24 weeks of treatment, etc.) and each subset with a reasonably low heterogeneity, the random-effect estimate may not make much sense. As already mentioned, when the number of trials is low, formal tests of homogeneity/inconsistency commonly fail to flag relevant heterogeneity/inconsistency (since underpowered). Another problem with heterogeneity refers to random-effect estimates across large and small trials. Sets of smaller trials inherently show higher between-study variance (τ^2) than the comparable sets of larger trials [23]. At the same time, estimate of τ^2 in a set of small trials with imprecise estimates (high within-study variance) may commonly be 0, although there is a substantial dispersion of effects [23]. Since in standard random-effect (e.g., DL) procedures one same estimate of τ^2 is used in weighting of all the trials, this could skew the estimates and the prediction intervals. The proportion of true heterogeneity between studies within the total heterogeneity (true/true+random) – I^2 – depends on trial size (within-study variance): in sets of large studies (low within-study variance; random component), actually small differences (low τ^2) between-study effects may result in high I^2 (since the contribution of the random part is low), while in sets of small trials (high within-study variance), I^2 could be low, despite a considerable dispersion of effects; consequently, the actual dispersion of effects “behind” one value of I^2 can be low to moderate or high [24]. Main points, (i) fixed-effect meta-analysis is rarely appropriate (e.g., studies replicated in design and clinical features with similar, consistent effect estimates); (ii) random-effect meta-analysis requires careful interpretation and should be always reported with prediction

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	intervals. Without them and without meta-regression, it makes little sense; (iii) choice of the method should not depend on the estimated heterogeneity/inconsistency; (iv) assessment of heterogeneity across a limited number of trials/small trials is problematic
Additional problems with small number of trials	When the number of trials is small, e.g., 2–4, it is questionable whether meta-analytical pooled estimates should be generated or is it more informative to simply provide individual study results [22]. The problem lies with the fact that in such cases the standard moment-based estimate of the between-study variance (τ^2) cannot be reliably estimated – as pointed out already by the authors some 25 year ago [25]. A solution might be the use of Bayesian hierarchical models for meta-analysis, or, in the frequentist framework – different other variance estimators. One example of an estimator that should be preferred is the so-called Hartung-Knapp-Siddik-Jonkman estimator that was shown to well outperform the DL estimator with a small number of trials/trials of unequal sizes (see [26, 27]). The pooled effect then has a sampling t-distribution with $k-1$ degrees of freedom. A DL estimate generated in standard meta-analytical “user-friendly” softwares can be corrected (HKSJ correction)
Problems with trials with low number/no events	Commonly, trials in depressed patients report no adverse events, overall or at least in one treatment arm; or the number of events is very low. Pooling of “sparse data” (few events, one-arm or overall zero-event trials) is a delicate issue – standard methods included in typically used meta-analysis softwares do not perform well in such situations – point estimates, but more so coverage probability of the confidence intervals, are biased. Alternative methods exist (see e.g., [28, 29])
Overall assessment of efficacy and of utility in treatment of depression	
Clinical relevance	Treatment of depressive disorders implies (a) reduction of depression, i.e., achieving a relevant clinical improvement/remission and, in responders, (b) maintenance of remission; based on the use of preferred instruments. In practical clinical terms, evidence of efficacy based on increased probability of remission/clinically relevant response or reduced risk of relapse is more meaningful than the one based on a difference in symptom severity scores. Duration of recommended <i>mainstream</i> treatments (across different depressive disorders) is at least 6 months (in cases where single episode is in place) and up to 2 years or longer – a conclusion about <i>full utility</i> of any CAM treatment for depressive disorders can only be based on the ability to achieve these goals. Other conclusions may pertain to parts of the process: e.g., efficacy in the initial short-term (e.g., 6–8 week) treatment
Overall body of data	One large, multicenter trial with low risk of bias with adequate outcome measures and duration may result in a high level of certainty about the treatment effect; however, strength of recommendations about <i>mainstream</i> treatments largely relies upon replication of the results – this is related to the nature of the disorder – and independent repeated trials are generally needed in order to exclude the chance (for pharmacological <i>mainstream</i> treatments, 2 independent trials are a regulatory requirement, see [21]). All other knowledge about the intervention, e.g., smaller dose-response trials and basic investigations elucidating possible mechanisms and similar, cannot replace the need for (replicated) empirical evidence about the relevant clinical outcomes

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Risk of bias	Biased trials leave uncertainty (greater with more severe bias) about the actual treatment effect (or its nonexistence). Severely biased trials, e.g., trials using a waiting list control (selection, performance, detection) even if large and indicating a large effect, leave a high level of uncertainty about whether a true effect exists at all
Inconsistency	In a single trial, inconsistency between treatment effects based on change in symptoms scores and treatment effects based on probability of remission/ response questions the existence of a true effect. Similarly, inconsistency between the primary and secondary outcomes (in regulatory <i>mainstream</i> pharmacological trials, e.g., proportion of responders based on HAM-D change and CGI-Improvement) questions the existence of an effect. Inconsistency of effects across several trials generally generates variable levels of uncertainty about the existence of an effect and/or its size. However, when several large, low risk of bias trials show effects that are all in the same direction, even if the indices of heterogeneity/inconsistency are high, this does not compromise the conclusion of efficacy – the heterogeneity is quantitative (there is an effect but estimates may vary in size) and not qualitative (some yield an effect, some do not or even suggest harm)
Imprecision	In general, imprecision <i>per se</i> raises (variable degree of) uncertainty about the treatment effect, but interpretation of imprecise estimates depends also on their location as well as the level of bias in the trials: imprecise estimates from low risk of bias trials that consistently show an effect result in a reasonably high certainty that the true effect indeed exists, but in a high uncertainty about its size; if consistently showing lack of an effect, then we can be reasonably certain that there is no (relevant) effect (although, a smaller effect cannot be excluded). Imprecise estimates from high risk of bias trials result in a very high uncertainty about the existence/nonexistence of an effect

^aAll criteria depicted in this table actually derive from the standardly used instruments for assessment of risk of bias in individual trials (e.g., Cochrane collaboration tool, RoB 2.0; <https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool>) or quality of systematic reviews (e.g., updated AMSTAR tool; <https://amstar.ca/>) and overall quality of evidence (e.g., GRADE; <https://cebgrade.mcmaster.ca/>). We did not systematically employ any of them, as this would render this chapter extremely extensive – however, it is clear that the content of the table reflects all of their main points

20.2 Biologically Based Therapies

20.2.1 Herbal Preparations

Some of the herbal preparations have a long-standing medicinal use in the Western World related to *depression*. Within the European Union, some have a specific regulatory status as *herbal drugs* [30] based on *traditional use* (weak requirements for evidence of efficacy, proven safety, pharmaceutical quality) for products intended for self-medication or based on the *well-established use* (efficacy needs to be proven).

20.2.1.1 St. John's Wort (SJW), *Hypericum perforatum* L., herba

Two European community monographs pertain to the plant – one for traditional use in adults for “relief of temporary mental exhaustion,” “aid in healing of minor skin wounds,” and “symptomatic relief of mild gastrointestinal discomfort” [31] (dry/liquid extracts, fresh plant juices, comminuted herbal substance, tinctures), the other one for well-established use [32] of specific (dried) alcoholic extracts for treatment (short-term) of mild-to-moderate depressive disorders. In brief [33, 34], (1). in Europe, *herbal drugs* need to be standardized to a total content of hypericin 0.1–0.3%, flavonoids minimum 6%, and hyperforin maximum 6% (PhEur 01/2017:1874); (2). other products (“supplements”) may largely vary; (3). hypericin and hyperforin inhibit monoaminergic transporters, and flavonoids inhibit monoaminooxidase; (4). *Hypericum* dry extract is a P-glycoprotein, CPY3A4, CYP2C9, and CYP2C19 inducer – concomitant use of a number of drugs is contraindicated, and relevant interactions may be expected with a number of others. Various guidelines [13–16, 35–37] address SJW (preferring standardized extracts) and warn about (quote, 37) “uncertainty about appropriate doses, persistence of effect, variation in the nature of preparations and potential serious interactions with other drugs.”

A variety of modalities were used in clinical settings, and a uniform conclusion might not be feasible. A recent thorough overview of systematic reviews/meta-analyses (SR/MA) of CAM in “clinical depression” [38] extracted 26 such studies. In respect to SJW, one recent SR/MA is of high quality [39]. We will address it briefly to illustrate the above points using the example of the outcome “proportion of responders (i.e., $\geq 50\%$ reduction in symptom severity)” vs. placebo. The study identified 18 such RCTs of SJW monotherapy with 2922 patients (mild-moderate MDD, 4–12-week duration) [39]. The reported pooled $RR=1.53$ (95%CI 1.19–1.97) favored SJW, but due to considerable heterogeneity, the evidence was classified as *moderate-quality evidence* (GRADE) [39]. Baseline disease severity, geographical location, study quality, or type of product could not explain the heterogeneity [39]. Seven of the RCTs were conducted with the extract coded LI 160 [39] [additional information in [34, 40]]. These 7 double-blind multicenter RCTs (with a total of 1171 patients) are outlined in Table 20.2 –they do not “flag” superiority of the extract over placebo in a 4–12-week treatment, inconsistency is high, and heterogeneity is considerable (prediction intervals extend from twice lower to three times higher response rates) demonstrating uncertainty about the effect/its size. This is a specific standardized product [34], and one can only speculate on the source of variability of the results. Uncertainty is high also with all 18 RCTs – we would add (based on the provided data) that the *range of effects* (RR) extends from 0.79 to 2.77 and 95% prediction intervals from 0.72 to 3.01. This uncertainty with a considerable proportion of trials qualified as “poor quality” [39] suggests that the overall quality of evidence should rather be judged as “low” (instead of moderate). Incidence of any adverse event did not differ vs. placebo [39]. Only one comparative double-blind trial (80 on SJW and 80 on sertraline) was extended to 24 weeks [41] suggesting consistently comparable symptom severity, i.e., “persistence of effect,” but lacked assay sensitivity; and one [42] large multicenter double-blind trial over

Table 20.2 Main characteristics of placebo-controlled parallel-group double-blind RCTs of St. John’s wort standardized extract LI 160 in adults with major depressive disorder (MDD) as identified from a recent systematic review [39], European Medicines Agency (EMA) updated (draft) assessment on *Hypericum perforatum* L., herba [34], and a previous systematic review [40]. Depicted are study-level relative risks (RR) for “treatment response” (i.e., ≥50% reduction in symptom scores) and a random-effect pooled estimate generated for the purpose of this overview^a

Study	Main study characteristics	LI 160	Placebo	RR (95%CI) ^b	Comment
Ref. 18 in [39]	Multicenter (Sweden), 4-week, mild-moderate MDD	3×300 mg/ day n=59	n=58	1.07 (0.67–1.70)	“Fair quality” [39], but 21/59 and 18/58 patients dropped out [34]
Ref. 20 in [39]	Two centers (USA), 12-week, moderately severe MDD	3×300 mg/ day n=35	n=35	1.81 (0.91–3.61)	“Poor quality” [39] (unclear risk of several potential biases)
Ref. 23 in [39]	Multicenter (USA), 8-week, moderately severe MDD	3×300 mg/ day n=113	n=116	0.88 (0.64–1.21)	“Fair quality” [39]
Ref. 48 in [39]	Multicenter (Germany), 6-week, MDD severity not reported	3×300 mg/ day n=53	n=55	3.03 (1.77–5.17)	“Poor quality” [39] (unclear risk of several potential biases)
Ref. 33 in [39]	Multicenter (Germany), 8-week, 50% mild, 50% moderate MDD	2×300 mg/ day n=100	n=100	1.20 (0.90–1.59)	“Good quality” [39]
Ref. 34 in [39] ^b	Multicenter (UK), 12-week, mild-moderate MDD	3×300 mg/ day n=123	n=124	0.97 (0.74–1.28)	“Poor quality” [39] (unclear risk of several potential biases)
Ref. 41 in [39]	Multicenter (USA), 8-week, mild-moderate MDD	3×300–4×300 mg/ day, n=98	n=102	1.42 (0.84–2.40)	“Good quality” [39]
Total (pooled)		581	590	1.28 (0.88–1.87)	t=1.59, df=6, P=0.162, τ ² =0.087, I ² =68%
Range of effects				0.71–2.30	
95% PI				0.54–3.00	

^aWe used relative risks as reported in [39] to generate a random-effect estimate (DL) with Hartung-Knapp-Sidik-Jonkman correction, just as in [39]
^bIn [39] this study was referenced under 34 – as a published abstract – and summarized as RR=1.47 (1.16–1.85). In the EMA assessment [34], the study is summarized as “no difference vs. placebo.” In a previous systematic review [40], data from this study regarding the response rate were summarized as 55/123 on LI 160 and 57/124 on placebo – RR=0.97 (0.74–1.28) as shown here

around 20 months suggested superiority to placebo in terms of relapse prevention (RR=0.70, 0.49–1.02) with comparable safety.

The overall body of evidence supports a conclusion that the *active principle* extractable from the plant might be useful in treatment of depressive disorders. So

far, this pertains to initial short-term treatment – but with quite some uncertainty, even for products with stringent quality controls.

20.2.1.2 Saffron, *Crocus sativus* L.

Extracts of the petals and stigma (contain around 150 different compounds) have a long-standing traditional use in a variety of health conditions. The antidepressant potential is ascribed to carotenoids *crocin* and *crocetin* (crocin) and *safranal*. They block the monoamine uptake and seem to be monoaminooxidase inhibitor(s) and (seemingly) 5-HT_{2C} receptor antagonist(s). In animal paradigms, crocin or saffron extracts showed effects similar to SSRIs with increased expression of brain-derived neurotrophic factor (BDNF) and cAMP response element in the hippocampus (see [43–49]). Limited toxicological evaluations have not indicated any specific major toxicity, except for a teratogenic potential of huge doses. Limited data in humans show bioavailability of oral crocin.

A number (in addition to [38], [43–49]) of SR/MAs addressing saffron was found (e.g., [50–57]) that all consistently concluded “efficacy” that is “comparable to antidepressants.” Table 20.3 summarizes double-blind **placebo-controlled** RCTs of “saffron” monotherapy: (a) all were done in one or a few hospitals in Iran; (b) different conditions were treated; (c) a variety of preparations were used; (d) all trials were small (20–30 subjects per arm; overall ~380 patients 1:1 saffron-placebo) with (i) common dropouts with “completers analysis,” (ii) occasionally erroneously reported “statistical significance,” and (iii) common use of patient-reported outcomes; (e) small MDD trials do suggest antidepressant effect; (f) mixed anxiety-depression disorder trials indicate possible effect but uncertainty is high; (g) and a possible effect is suggested in women with postpartum depression. No data pooling is needed to see that this is suggestive data, but uncertainty is very high and additionally complicated with the uncertainty about the used preparations.

Table 20.4 summarizes double-blind RCTs of **saffron vs. antidepressants**. The same comments hold as above. Additional limitation – no placebo arm, so no assay sensitivity – all studies reported “lack of statistical significance vs. active controls” (which is of questionable value in this setting – see Table 20.1). However, in all trials, depression end-of-treatment scores were a bit higher with saffron vs. controls. With so different settings, data pooling is not really meaningful – but for a “quick orientation,” we provide a pooled estimate across 7 RCTs using Hedges’ *g* by random-effect method with HKSJ correction: saffron vs. active control difference regarding the end-study HAM-D score is 0.27 with 95%CI 0.09 to 0.44, *t*=3.716, *df*=6 *P*=0.0098, τ^2 =0.000, *I*²=0.00% (95% CI 0.00–58.5), suggesting a consistent and homogeneous “mild-to-moderate” *inferiority* of saffron vs. active controls. So, these studies *should not be perceived* as evidence of “efficacy of saffron preparations.”

Two small single-center 4-week studies in Iran [72, 73] (*n*=20 per arm) suggested some [72] or none [73] additional benefit of crocin extract added to SSRI. The only RCT conducted *outside Iran* was an 8-week, double-blind RCT in Australia (160

Table 20.3 Summary of double-blind placebo-controlled RCTs of “saffron” monotherapy in depressive disorders in adults

Study	Main study characteristics	Saffron (test)	Placebo	Outcome	Comment
[58] Iran 2005	Single-center (Iran); DSM-IV MDD, HAM-D ≥ 18 , 6 weeks	Alcoholic stigma extract, no details 2×15 mg/day; n=9	n=9	HAM-D reduction end vs. baseline Saffron: -12.2 ± 4.7 Placebo: -5.1 ± 4.7	Except randomization, all other methodological aspects unclear
[59] Iran 2006	Single-center (Iran); DSM-IV MDD, HAM-D ≥ 18 , 6 weeks	Alcoholic petal extract, no details 2×15 mg/day; n=20	n=20	HAM-D reduction end vs. baseline Saffron: -14.0 ± 5.5 Placebo: -5.1 ± 4.6	Appears of good quality LOCF for 4 dropouts
[60] Iran 2016	Single-center (Iran); DSM-IV mild-moderate mixed anxiety-depression disorder, 12 weeks	Dried stigma, no details 2×50 mg/day; n=30	n=30	BDI reduction end vs. baseline Saffron: -6.7 ± 2.7 Placebo: -4.4 ± 4.6 Reported: t -1.516 , df 52, $P < 0.05$	6 dropouts, analysis for completers; difference in reduction reported $P < 0.05$, but it is not – $P = 0.136$
[61] Iran 2018	Two hospitals in Teheran (Iran); DSM-IV mild-moderate MDD (HAM-D ≤ 22) postmenopausal women with hot flushes, 6 weeks	Alcoholic stigma extract: 1.65–1.75 mg crocin/15 mg 2×15 mg/day; n=30	n=30	HAM-D reduction end vs. baseline Saffron: -7.1 ± 4.4 Placebo: -4.4 ± 2.6 Proportion $\geq 50\%$ score reduction Saffron: 13/30; placebo: 5/30	4 dropouts, analysis for completers; blinded outcome assessment uncertain

(continued)

Table 20.3 (continued)

Study	Main study characteristics	Saffron (test)	Placebo	Outcome	Comment
[62] Iran 2017	Three hospitals in Teheran (Iran); breastfeeding mothers with “psychiatrist-assessed mild-moderate postpartum depression,” 8 weeks	Dried, grounded saffron, ~5 mg crocin/15 mg 2×15 mg/day; n=30	n=30	BDI at end (~20 at baseline) Saffron: 8.4±20.3 Placebo: 15.3±29.6 Proportion ≥50% score reduction Saffron 20/30; placebo: 2/30	The end-study score reported “significantly different” by t-test, but it is not – df 58, t=1.05, P=0.148
[63] Iran 2018	Single-center (Iran); DSM-IV mild-moderate anxiety-depression + T2DM, 8 weeks	Hydroalcoholic extract, no detail 2×15 mg/day n=27	n=27	HAM-D at end (~30 at baseline) Saffron: 24.6±9.2 Placebo: 27.8±13.6	4 dropouts, 25 and 25 completers analyzed; “no effect on depression”
[64] Iran 2019	Single-center (Iran); DSM-V mild-moderate MDD + overweight women, 12 weeks	<i>Crocus sativus</i> capsules, no detail 2×15 mg/day, n=36	n=37	BDI at end (~22 at baseline) Saffron: 13.8±8.9 Placebo: 17.9 ±8.2 (unadjusted for baseline change –8.4±5.9 vs. –3.9±5.5)	9 and 12 dropouts (~30%), 27 and 25 completers analyzed. Reported P<0.05, but it is not – t=–1.90, df=50, P=0.063

BDI Beck’s Depression Inventory, *HAM-D* Hamilton Depression Rating Scale, *LOCF* last observation carried forward, *T2DM* type 2 diabetes mellitus

randomized, 139 per protocol and analyzed) – MDD patients on antidepressants but still depressed received placebo or 2×1 tablet/day stigma extract standardized to >3.5% crocin and safranal [74]. No difference vs. placebo was observed based on MADRS self-reported score; but “significant difference” was reported regarding clinician-rated MADRS scores – still, the reported end-study scores (mean±SE 13.03±1.0 n=72 vs. 15.43±1.05, n=67) only mildly differed (difference –2.40, 95%CI –5.26 to 0.47, t=–1.656, df=137, P=0.100). In all trials, tolerability was similar to placebo and somewhat better than with antidepressants, except for a few cases of hypersensitivity to saffron.

The entire body of data about saffron extracts should be viewed as a “proof of the concept” however burdened with serious uncertainty.

Table 20.4 Summary of double-blind active controlled RCTs of “saffron” monotherapy in depressive disorders in adults

Study	Main study characteristics	Saffron (test)	Control	Outcome	Comment
[65] Iran 2004	Single-center; DSM-IV MDD, HAM-D ≥ 18 , 6 weeks	Alcoholic stigma extract, no details 3×30 mg/day; n=15	Imipramine 3×100 mg/ day n=15	HAM-D at end (~19 at baseline) Saffron: 8.8±1.7 Imipramine: 8.0±1.7	Small, no placebo arm – no assay sensitivity
[66] Iran 2005	Single-center; DSM-IV MDD, HAM-D 18–25, 6 weeks	Alcoholic stigma extract, 0.3– 0.35 mg safranalin/15 mg 2×15 mg/day; n=20	Fluoxetine 2×10 mg/ day n=20	HAM-D at end (~23 at baseline) Saffron: 10.2±2.7 Fluoxetine: 8.6±2.7	Small, no placebo arm – no assay sensitivity. One dropout each group
[67] Iran 2007	Single-center; DSM-IV MDD, HAM-D ≥ 18 , 8 weeks	Alcoholic petal extract, 0.3– 0.35 mg safranalin/15 mg 2×15 mg/day; n=20	Fluoxetine 2×10 mg/ day n=20	HAM-D at end (~22.5 at baseline) Saffron: 10.2±10.7 Fluoxetine: 9.0±10.7 Proportion $\geq 50\%$ score reduction Saffron 15/20, fluoxetine 17/20	Small, no placebo arm – no assay sensitivity. One dropout each group
[68] Iran 2015	Single-center; DSM-IV MDD patient with previous PCI, 6 weeks	Alcoholic stigma extract, 0.13– 0.15 mg safranalin, 1.65–1.75 crocin/15 mg 2×15 mg/day, n=22	Fluoxetine 1×20 to 2×20 mg/ day n=22	HAM-D at end (~17.1 at baseline) Saffron: 5.5±4.4 Fluoxetine: 4.5±4.4 Proportion $\geq 50\%$ score reduction Saffron 17/20, fluoxetine 16/20	Small, no placebo arm – no assay sensitivity. Two dropouts each group, completers analyzed

(continued)

Table 20.4 (continued)

Study	Main study characteristics	Saffron (test)	Control	Outcome	Comment
[69] Iran 2017	Two hospitals; DSM-V mild-moderate MDD with anxious distress, 6 weeks	Saffron extract, crocin 1.65–1.75 mg/15 mg 2×15 mg/day, n=33	Citalopram 2×20 mg/day N=33	HAM-D at end (~17.3 at baseline) Saffron: 7.1±5.8 Citalopram: 6.2±3.6 Proportion ≥50% score reduction Saffron 22/30, citalopram 27/30	Small, no placebo arm – no assay sensitivity. Three dropouts each group, completers analyzed
[70] Iran 2016	3 hospitals; DSM-IV mild postpartum depression, HAM-D 10–18, 6 weeks	Saffron extract, crocin 1.65–1.75 mg/15 mg 2×15 mg/day, n=34	Fluoxetine 2×20 mg/day n=34	HAM-D at end (~16.7 at baseline) Saffron: 9.3±2.0 Fluoxetine: 9.0±1.7 Proportion ≥50% score reduction Saffron 13/32, fluoxetine 16/32	Small, no placebo arm – no assay sensitivity. Two dropouts each group, completers analyzed
[71] Iran 2019	Single-center; DSM-V MDD age 60–70, 8 weeks	Saffron extract, no details 1×60 mg/day, n=25	Sertraline 1×100 mg/day n=25	HAM-D at end (~21.2 at baseline) Saffron: 9.9±4.5 Citalopram: 8.8±4.5 Proportion ≥50% score reduction Saffron 17/25, fluoxetine 14/25	Small, no placebo arm – no assay sensitivity. LOCF for dropouts

HAM-D Hamilton Depression Rating Scale, *LOCF* last observation carried forward, *PCI* percutaneous coronary intervention

20.2.1.3 Curcumin

European community monographs [*Curcuma longa* L., rhizome (*Curcuma domestica* L.) and *Curcuma Xanthorrhiza* Roxb., rhizome (Javanese turmeric)] [75, 76]] pertain to *traditional use* of various extracts or comminuted substance for mild digestive disturbances. However, curcumin modulates monoaminergic neurotransmission, activates hypothalamic-pituitary-adrenal (HPA) axis, suppress inflammation, stimulates BDNF production, and shows antidepressant effect in animal paradigms [48, 77].

Two recent SE/MAs addressed RCTs of curcumin in clinical depression [78, 79] [and other “depressive difficulties” [79]] indicating rather large effects of curcumin. Clinical heterogeneity of these trials (Table 20.5) questions the meaning of pooled estimates. Also, it appears that the reported pooled effects might have been too enthusiastic (Table 20.5): (i) uncertainty with the 7 MDD trials is rather high due to small single-center trials, attrition, and risk of other biases; (ii) heterogeneity is rather high – prediction intervals extend to up to Hedges’ g 0.392 (i.e., “against” curcumin vs. placebo or no treatment); (iii) with exclusion of the open-label vs. “no treatment” control trial with huge attrition and the largest effect, heterogeneity is lower, but the 95%CI around the estimate is -0.634 to 0.018 (Table 20.5); (iv) with exclusion of both open-label trials vs. “no treatment” control, there is no heterogeneity, and the effect is minor (Hedges’ $g < 0.25$ is generally considered as an “irrelevant effect”) (Table 20.5).

The overall body of data suggests that curcumin could be a useful (presumably adjunctive) treatment for depression – but clinical data are at the exploratory phase.

20.2.1.4 Lavender (*Lavandula angustifolia*)

Lavender was extensively elaborated in the previous text on CAM for anxiety [3]. In a multicenter high-quality 10-week double-blind trial, an industrial product Silexan® 1×80 mg/day ($n=159$, by intent-to-treat) was superior to placebo ($n=156$) in adults with mixed depression-anxiety disorder (ICD-10) in terms of MADRS reduction (difference -3.53 , 95%CI -5.44 to -1.61), with more “responders” (40.2% vs. 32.1%), and a somewhat greater clinical global impression-improvement score [88]. Another independent similar trial would confirm these observations for a “moderate level” of certainty about the effect of this product in initial short-term treatment of this disorder.

Three small single-center 4–8-week trials in Iran ($n=15$ –40 per arm) indicated that adding lavender tincture [89] or tea [90] to imipramine [89] or citalopram [90], but not to venlafaxine [91], might contribute to symptom severity reduction in MDD patients by a small amount. This “adjunctive” concept yet needs to be evaluated.

Table 20.5 Summary of RCTs of curcumin (commercial oral formulations) in MDD. We provide also pooled estimate across the 7 trials^a

Study	Main study characteristics	Test	Control	Comment
[80] Israel 2013	Single-center; DSM-IV MDD, HAM-D ≥ 21 , 5 weeks, DB	SSRI/SNRI + 1×500 mg curcumin extract, n=20	SGA + placebo, n=20	Small but quality trial. Provides HAM-D at start and at end for 20 and 19 patients; indicates a trend of an effect
[81] Australia 2014	Single-center; DSM-IV MDD, 8 weeks, DB	2×500 mg/day curcumin extract; n=28	Placebo, n=28	Small but generally quality trial. Provides IDS at start and end. Only completers analyzed [27, 25] ^b
[82] India 2014	Single-center; DSM-IV MDD, 6 weeks, observer blind	Fluoxetine + 2×500 mg/day curcumin n=20	Fluoxetine n=20	Small. Provides HAM-D at start and at end. Overall 17 and 18 completers analyzed. Suggests a huge effect
[83] 2015 Iran	Single-center; DSM-IV MDD, 8 weeks, open label	Antidepressants + 2×500 mg/day curcumin, n=75	Antidepressants, n=65	Huge dropout [14 and 15], only completers analyzed. Provides BDI-II at start and at end. Suggests huge effect
[84] China 2015	Single-center; DSM-IV MDD, HAM-D 10–18, 6 weeks, DB	Escitalopram + 2×500 mg/day curcumin, n=54	Escitalopram + placebo, n=54	Generally good quality, but 50 and 50 completers analyzed. Provides HAM-D at start and change to week 6
[85] Australia 2017	Single-center; DSM-IV MDD, 12 weeks, DB	2×250 mg curcumin n=28 2×500 mg curcumin n=33	Placebo n=36	Small but generally good-quality trial. Provides IDS at start and end; completers only [56 and 31] analyzed ^c

(continued)

Table 20.5 (continued)

Study	Main study characteristics	Test	Control	Comment
[86] Thailand 2018	Single-center; DSM-IV MDD, MADRS>20, 12 weeks, DB	2×250 to 2×750 mg/day curcumin, n=33	Placebo n=32	Small but generally good-quality trial. Provided MADRS at start and end. Only completers [30 and 31] analyzed
^d Pooled random-effect Hedges' <i>g</i> curcumin-control end-study score: −0.388 (95%CI −0.734 to −0.042), df=6, t=−2.744, P=0.034, τ ² =0.072, I ² =53% (0.0–80.0)				
95% Prediction intervals for Hedges' <i>g</i> = −1.168 to 0.392; range of effects= −1.024 to 0.048				
Without the open-label trial [82] vs. “no treatment” with huge dropout: −0.308 (−0.634 to 0.018), df=5, t=−2.435, P=0.060, τ ² =0.039, I ² =38% (0.0–75.0)				
95% Prediction intervals for Hedges' <i>g</i> = −0.959 to 0.343; range of effects= −0.702 to 0.086				
Without both open-label trials [82, 83] vs. “no treatment”: −0.199 (95%CI −0.447 to 0.049), df=4, t=−2.230, P=0.089, τ ² =0.000, I ² =0.0% (0.0–66.0)				

HAM-D Hamilton Depression Rating Scale, IDS Inventory of Depressive Symptomatology, MADRS Montgomery-Asberg Depression Rating Scale

^aNo study reported the baseline-adjusted change in score, so it was unclear how “change vs. baseline” was determined in the published meta-analyses. As “pre-post” approximations are not recommended [87], we used end-study data to calculate Hedges' *g*. We used baseline data for the same purpose (interestingly, in all trials, baseline scores were high in control vs. curcumin groups by a small amount). We then corrected the end-study estimates for this small difference. We used HKSJ correction

^bIt seems that all dropouts occurred after week 4, so we used week 4 data to avoid attrition bias (possible with this small sample)

^cScores and differences vs. placebo were identical for lower and higher curcumin dose – the two groups are pooled (higher precision, avoids “unit of analysis” bias that was possible in the published meta-analyses since it was not explicitly reported how this multiarm trial was handled)

^dRandom effects (DL) with HKSJ correction

20.2.1.5 *Rhodiola rosea* L. (Roseroot)

European community monograph [*Rhodiola rosea* L., rhizome et radix [92]] supports traditional use of dried alcoholic extracts for “temporary relief of stress, fatigue, and sensation of weakness.” Of more than 140 various constituents, *salidroside*, *tyrosol*, *triandrin*, and *rosavin* are thought to be relevant for the antidepressant effects in animal paradigms and complex molecular mechanisms involving expression of BDNF, CREB, serotonin receptors, monoamine and NPY production, MAO inhibition, and many others (overviewed in [93]). In three small 6–12-week single-center but otherwise high-quality RCTs in mild-moderate MDD (Table 20.6), *Rhodiola* extract monotherapy was superior to placebo [94], and combined with sertraline, it was either not superior [95] or superior [96] to placebo. *Rhodiola* yet needs to be clinically evaluated.

Table 20.6 Summary of RCTs of *Rhodiola rosea* (standardized extracts, commercial oral formulations) in MDD

Study	Main study characteristics	Test	Control	Comment
[94] Armenia 2007	Single-center; DSM-IV MDD, HAM-D ≥ 21 , 6 weeks, DB	SHR-5 extract 1×340 mg/d n=31 2×340 mg/d n=29	Placebo n=29	Baseline HAM-D scores 23.7, 23.2, and 22.0 reduced to 16.0±4.6 with lower and to 16.7±4.2 with higher SHR-5 dose vs. to 23.4±3.8 with placebo, showing superiority of both doses to placebo
[95] USA 2015	Single-center; DSM-IV mild-moderate MDD, 12 weeks, DB	SHR-5 extract 1×340 to 3×340 mg/d n=20	Placebo, n=18 Sertraline n=19	Baseline-adjusted HAM-D reduction: −8.2 (95%CI −12.7 to 3.6) with sertraline, −4.6 (−8.6 to −0.6) with placebo, and −5.1 (−8.8 to −1.3) with SHR-5, not showing superiority over placebo
[96] China 2020	Single-center; DSM-IV mild-moderate MDD, 12 weeks, DB	Sertraline + 1×300 mg/d extract n=34 Sertraline + 2×300 mg/d extract n=33	Sertraline+placebo n=33	Baseline HAM-D scores 23.2, 23.3, and 23.1 – reduced to 10.6±1.0 with low dose and to 12.7±0.9 with high dose <i>Rhodiola</i> extract vs. to 15.9±1.7 with placebo showing superiority of both doses vs. placebo

20.2.1.6 Chinese Herbal Medicine (CHM)

The topic is complex: (a) CHM refers to hundreds of different plants, typically used in mixtures [97]; (b) hundreds of trials have been conducted with tens of meta-analyses, but almost exclusively in China/Chinese language; (c) a large number of studies pertain to “depression” in various health conditions, but not to specific depressive disorders [e.g., in poststroke patients [98]]; (d) primary studies are commonly of low quality – small trials, poorly controlled, susceptible to various biases [97]. We would like to point out the following: (a) CHM is a part of a specific cultural and historical milieu; (b) under such conditions, open-label, “no treatment control” trials, particularly if small, are highly likely to yield skewed estimates that may not be generalizable, particularly not to other societal and cultural settings. To illustrate typical data pertaining to CHM, we address several SR/MAs.

Yeung 2014 [97] Of the identified 296 RCTs, 21 were considered, as they had a modified Jadad score of at least 3. Among the 21, 5 were Iranian saffron trials (see above), and these were the only trials judged as “low risk of bias on all items” [97]. All others were Chinese trials; however, only some could have been double-blind as they used a pillled CHM vs. antidepressant or had a double-dummy design. We used

Table 20.7 Summary of RCTs of *Chinese herbal medicine* (CHM) depicted as double blind in [97] vs. placebo or active treatment (using double-dummy design) in MDD patients

Main study characteristics	Outcome	Comment
CHM vs. placebo; two 6-week RCTs, 116 on CHM (two different), 72 on placebo	End-study HAM-D mean difference CHM-PBO −7.4 (−57.0 to 42.1), $\tau^2=27.95$, $I^2=91.4\%$, $t=-1.908$, $df\ 1$, $P=0.307$	CHM <PBO in both studies, but huge uncertainty
CHM vs. active treatment; two 6-week RCTs of Jieyu vs. maprotiline or venlafaxine (70 on CHM, 74 control)	End-study HAM-D identical for Jieyu vs. active in both trials	No assay sensitivity, hence no evidence of efficacy
CHM vs. active treatment; 6-week trial of Qican Fukang (n=445 of 512 randomized) vs. fluoxetine (n=438/512)	End-study HAM-D higher with Qican Fuckang (difference 1.40, 95%CI 0.76–2.04, $t=4.285$, $df=871$, $P<0.001$)	Huge attrition. Likely biased; suggests inferiority

the data [97] to repeat the analysis for these few trials – Table 20.7: except for uncertainty, nothing much could be concluded. Several other SR/MAs had different topics but shared common features: 4–12-week trials, all single-center and open-label vs. antidepressants or as add-on vs. no add-on to antidepressants, with common patient attrition (susceptible to a range of biases) (Table 20.8). Considering Chinese patients, it is reasonable that at least some CHM formulas may be useful in treatment of depressive disorders, alone or as add-on treatments. However (a) there is a considerable uncertainty about the effect/its size even for those most likely to be useful (Table 20.8); (b) the benefit of complementary (add-on) use appears intuitive, but without a control, one cannot distinguish the effect of the intervention from the effect of the act of intervening. It is unclear to what extent would CHM be of use in non-Chinese patients.

20.2.1.7 Other Herbal Preparations

A number of herbal preparations have been “tried” in individual small trials related to depression (e.g., see 50 for an overview) which at this moment do not allow any conclusions.

20.2.2 Nutrients/Nutritional Supplements (“Nutraceuticals”)

20.2.2.1 Omega-3 Polyunsaturated Fatty Acids (n-3 PUFA)

n-3 PUFAs modulate monoaminergic transmission and HPA axis activity and BDNF expression, have anti-inflammatory properties, and decrease depression-like behaviors in animal models (see [48]). A number of trials have been conducted and a

Table 20.8 Summary of Chinese meta-analyses on *Chinese herbal medicine* (CHM) for depressive disorders (MDD)

Study	Outcome	Comment
Man 2014 [99]: Xiaoyao formula as add-on to antidepressants (all open-label, no-treatment control trials)	9 RCTs, 337 patients CHM, 338 controls. Conclude <i>superiority</i> of add-on: CHM-control end-study HAM-D = -2.15 (-3.56 to -0.74)	Considerable heterogeneity ($\tau^2=3.671$, $I^2=82.0\%$) (uncertainty): range of effects -5.99 to 1.68 and 95% prediction intervals from -6.99 to 2.67
Zheng 2016 [100]: Wuling formula either vs. SGA or as add-on (vs. no add-on)	Comparison to SGA (4 trials, 172 patients CHM, 168 SGA) – similar end-study HAM-D scores. For add-on vs. no add-on (4 trials, 114 CHM, 116 controls): concluded <i>superiority</i> in attainment of response	Comparison to SGA – no assay sensitivity, hence no evidence of efficacy. Comparison to no add-on used fixed-effect pooling. We recalculated by random effects (and HKSJ correction): $RR=1.17$ (95%CI 0.75 – 1.84), $t=1.117$, df 3, $P=0.345$, $\tau^2=0.026$, $I^2=44.0\%$, range of effects 0.85 to 1.61 , 95% prediction intervals 0.47 to 2.95 – i.e., “no difference,” huge uncertainty
Sheng 2017 [101]: Guipi formula as add-on to antidepressants (all open-label, no-treatment control trials)	Conclude <i>superiority</i> vs. no add-on: end-study HAM-D (8 trials, 282 CHM, 278 controls): mean $\Delta=-3.09$ (-4.11 to -2.07), $\tau^2=1.45$, $I^2=71\%$	Heterogeneity is considerable (hence the uncertainty), e.g., range of effects -5.50 to -0.68 , 95% prediction intervals are -6.32 to 0.14 (from large effect to no effect)
Sun 2018 [102]: Chai Hu Shu San formula vs. no treatment or vs. SGA or as add-on to SGA vs. no add-on (total of 42 open-label trials)	Concluded <i>superiority</i> vs. SGA based on HAM-D response rates in MDD patients (no major comorbidity) (7 RCTs, 263 CHM, 226 SGA)	We recalculated with HKSJ correction: $RR=1.13$ (95%CI 0.84 – 1.52), $t=1.02$, df 6, $P=0.345$, $\tau^2=0.033$, $I^2=75.2\%$, range of effects 0.79 – 1.62 , 95% prediction intervals 0.64 – 1.98 , i.e., “no difference,” huge uncertainty
Li 2019 [103]: 12 different formulas vs. no treatment or vs. SGA in people with MDD and malignancy (all open label)	Concluded superiority vs. SGA based on end-treatment depression SMD -0.57 , $P=0.03$ (6 trials, CHM 223, SGA 223)	We recalculated with HKSJ correction: SMD -0.57 (95%CI -1.25 , 0.11), $t=-2.17$, df 5, $P=0.083$, $\tau^2=0.33$, $I^2=84\%$, range of effects -1.72 to 0.58 , 95% prediction -2.32 to 1.18 – i.e., “no difference,” huge uncertainty

(continued)

Table 20.8 (continued)

Study	Outcome	Comment
Yang 2020 [104]: formulas that contain <i>Bupleurum chinense</i> – include Xiaoyao, Chai Hu Shu Gan San, and >20 others	Based on 30 RCTs (3459 patients) vs. SGA (all open label), conclude <i>superiority</i> to SGA: SMD in end-study scores= −0.35 (95% CI −0.52 to 0.18), I ² =81%; but warn “about biases and heterogeneity that could not be explained by subgroup analyses.” Assigned is “very low quality of evidence” (GRADE)	We used the reported 30 SMDs (and confidence intervals) to determine measure of heterogeneity (τ^2) in order to better illustrate the extent of heterogeneity: the range of effects (SMDs) based on the reported data is from −1.19 to 0.48, i.e., from a large benefit of CHM to a considerable harm. 95% prediction intervals are −1.22 to 0.52. The uncertainty about the effect is considerable

SGA second-generation antidepressants

number of SR/MAs. Benefits should be expected from eicosapentaenoic acid (EPA) or mixtures in which it prevails and not from docosahexaenoic acid (DHA) (e.g., see discussion in [105]). A recent single-center double-blind 12-week RCT in 88 adults with MDD demonstrated higher remission rates with monotreatment with EPA (3.0 g/day) (51.9%) or EPA 1.5 g/day + DHA 0.7 g/day (53.8) vs. DHA 1.4 g/day (34.3%) [106].

EPA Monotreatment Based on the published SR/MAs [105, 107–112], we identified RCTs of EPA/EPA-dominant mixtures as monotreatment. One small double-blind 8-week RCT in 2009 [113] (MDD, EPA 1.0 g/day vs. placebo) suggested possible benefit of EPA, but of 57 enrolled subjects, only 24 were analyzed; hence it should be disregarded. Other RCTs are outlined in Table 20.9. Two small trials with quite some attrition pertain to perinatal MDD with opposing findings – no effect of EPA or a greater reduction of HAM-D with EPA. *Of notion*, one recent meta-analysis [114] addressed n-3 PUFA specifically for maternal depression and concluded benefits of PUFA but included (a) one small trial without clinically diagnosed depression and (b) the trials depicted in Table 20.8, but erroneously handled the data – so, it should be disregarded. Further trials (Table 20.9) were also small with varying results and limitations. We warn that one SR/MA [108] erroneously included a trial not in MDD [115] and another one that did not compare PUFA to placebo [116]. RCTs found through additional search, one in MDD patients with cardiovascular comorbidities [117] and one in adolescents with MDD [118], did not indicate benefits of EPA monotreatment (Table 20.9). Pertinent to the childhood/adolescent MDD, a recent SR/MA [119] included 4 small single-center 10–16-week RCTs of EPA vs. placebo – based on a total of 64 EPA-treated and 73 placebo-treated children; no signal of a potential benefit of EPA monotreatment was observed. Overall, (a) pooling of data depicted in Table 20.9 is meaningless; (b) so far, data do not support efficacy of EPA monotreatment in adults or children with MDD.

Table 20.9 Summary of RCTs of EPA monotreatment in depressive disorders identified through two published SR/MA [108, 112] and through our literature search (we retrieved all individual full-text trials, but those identified from published SR/MAs are referred as such)

Study	Main study characteristics	Outcome	Comment
Ref. 17 in [112] 8 weeks, DB	DSM-IV perinatal MDD, single-center EPA 1.1+DHA 0.8 g/day n=31 Placebo n=28	HAM-D: EPA 18.9 (3.4) to 12.8 (5.5) n=28 completers PBO 17.4 (2.2) to 9.9 (4.7) n=23 completers Difference in slope over 3 visits (baseline and MDD history-adjusted) EPA-PBO beta=0.2, z=1.15, P=0.250	Considerable dropout. Unclear how data extracted in MA [112]. HAM-D reduction somewhat greater with placebo
Ref. 19 in [112] 8 weeks, DB	DSM-IV perinatal MDD, single-center EPA 2.2+DHA 1.2 g/day n=18 Placebo n=18	HAM-D: EPA 22.3 (5.0) to 9.9 (4.3) n=17 ITT (4 imputed) PBO 22.3 (3.9) to 14.6 (4.8) n=16 (5 imputed) Baseline-adjusted difference in end-study HAM-D EPA-PBO= -4.70 (95%CI -7.9 to -1.5)	Considerable dropout. Unclear how data extracted in MA [112] Supports effect of EPA
Ref. 24 in [112] 8 weeks, DB	DSM-IV MDD or dysthymia in elderly women, single-center EPA 2.5 + DHA 0.83 g/day n=22 Placebo n=24	Geriatric Depression Scale: EPA 17.1 (3.6) to 12.6 (4.3) n=22 PBO 16.7 (4.3) to 15.9 (5.4) n=24 Baseline-adjusted difference EPA-PBO= -3.2 (-5.9 to -0.6)	Small, but generally good quality. Supports effect of EPA
Ref. 28 in [112] 8 weeks, DB	DSM-IV MDD adults, two hospitals in Boston (just as a single-center) EPA 1.0 g/day n=60 Placebo n=59	HAM-D: EPA baseline 19.5 (3.4), PBO baseline 19.2 (3.1) Baseline-adjusted change EPA -10.34 (0.62) ITT Baseline-adjusted change PBO -9.49 (0.61) ITT EPA-PBO difference= -0.85 (95%CI -2.57 to 0.87)	Only two drop-outs with LOCF imputation. Quality trial. Does not support efficacy of EPA
Ref. 29 in [112] 8 weeks, DB	DSM-IV MDD adults, two hospitals in Boston (just as a single-center) EPA 1.06 + DHA 0.26 mg/day n=52 Placebo n=52	HAM-D baseline values not reported Baseline-adjusted change EPA -10.14 (0.57) ITT Baseline-adjusted change PBO -9.72 (0.55) ITT EPA-PBO difference= -0.42 (95%CI -1.99 to 0.1.15)	Poorly reported, but otherwise quality trial. Does not support efficacy of EPA
Ref. 30 in [112] 12 weeks, DB	DSM-IV MDD in multiple sclerosis, single-center EPA 1.95 + DHA 1.35 g/day n=21 Placebo n=18	MADRS baseline: EPA 18.4 (5.3), PBO 19.1 (4.9). Age and MS duration-adjusted end-study values: EPA 10.9 (2.0) n=15, PBO 9.1 (1.3) n=16 (lower values and greater reduction with placebo)	Small with attrition, otherwise quality trial. Not clear how data extracted for MA [112]. Does not support efficacy of EPA

(continued)

Table 20.9 (continued)

Study	Main study characteristics	Outcome	Comment
[117], 12 weeks, DB	DSM-IV MDD in patients with CVD, single-center EPA 2.0 + DHA 1.0 g/day n=30 Placebo n=29	HAM-D baseline: EPA 19.4 (4.2), placebo 19.2 (3.6) Change vs. baseline EPA: −5.1 (4.1), placebo −4.1 (3.4) Difference in change EPA- PBO=−1.0 (−3.0 to 1.0)	Small but generally good quality. Does not support efficacy of EPA
[118], 10 weeks, DB	DSM-IV MDD in adolescents (12–19 years), single-center EPA up to 2.4 +DHA 1.2 g/day n=21 Placebo n=27	Children's Depression Rating Scale-revised: EPA 49.5 (8.2) to 36.5 (10.0), n=18, PBO 50.2 (8.9) to 35.2 (10.6), n=21 Baseline-adjusted EPA-PBO difference in end-study score= 1.81 (−3.31 to 6.94) (higher with EPA)	Small with attrition (LOCF imputed), otherwise good quality. Does not support efficacy of EPA

EPA Add-on to Antidepressants in MDD The topic was addressed in [105]. It included 10 double-blind RCTs (3–12 weeks), limited in that (a) all were single-center, small, with a total of 212 EPA-treated and 190 placebo-treated patients; (b) all were based on “completers” analysis, commonly with substantial dropout. The pooled effect suggests a benefit of EPA but heterogeneity is high ($\tau^2=0.2015$, $I^2=64\%$) [105]. We found three additional trials that “fit” into this variability. One 12-week double-blind single-center trial in Iran [120] (MDD) with sertraline + 1 g/day n-3 PUFA (n=25) vs. sertraline + placebo (n=25) indicated a large PUFA effect. In another 10-week high-quality double-blind RCT in the USA [121], patients with MDD and coronary heart disease were randomized to sertraline+EPA 2 g/day (n=72) or sertraline+placebo (n=72). The end-of-trial baseline-adjusted HAM-D score was lower with placebo (7.2) than with EPA (8.0). Finally, in an older double-blind 12-week trial [122], end scores were somewhat lower with EPA add-on (1–4 g/day, n=52) (12.1) than with placebo (n=18, 14.2). When these three were added to the above meta-analysis (a total of 362 EPA-treated and 305 placebo-treated patients), the effect was greater, but so was heterogeneity and uncertainty about the effect: Hedges' $g=-0.617$ (95%CI −1.22 to −0.02), $df=12$, $t=-2.235$, $P=0.045$, $\tau^2=0.513$, $I^2=85\%$, range of effects −2.05 to 0.82, and 95% prediction intervals −2.27 to 1.03. Safety of EPA is comparable to placebo.

Overall, data suggest a possible benefit from EPA in depressive disorders, but uncertainty about the effect, its possible moderators, and optimal dosing is very high.

Comment A recent meta-analysis of PUFA [111] included 26 RCTs with monotreatment, add-on treatment, clinical depression, depressive difficulties, and with or without major comorbidities – clinical settings that hardly should be pooled jointly. The pooled estimate for PUFA-placebo difference in end-study depression score = −0.28 (95%CI −0.47 to 0.09) based on 1089 and 1071 patients suggests “efficacy” but “with caution due to heterogeneity” [111]. In fact, the estimate does

not mean much: with the reported τ^2 of 0.19, the range of effects extends between -1.152 (large benefit from PUFA) and 0.592 (a considerable harm from PUFA), and the 95% prediction intervals extend from -1.19 to 0.63 , without a clue in which settings to expect the benefit and in which not. So, meta-analyses can be of no practical use [see a similar comment [123] on one of the MAs addressed here [112]].

20.2.2.2 S-Adenosyl Methionine (SAmE)

SAmE is involved in generation of a number of endogenous anti-inflammatory, neurotrophic, and antioxidant molecules, as well as in DNA synthesis and repair. In animal models, it stimulates monoaminergic neurotransmission and has biological and behavioral effects similar to antidepressants [48, 124, 125]. A Cochrane review in 2016 [126] included only two RCTs and excluded a large number of others due to “poor data reporting.” A review in 2017 [125] listed 18 RCTs vs. placebo (in [11], the results favored SAmE; mostly in 1970s to 1990s) and 21 RCTs in which SAmE was comparable to TCA (mostly in the 1970s to 1990s). We retrieved RCTs published since 2000 till February 29 2020 – all were done in adults with MDD and are summarized in Table 20.10. Two larger trials in Italy [127, 128] demonstrated identical outcomes for oral or intramuscular SAmE vs. standard imipramine over 6 weeks – however, these trials should not be viewed as evidence of efficacy (no assay sensitivity). Other trials were small, some burdened with a considerable attrition (Table 20.10). One small trial suggested efficacy of SAmE as augmentation to escitalopram [129], while the other failed to do so [130]. Two comparisons of SAmE monotherapy to placebo [131, 132] each failed to demonstrate superiority over 8–12 weeks. Outcomes were slightly in favor of SAmE in both trials (Table 20.10). Comparison to escitalopram in [131] is meaningless (Table 20.10). Tolerability of SAmE was not relevantly different from placebo. Currently, data could be viewed as indicative albeit burdened with uncertainty.

20.2.2.3 Methylfolate and Precursors (Folic or Folinic Acid) (Alone or with Vitamins B6 and B12)

Methylfolate may be supplemented as precursors (folic or folinic acid) or as methylfolate. Bioavailability of methylfolate (oral) is by far the highest when supplemented as such [48]. Methylfolate is involved in complex metabolic processes, including synthesis of monoaminergic neurotransmitters and SAmE. Several SR/MAs of RCTs addressed folates as augmentation to antidepressants [105, 134–139]. Their results might be confusing since estimates commonly include different folate preparations, depressive disorders, and “depressive difficulties.” We tried to summarize outcomes by setting (only depressive disorders) (Table 20.11). Data on folic acid (FA) lower (<5 mg/day) or higher dose (5–10 mg/day) come from two medium-sized quality trials and five small trials, most of which are at high risk of various

Table 20.10 Summary of RCTs of SAMe in depressive disorders since 2000

Study	Main study characteristics	Treatments and outcomes	Comment
6 weeks, DB Italy [127, 128]	SAMe po vs. imipramine po, DSM-IV MDD, HAM-D ≥ 18 , multicentric	SAMe up to 1600 mg/ day n=143, base HAM-D=25.1 (4.9) Imipramine to 150 mg/day n=138, base HAM-D=25.5 (5.2) Reduction: SAMe −12.6 (9.0), imipramine −13.1 (9.5) SAMe-imipramine =0.50 (−1.7 to 2.7) Response: SAMe 51%, imipramine 57% RR= 0.89 (0.72–1.11)	Trials were conducted under identical protocols (except for administration route) – quality trials, but due to lack of a placebo arm, they lack assay sensitivity. Hence indicative but formally not proving efficacy
6 weeks, DB Italy [127, 128]	SAMe im vs. imipramine po, DSM-IV MDD, HAM-D ≥ 18 , multicentric	SAMe up to 400 mg/ day n=146, base HAM-D=24.3 (4.0) Imipramine to 150 mg/day n=147, base HAM-D=26.0 (4.5) Reduction: SAMe −12.6 (7.3), imipramine −13.1 (7.4) SAMe-imipramine = 0.50 (−1.2 to 2.2) Response: SAMe 59%, imipramine 50% RR=1.17 (0.95–1.45)	
6 weeks, DB USA [129]	SAMe+SSRI vs. placebo+SSRI , DSM-IV MDD HAM-D ≥ 16 despite treatment with SSRI, single-center (augmentation)	SAMe 2×400 mg/day n=39, base HAM- D=19.1 (3.1) SSRI standard+placebo n=34, base HAM- D=19.9 (3.0) Reduction: SAMe −7.4 (8.7), placebo −4.0 (8.7) SAMe-placebo=−3.4 (−7.5 to 0.67) P=0.100 Response: SAMe 20/39, placebo 7/34 RR=3.22 (1.58–8.24)	Small but quality trial. Add-on SAMe superior to add-on placebo. Suggests efficacy of SAMe

(continued)

Table 20.10 (continued)

Study	Main study characteristics	Treatments and outcomes	Comment
8 weeks, DB Australia [130]	SAMe+SGA vs. placebo+SGA , DSM-V MDD MADRS ≥ 18 despite SGA, two sites in Australia (augmentation)	SAMe 2×400 mg/day n=55, base MADRS=25.7 (5.3) SGA standard+placebo n=52, base HAM-D=25.6 (5.5) SAMe reduction –11.4 (7.5), response 53.4% Placebo reduction –12.1 (7.0), response 50.0%	Huge attrition (30%) – only completers analyzed. Not superior to placebo. Does not suggest efficacy of SAMe
12 weeks, DB USA [131]	SAMe vs. escitalopram vs. placebo DSM-IV MDD, single-center	SAMe 1600–3200 mg/day n=64, base HAM-D=19.0 (5.1) Escitalopram 10–20 mg/day n=65, base HAM-D=19.2 (4.9) Placebo n=60, base HAM-D=19.4 (4.1) SAMe end HAM-D=12.8 (7.4), response 35% Escitalopram end HAM-D=12.9 (7.0), response 34% Placebo end HAM-D=14.3 (6.9), response 30%	Huge attrition – nearly half LOCF imputation. No treatment superior to placebo. Does not suggest efficacy of SAMe
8 weeks, DB Australia [132]	SAMe vs. placebo , DSM-V MDD, MADRS 18–24, two in sites Australia	SAMe 2×400 mg/day n=25, base MADRS=22.4 (2.0) Placebo n=24, base MADRS=22.2 (3.1) SAMe end MADRS=9.9 (2.4), HAM-A=7.1 (2.2) resp. 54.5% Placebo end MADRS=12.5 (2.5), HAM-A=7.4 (2.2), resp. 52.6%	Attrition high – 3 SAMe and 5 placebo – only completers analyzed. Does not suggest efficacy of SAMe

(continued)

Table 20.10 (continued)

Study	Main study characteristics	Treatments and outcomes	Comment
[133] post hoc analysis of 130	Nonresponders to SAMe/escitalopram or placebo by week 6 received a doubled dose to week 12	SAMe 3.6 g/day – week 6 HAM-D=15.8 (4.3) to 3.4 (5.4) n=16 Escitalopram – week 6 HAM-D=17.3 (4.7) to 14.0 (5.3) n=23 Placebo-week 6 HAM-D=16.9 (3.6) to 13.3 (6.3) n=26	In line with the main result – does not support efficacy of SAMe

biases, with no indication of dose dependency (Table 20.11). Larger trials [143, 144] do not indicate efficacy in initial treatment, but one [143] indicated less relapse over 1 year of treatment (Table 20.11). Some smaller trials also indicate an effect. One small 6-week double-blind trial in India [146] suggested a greater symptom reduction when 5 mg/day FA (n=19) was added to fluoxetine vs. 1.5 mg/day (n=20). We provide a pooled estimate (Table 20.11) of differences in end-study scores (FA - control) to illustrate this variability: it slightly favors FA; heterogeneity is very high and 95% prediction intervals extremely wide (from large benefit to large harm) (Table 20.11) illustrating considerable uncertainty – data do not support efficacy but also do not exclude a possible mild effect (Table 20.11). Data on *methylfolate* come from two single-center 4-week trials [147]: 7.5 mg/day did not differ from placebo, while 15 mg/day did not differ in one trial and resulted in a greater HAM-D reduction in the other one (Table 20.11). In one older double-blind 6-month trial [148], 15 mg/d resulted in better HAM-D score than placebo, but 11/13 on methylfolate were treated with antidepressants vs. 6/11 on placebo. Overall, uncertainty about folate effect is very high.

In one small open-label 6-week RCT, patients with low-normal B12 level treated with antidepressants + intramuscular vitamin B12 (n=34) experienced a greater reduction in HAM-D (by 11.1±4.6 points) than patients not receiving B12 (n=39) (by 5.0±3.4 points) [149].

20.2.2.4 L-Acetylcarnitine (LAC)

LAC is involved in energy metabolism and acetylates the transcription factor NF-κB and certain histones, resulting in increased expression of glutamate type 2 receptors – a presumed mechanism of antidepressant effects in animal paradigms (see [150]). As recently reviewed [151, 152], data in depressive disorders are scarce. Trials of LAC (1.5–3.0 g/day) vs. placebo date to late 1980s and 1990s in Italy: 5 single-center 6–8-week RCTs (overall 96 on LAC, 96 placebo) in mainly elderly with dysthymia (one trial in MDD) indicated huge effects (pooled Hedges’ g around 1.2) [151]. A more recent single-center 8-week open-label RCT in Russia [153] in MDD patients reported greater HAM-D reduction when LAC was added to

Table 20.11 Summary of RCTs of folic acid (FA) or methylfolate (MTHF) as adjunctive to antidepressants (AD)

Setting/ study	Main study characteristics	Treatments and outcomes	Comment
<i>Folic acid</i>			
[140] Turkey ^a	Single-center, open-no-treatment control, 6 weeks, DSM-IV MDD	Escitalopram+2.5 mg/d FA n=20, MADRS 30 (4.8) to 18.8 (5.8) Escitalopram alone n=15 n=15, MADRS 32 (8.7) to 16.2 (8.7)	Open-label, no-treatment control. Does not suggest efficacy
[141] UK	Single-center, DB, 10 weeks, DSM-III MDD HAM-D ≥20	Fluoxetine + 0.5 mg/d FA n=51, HAM-D 26.0 (4.5) to 8.8 (6.2) Fluoxetine+PBO n=58, HAM-D 26.6 (4.8) to 11.2 (7.2) Response: FA 42/51 (82.4%) vs. PBO 36/58 (62.1%)	10–20% dropouts. Only completers analyzed. More reduction with FA
[142] Iran	Single-center, DB, 8 weeks, DSM-IV MDD	Citalopram+2.5 mg/d FA n=45, HAM-D 34.4 (9.0) to 21.9 (9.4) Citalopram+PBO n=45, HAM-D 35.8 (9.6) to 27.2 (11.2)	Overall good quality. More reduction with FA
Zhang in [139] Chinese language	CCMD-3 MDD, 6 weeks, low quality (likely open-label)	Venlafaxine+1.2–2.4 mg/d FA n=26 (other data not known) Venlafaxine alone n=27 (other data unknown) Reported standardized mean difference −0.87 (−1.43, −0.3)	A lot of unknowns, but reported [139] to be of high risk of several biases, low quality
[143] Australia	Single-center, DB, 12-week DSM-IV MDD MADRS ≥20, age ≥50 Extended to 52 weeks	Citalopram+2 mg/d FA (+B6&B12 25/0.5) n=76, MADRS 27 (5) Citalopram+ placebo n=77, MADRS 26 (5) Reduction at week 12: FA −16.4 (9.6), placebo −18.1 (9.6)	Good quality. Slightly more reduction with placebo, but less relapse with FA (week 12–52) 8.6% vs. 17.5%
[144] UK	Community-based, DB, 12 weeks, moderate-severe depression	Any AD + 5 mg/d FA n=223, MADRS 28 (7) to 21.8 (10.1) Any AD + placebo n=217, MADRS 29 (7) to 21.6 (10.7)	High quality, limited dropout. Does not suggest efficacy of FA
[145] Venezuela	Single-center, DB, 6 weeks, DSM-IV MDD	Fluoxetine+10 mg/d FA n=10?, HAM-D 22.5 (1.5) to 7.5 (5.8) Fluoxetine+PBO n=10?, HAM-D 21.9 (1.5) to 11.4 (4.9)	27 randomized, 7 dropouts, only completes analyzed, number/arm not known. More reduction with FA
Overall ^b	FA n=451, placebo n=449 Hedges' g =−0.126 (95% CI −0.569 to 0.317) df=6, t =−0.696, P =0.513, 95% prediction −1.33 to 1.08		
<i>MTHF</i>			

(continued)

Table 20.11 (continued)

Setting/ study	Main study characteristics	Treatments and outcomes	Comment
[147] USA 7.5 mg/d	Single-center, DB, 4 weeks, DSM-IV MDD, depressed despite SSRI	SSRI+MTHF n=36, HAM-D 18.8 (4.2) reduced by 4.3 (5.0) SSRI+placebo n=112, HAM-D 19.9 (4.8) reduced by 6.3 (6.6) Nonresponders crossed to 15 mg MTHF (n=35) or placebo (n=33) for 30 days: reduction 3.1 (4.2) and 2.1 (4.9)	20% dropout. Completers analyzed. Greater initial reduction with placebo. Similar with placebo and 15 mg/d after switch
[147] USA 15.0 mg/d	Single-center, DB, 4 weeks, DSM-IV MDD, depressed despite SSRI	SSRI+MTHF n=19, HAM-D 21.2 (4.1) reduced by 7.5 (5.5) SSRI+placebo n=56, HAM-D 21.2 (3.2) reduced by 4.4 (5.8) Nonresponders crossed to 15 mg MTHF (n=18) or placebo (n=21) for 30 days: reduction 3.8 (6.2) and 1.1 (4.7)	20% dropout. Completers analyzed. Greater reduction with MTHF – initial and after switch

^aReported median and range, means (SD) derived
^bRandom effects (DL) with HKSJ correction

antidepressants (n=20) than when it was not. In a double-blind 12-week comparison, LAC (1.0 g/day) (n=94) was not non-inferior to amisulpride (n=99) in patients with DSM-IV dysthymia [154] – HAM-D reduction was by 0.78 (−0.87 to 2.46) points less with LAC (although, the concept is meaningless without a placebo arm!). In a similar 7-week trial in elderly with dysthymia [155], LAC (3 g/day) (n=41) was comparable to fluoxetine 20 mg/day (n=39). Overall, clinical data on LAC are at the level of a proof of concept but burdened with uncertainty.

20.2.2.5 Probiotics

An SR/MA in 2016 [156] identified one RCT in MDD. An SR/MA in 2019 [157] identified two more in MDD and found a large effect of probiotics (3 RCTs) [157]. However, a large network meta-analysis concluded that probiotics were no different from placebo [158]. We identified five RCTs of probiotics in MDD (Table 20.12): (a) three small trials in Iran consistently indicated a large effect vs. placebo. Note that standard error of τ^2 is rather large and upper confidence limit of I^2 is 73%. Hence, although the results seem consistent, there is “latent” uncertainty. One open (no-treatment control) trial in resistant depression [162] and one double-blind RCT vs. placebo burdened with high attrition [163] yielded large effects (Table 20.12) – but uncertainty is high. Overall, data represent a reasonable “proof of the concept” that probiotics *could* be useful but yet need to be evaluated.

Table 20.12 Summary of RCTs of probiotics for treatment of depressive disorders

Study	Main study characteristics	Treatments and outcomes	Comment
[159] Iran DSM-IV MDD	Probiotic (<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i>) monotreatment vs. placebo , single-center, DB, 8-week	Probiotic n=20, placebo n=20, ITT (BDI scores) Adjusted change vs. baseline: −5.3 (SE 1.2) vs. −1.8 (SE 1.2) Difference in change (Hedges’ g): −0.639 (SE 0.318)	Single-center, small, but otherwise high quality, only a few dropouts. Suggests superiority vs. placebo
[160] Iran DSM-V MDD	Probiotic (<i>L. casei</i> , <i>L. acidophilus</i> , <i>L. bulgaricus</i> , <i>L. rhamnosus</i> , <i>B. breve</i> , <i>B. longum</i> , <i>S. thermophilus</i>) with fluoxetine vs. placebo add-on , 2 hospitals, DB, 10 weeks	Probiotic n=20, placebo n=20, ITT (HAM-D scores) Unadjusted: 22.9 (3.7) to 3.7 (3.5) and 22.5 (3.5) to 4.8 (3.1) Difference in end scores (Hedges’ g): −0.325 (SE 0.312)	Single-center, small, but otherwise high quality, no dropouts. Tends to superiority vs. placebo
[161] Iran MDD	Probiotic (<i>L. helveticus</i> , <i>B. longum</i>) monotreatment vs. placebo , single-center, DB, 10 weeks	Probiotic n=36, placebo n=38, ITT (BDI scores) Raw scores: 18.3–9.0 and 18.7–15.5, report “adjusted standardized difference in change: −0.540, p=0.008” Difference in change (Hedges’ g)=−0.534 (SE 0.201)	Single-center, small, otherwise high quality. A few dropouts. Suggests superiority vs. placebo
Pooled^a	Probiotic n=78, placebo n=75 Hedges’ g=−0.509 (95% CI −0.841 to −0.177), t=−6.602, P=0.022, τ² 0.000 (SE 0.075), I²=0.0% (95% CI 0–73%)		
[162] Japan DSM-IV MDD	Probiotic CBM588 with antidepressant vs. no add-on , single-center, open, 8 weeks in treatment-resistant patients	Probiotic n=20, no add-on n=20, ITT (HAM-D scores) Start values: 31.9 (2.8) and 31.8 (4.9). Report change of −19.5 (SE 0.51) and −0.1 (SE 0.8). Difference in change (Hedges’ g)= −6.50 (SE 0.81)	Small, single-center, open, not controlled, suggests superiority vs. placebo, but unrealistically large effect

(continued)

Table 20.12 (continued)

Study	Main study characteristics	Treatments and outcomes	Comment
[163] Poland DSM-IV MDD	Probiotic (<i>L. plantarum</i>) monotreatment vs. placebo , single-center, DB, 8 weeks	Probiotic n=30, placebo n=30, not ITT (HAM-D scores) Unadjusted: 21.5 (6.0) to 6.0 (3.7) and 22.0 (7.9) to 10.0 (7.5) Difference in end scores (Hedges' g): −0.712 (SE 0.298)	Small, single-center large attrition (25%), completers only analyzed. Suggests superiority vs. placebo

^aRandom-effects (DL) with HKSJ correction

20.2.2.6 Inositol

Several SR/MAs addressed RCTs of inositol for depression [105, 137, 162, 163]. Three 3–6-week trials, double-blind, as add-on to antidepressants (43 inositol, 42 placebo), consistently showed no benefit. One 4-week RCT evaluated monotreatment [164] in 39 MDD or bipolar/depressed patients, 11 of which dropped out (13 on inositol, 15 on placebo) and reported a “significant difference” in HAM-D score reduction [164]. Since individual data are available [164], we recalculated baseline-adjusted change in the two arms as −11.3 (SE 2.7) and −4.2 (SE 2.5). Although suggestive of efficacy, this trial is burdened by a huge dropout. Two RCTs vs. placebo [165, 166] addressed inositol for DSM-IV premenstrual dysphoric disorder (PMDD). One [165] indicated no effect in 11 women in a crossover design (Hedges’ $g=-0.466$, 95%CI −1.314 to 0.381), while the other one [166] indicated a huge effect (inositol $n=37$ placebo $n=34$, Hedges’ $g=-1.755$, −2.305 to −1.206). Pooled across two trials, $g=-1.147$, 95%CI −9.323 to 7.029, $df=1$, $t=-1.782$, $P=0.325$, $\tau^2=0.708$, and $I^2=85\%$. Although data might be viewed as suggestive, uncertainty is huge. Overall, data on inositol in MDD or PMDD are minor not allowing any conclusions.

20.2.2.7 Vitamin D

A large number of systematic reviews addressed vitamin D supplementation for depression in deficient and non-deficient subjects (e.g., [48], [105], [137], [167–170]). They might be confusing since they “mix” different settings and types of studies. Table 20.13 summarizes RCTs of vitamin D – alone or as add-on to antidepressants – in clinical depression. Only 4 small RCTs exist, double-blind and of good quality with a total of 105 patients on vitamin D and 111 on placebo. Three Iranian trials yielded huge effects in favor of vitamin D; one Danish was slightly in favor of placebo. The pooled estimate is largely imprecise; heterogeneity is huge – although the pooled effect “tends” to favor vitamin D, the uncertainty is immense.

Table 20.13 Randomized controlled trials of vitamin D for treatment of depressive disorders. Listed is also [175] one “no treatment” control trial in Italy

Setting/study	Main study characteristics	Treatments and outcomes	Comment
[171] Iran 2012	Single-center, 1500 IU/day <i>add-on to fluoxetine</i> , vs. placebo , DB, DSM-IV MDD, 8 weeks	Vit D +fluoxetine n=20, HAM-D 29.4 (5.2) to 11.7 (4.6), ITT Fluoxetine + placebo n=20, HAM-D 30.2 (5.8) to 17.2 (4.2), ITT Reported “significant difference” in end-study HAM-D Difference in end-study score: Hedges’ $g = -1.224$ (SE 0.346)	Generally good quality. No dropouts. Suggests efficacy
[172] Iran 2016	Single-center, <i>single oral dose</i> 50 000 IU vs. <i>placebo</i> , DSM-IV MDD, HAM-D ≥ 17 , DB, 8 weeks	Vit D n= 20, 18 analyzed; adjusted BDI change -8.0 (SE 1.6) Placebo n= 20, 18 analyzed; adjusted BDI change -3.2 (SE 1.6) Difference in change: Hedges’ $g = -0.675$ (SE 0.326)	Generally good quality, minor dropout. Suggests efficacy
[173] Iran 2018	Single-center, vit D 50000 IU/week vs. placebo , elderly, mild-moderate depression, DB, 8 weeks	Vit D n= 40, 39 analyzed; change in GDS-15 -1.76 (1.3) Placebo n= 40, 39 analyzed; change in GDS-15 0.027 (0.95) Reported “significant difference in GDS-15 change Difference in change: Hedges’ $g = -1.554$ (SE 0.259)	Generally good quality. Suggests efficacy

(continued)

Table 20.13 (continued)

Setting/study	Main study characteristics	Treatments and outcomes	Comment
[174] Denmark 2019	Single-center, vit D 2800 IU/day <i>add-on to SGA</i> , vs. placebo DB, ICD-10 depressive episode, 12 weeks	Vit D + SGA n=28, HAM-D 18.4 (5.7) to 10.6 (5.4), ITT SGA + placebo n=34, HAM-D 18.0 (6.0) to 9.5 (5.5), ITT Difference in end-score: Hedges' g= 0.199 (SE 0.256)	Generally good quality. After week 12 some dropouts, but HAM-D values remained unchanged to week 24.
Overall^a vit D n=105, plac n=111 Hedges' g=−0.807 (95%CI −2.041 to 0.427) df=3, t=−2.081P=0.129, range −2.49 to 0.79, 90% prediction −3.40 to 1.78			
[175] Italy 2011	Single-center, single oral dose 300 000 IU <i>add-on to antidepressants</i> , open-label, no-treatment control, DSM-IV MDD, elderly, 4 weeks	Vit D + antidepressant n=24, HAM-D 21.1–19.1 Antidepressant n=15, HAM-D 21.5–22.7 Reported “significant difference” in end-study HAM-D Difference in end-study score: Hedges' g= −0.573 (SE 0.336)	Severe risk of several biases. Poorly reported. Apparently not randomized. Suggests efficacy

^aRandom-effects (DL) with HKSJ correction – DOES NOT include the non-randomized, non-controlled Italian trial

20.2.2.8 Testosterone

A recent high-quality SR/MA evaluated testosterone supplementation for “depressive symptoms” in men [176]. Among 27 included RCTs, 7 placebo-controlled trials (149 testosterone, 153 placebo patients) evaluated it as adjunctive to antidepressants in MDD or dysthymia over 6–12 weeks (1 trial in hypogonadal men, 1 in men with AIDS wasting syndrome). Using the same method as the authors [176], we provide estimates for these 7 specific trials: (a) Hedges' g for end-study depression scores, testosterone-placebo=−0.282 (95%CI −0.615, 0.053), t=−2.07, P=0.084, τ^2 =0.000, I^2 =22.2%, and 95% prediction −0.631 to 0.069; (b) 5 trials reported response rates, OR=2.19 (95%CI 0.74–6.48), τ^2 =0.076, I^2 =39.0%, df 4, t=2.01, P=0.115, and 95% prediction 0.48–10.0. All trials were single-center and small but graded for quality as Jadad score 3–5 [176]. Overall, they suggest a modest benefit of supplemental (to antidepressants) testosterone in elderly depressed men, but there is considerable uncertainty.

20.2.2.9 Zinc

A recent SR/MA found 3 double-blind 6–12-week placebo-controlled trials of zinc supplementation to antidepressants [105] – SMD zinc-placebo for end-study depression scores = -0.66 (95% CI $-1.06, -0.26$), $P < 0.01$ – suggesting a marked effect. However, data pertain to only 54 (zinc) and 50 (placebo) patients, and attrition was a problem in all trials. We recalculated using the appropriate method for small number of trials to illustrate uncertainty = -0.68 ($-1.30, -0.06$), $df\ 2$, $t = -3.49$, $P = 0.040$, $\tau^2 = 0.0595$, and 95% prediction -2.03 to 0.66 (i.e., from huge benefit to considerable harm). Empirical data on zinc supplementation are at the level of “early proof of concept.”

20.2.2.10 Other Nutrients

Creatine, vitamin C, amino acid mixtures, dehydroepiandrosterone, citicoline, tryptophane (L- or DL-tryptophane), selenium, magnesium, and calcium were all evaluated in one or a few small single-center trials, typically as add-on to antidepressants with variable outcomes – see, e.g., [48], [105], [137] for *more enthusiastic* overviews – but body of data is even more scarce and heterogeneous than those presented.

20.2.2.11 Nutrient Mixtures

A recent double-blind placebo-controlled 8-week RCT in MDD patients ($N = 158$) in Australia evaluated a mixture of nutrients (SAMe 800 mg/day, folinic acid 0.5 mg/day, vitamin B12 0.2 mg/day, EPA 1000 mg + DHA 656 mg/day, zinc 30 mg/day, vitamins C, B6 and E and 5-hydroxytryptophane) as adjunctive to SGA [177]. After 8 weeks of treatment, MADRS reduction was more pronounced with placebo (-11.7 ± 7.8 vs. $-9.9 \pm SD\ 8.6$), and proportion of responders was higher (51% vs. 40%).

Other treatments are addressed individually. They share a common characteristic – “sham” that would be indistinguishable from the intervention (provides the same level of expectations) and clearly has no beneficial (not to “deflate” the effect of an intervention) or harmful effect (not to “inflate” the effect of intervention) may be difficult to achieve. Controls like “treatment as usual,” wait list, or no treatment are common – but inherently susceptible to a variety of biases (see Table 20.1) and should not be mixed with adequately controlled trials. Non-inferiority vs. an “established active treatment” is likely a meaningless concept when no “true placebo” arm can be included. Superiority vs. an “established active treatment” in an open-label design is much more informative if adequate assessor blinding is achieved (see Table 20.1).

20.3 Light Therapy (LT)

LT has been recently addressed as “CAM” [38] but also as an “acknowledged anti-depressant strategy” [178]. An SR/MA in 2004 [179] evaluated RCTs of LT vs. sham in nonseasonal depression suggesting benefits of short-term (up to 1 week) but not of longer (2–8 weeks) treatments (Table 20.14). Another SR/MA addressed only seasonal affective disorders [180] to indicate benefit in short-term treatment (up to 3 weeks) (Table 20.14). We recalculated data to illustrate uncertainty – even where the effect is indicated, heterogeneity is high, and 95% prediction intervals extend to “no effect” or even “harm” (Table 20.14). Three further SR/MA [181–183] addressed LT in nonseasonal depression – we extracted data on ten double-blind RCTs vs. sham in which specifically MDD, dysthymia, or sporadically bipolar-depressed (nonpsychotic) patients were included (Table 20.14): (a) in patients predominantly <60–65 years, LT might be useful in short-term (1–3 weeks) and less so in medium-term treatment (to 8 weeks); (b) in patients >60 years, it might be useful short-term but likely not in longer treatment. In a 12-week open-label RCT (N=64), combined wake-LT added to a “standard treatment” provided a greater initial symptom reduction than the “standard” but the difference was lost over time [184]. One recent SR/MA reported “superior end-study scores” for LT combined with antidepressants vs. antidepressants+sham in nonseasonal disorders (4 double-blind RCTs, 3–8 weeks, 106 LT vs. 106 control) [185]. However, recalculated data warn about uncertainty: $SMD=-0.51$ (-1.31 to 0.29), $t=-2.01$, $P=0.137$, $\tau^2=0.183$, $I^2=47\%$, range -1.37 to 0.25 , and 95% prediction -2.65 to 1.63 . Finally, one 6-week double-blind RCT in postpartum depression (10 LT vs. 5 controls) [181] and one 12-week double-blind RCT for MDD in parkinsonian patients (N=83) indicated no benefit of LT [186]. Overall, data on LT are fragmentary. A short-term benefit in seasonal and nonseasonal depressive disorders is suggested, but uncertainty is high.

20.4 Acupuncture

At least five professional guidelines on depression address acupuncture (USA, Canada, China), three advising against use, and two advising in favor [187]. Quality of evidence for “clinical depression” was recently judged as “low” or “very low” [38]. A very recent overview of SR/MAs found 39 studies (24 Chinese, 15 non-Chinese) and concluded (quote) “The reporting quality is poor and the overall risk of bias of RCTs is high. Therefore, the results may not be reliable” [188]. A recent review [189, 190] identified seven double-blind controlled RCTs of manual acupuncture (196 treated, 222 sham), five of electroacupuncture (90 treated, 161 sham), and two of laser acupuncture (43 treated, 56 sham) in depressive disorders (predominantly MDD) reporting end-study depression symptom scores. Lower scores (vs. control) were reported with manual or laser procedure. We recalculated results using appropriate methodology (see Table 20.1): Hedges’ $g=-0.54$ (-1.06 , -0.02),

Table 20.14 Summary of SR/MAs of light therapy (LT) for depressive disorders

Study	Main characteristics	Reported outcomes	Comment ^a
[179] Nonseasonal	RCTs of LT vs. control in mostly MDD, but also nonpsychotic bipolar-depressed and dysthymia (in some trials). Attrition and assessment bias – high risk. LT, various; control, mostly dim red light and ionizer	Difference in clinician-rated end-study scores Up to 1 week – 9 RCTs (268 patients) Benefit: SMD= −0.35 (−0.61 to −0.1) P=0.01 8 days to 8 weeks – 5 RCTs (118 patients) “No difference”	Fixed-effect meta-analysis does not seem appropriate. 1-day studies do not seem of interest. Recalculated (random, HKSJ correction): Up to 1 week (7 trials, 103 treated vs. 91 controls) SMD= −0.46 (−1.33, 0.42), t=−1.28, P=0.249, τ^2 =0.709, I^2 =74.4%, range: −2.14 to 1.22; 95% prediction: −2.81 to 1.89 8 days to 8 weeks (5 trials, 64 treated vs. 54 controls) SMD= 0.05 (−0.71 to 0.82), t=0.19, P=0.859, τ^2 =0.232, I^2 =56.1%
[180] Seasonal	MDD and sporadically bipolar (nonpsychotic) patients. Trials of 1–6 weeks with at least 10 subjects per arm. Only “higher-quality trials.” LT, bright white; control, dim red, dawn placebo or negative ionizer	Difference in end-study depression scores 8 RCTs (179 light vs. 168 controls) Benefit: SMD= −0.54 (−0.95 to −0.13) Indicated: effect at earlier weeks (e.g., 2 nd or 3 rd), not at later [4–6]	Recalculated considering low number and small trials Overall: SMD= −0.55 (−1.06, −0.34), t=−2.52, P=0.040, τ^2 =0.2945, I^2 =71.8%, range −1.64 to 0.54; 95% prediction: −1.98 to 0.88 1–3 weeks (5 trials, 90 light vs. 85 controls) SMD= −0.89 (−1.59, −0.20), t=−3.56, P=0.023, τ^2 =0.2145, I^2 =60.6%, range: −1.82 to 0.04; 95% prediction: −2.57 to 0.78 4–6 weeks (3 RCTs 89 light vs. 83 controls) SMD= −0.04 (−0.35, 0.26), t=−0.62, P=0.597, τ^2 =0.002, I^2 =0.0 (0–53%) range: −0.13 to 0.05; 95% prediction: −1.105 to 1.015

[181–183] Nonseasonal (some pertain to elderly)	RCTs of LT vs. control in MDD (or also dysthymia in elderly); in some trials also some bipolar-depressed nonpsychotic. Reviews focused on elderly [182, 183] included also “depressive difficulties.” LT, bright light; control, day light, dim light or negative ionizers We extracted 10 RCTs of specifically “depressive disorders” (except for one with postpartum depression) to generate pooled estimates of LT-control difference	Difference in end-study scores LT-control 10 RCTs 1–8 weeks, 271 light vs. 274 controls 3 RCTs 1–3 weeks, 89 light vs. 93 controls 7 RCTs 4–8 week, 182 light vs. 181 controls 7 RCTs different age, 171 light vs. 171 controls 3 RCTs >60 years, 100 light vs. 103 controls 2 RCTs 1–3 weeks, different age 47 vs. 46 5 RCTs 4–8 weeks, different age 124 vs. 125 1 RCT 1–3 weeks age >60 years 42 vs. 47 2 RCTs 4–8 weeks age >60 years 58 vs. 56	SMD= −0.52 (−0.86, −0.18), t=−3.48, P=0.007, τ^2=0.164, I²=59%, range: −1.33, 0.29; 95% prediction: −1.52 to 0.47 SMD= −0.75 (−1.21, −0.28), t=−6.84, P=0.021, τ^2=0.098, I²=0 (0–59%), 95% prediction: −2.61 to 1.12 SMD= −0.43 (−0.94, 0.08), t= −2.08, P=0.087, τ^2=0.233, I²=66%, range: −1.399 to 0.533; 95% prediction −1.78 to 0.92 SMD= −0.65 (−1.04, −0.25), t=−3.99, P=0.007; τ^2=0.124, I²=36.4%, range: −1.35 to 0.05; 95% prediction: −1.64 to 0.35 SMD= −0.26 (−1.57, 1.04), t=−0.86, P=0.479, τ^2=0.203, I²= 79%, range: −1.16 to 0.45; 95% prediction: −7.16 to 6.34 SMD = −0.66 (−2.99, 1.67), t=−3.60, P=0.172, τ^2=0.016; − 95% prediction: −2.99 to 1.67 SMD = −0.64 (−1.29, 0.00), t=−2.77, P=0.05, τ^2=0.196, I²=54.5%, range: −1.53 to 0.24; 95% prediction: −2.24 to 0.95 SMD= −0.830 (−1.25, −0.407), z=3.84, P<0.001 SMD= 0.04 (−0.72 to 0.80), t=0.65, P=0.634, τ^2=0.000

^aAll pooled estimates by R (meta), Sidik-Jonkman variance estimator with HKSJ adjustment

$t=-2.39$, $P=0.044$, $\tau^2=0.361$, $I^2=75.5\%$, range -1.74 to 0.66 , 95% prediction -2.06 to 0.98 – data indicate benefit, but heterogeneity is large resulting in a considerable uncertainty. A total of 32 pairwise comparisons between acupuncture ($N=1598$) and SGA/TCA ($N=1529$) were reported [189] – all Chinese trials, open-label. For all types of acupuncture, superiority is suggested with an overall SMD in end-study depression $= -0.23$ (-0.4 , -0.05), $P=0.01$. We recalculated to illustrate uncertainty: $\tau^2=0.272$, $I^2=80\%$, range -1.22 to 0.80 , and 95% prediction -1.31 to 0.86 . An SR/MA addressed RCTs of acupuncture + SSRI/SNRI ($n=438$) vs. SSRI/SNRI ($n=439$) (no add-on control) in 13 Chinese trials indicating around 22% higher risk of response. To illustrate uncertainty, $\tau^2=0.024$, $I^2=48$, range 0.89 – 1.66 , and 95% prediction 0.85 – 1.75 . An SR/MA on “perimenopausal depression” [190] indicated considerably higher response rates for acupuncture vs. SSRI/SNRI (14 open-label Chinese trials, 4–12 weeks, 511 acupuncture, 513 antidepressants; $OR=2.68$, 1.84 – 3.90 , $P<0.001$). We recalculated: $RR=1.12$ (1.05 – 1.19), $t=3.86$, $P=0.002$, $\tau^2=0.008$, $I^2=21\%$, range 0.94 – 1.33 , and 95% prediction 0.91 – 1.37 . Similar were observations of a meta-analysis of 4 open-label Chinese trials vs. antidepressants in postpartum depression [191]. Overall, (1). double-blind RCTs vs. sham indicate efficacy. Uncertainty (about effect/size) is considerable and arises from (i) biases commonly present even in these trials; (ii) small, single-center samples; and (iii) heterogeneity of effects (illustrated by “range of effects” and “prediction intervals”). (2). A variety of procedures (points) have been evaluated, and applicability to non-Chinese subjects is questionable.

20.5 Mindfulness Methods and Others that Include Meditation

Mindfulness-based cognitive therapy (MBCT) and stress reduction (MBSR) are well defined 8-week programs and are more thoroughly evaluated “types” of mindfulness-based treatments. A range of other procedures that incorporate elements of mindfulness exist [192].

MBCT for Acute Episodes Two SR/MAs [193, 194] combined report on 12 RCTs of MBCT (alone or adjunctive to antidepressants) in acute MDD. Of those, eight are controlled by active treatments [all graded at high risk of bias [193, 194]]. We use reported [194] data for these trials of MBCT ($n=249$) vs. various controls ($n=244$ – psychoeducation, CBT, rest and music, walking+treatment as usual, etc.) on end-study depression scores: $SMD= -0.33$ (95%CI -0.78 , 0.11), $t=-1.76$, $P=0.122$, $\tau^2=0.213$, $I^2=71.3\%$, range of effects -1.25 to 0.59 , and 95% prediction -1.56 to 0.89 . Data suggest a mild benefit, but uncertainty is high (bias, imprecision, heterogeneity).

MBCT for Prevention of Relapses Individual-patient data meta-analysis of RCTs in MDD patients in remission with 60 weeks of follow-up included 9 RCTs; in 5,

MBCT alone was compared to maintenance antidepressants (3 trials) or as add-on to antidepressants (1 trial) or to psychological treatment (1 trial) (total MBCT $n=443$ vs. 442 active controls): risk of relapse was consistently lower with MBCT – pooled $HR=0.79$ (0.64–0.97). No trial was blinded and blinded outcome assessment was problematic in 4/5 trials [195]. Another SR/MA [196] identified 5 RCTs of MBCT ($N=241$) vs. “treatment as usual” ($N=233$) (by design – lower level of evidence) for relapse prevention over 12 months (we recalculated in line with Table 20.1): $HR=0.74$ (0.33–1.64), $t=-1.06$, $P=0.349$, $\tau^2=0.319$, and $I^2=69\%$ – although an effect is suggested, imprecision and heterogeneity are extremely high. A 26-month extension study of 46 patients on MBCT vs. 46 on a health enhancement program indicated similar outcomes at 12 and 26 months in terms of disease severity and relapses [197]. An open-label multicentric 15-month Dutch study indicated a greater risk of relapses ($RR=1.50$, 95%CI 1.11–2.04; $P=0.02$; $HR=1.59$, 1.10–2.31) in patients treated with MBCT+antidepressants with gradual withdrawal of antidepressants vs. no withdrawal ($n=128$ and $n=121$, ITT) [198]. Blinded outcome assessment was adequately achieved, but dropout was considerable (28% and 31%, respectively). Overall, MBCT might be superior to antidepressants or other psychological treatments for relapse prevention over 1 year – but, uncertainty is high. Longer-term benefits vs. other options are highly uncertain.

Other Methods In a recent RCT in Hong Kong, behavioral activation with mindfulness was superior to “treatment as usual” regarding depression symptoms (BDI $SMD=-0.46$, -0.76 to -0.16) and occurrence of major depressive episodes (10.8% vs. 26.8%) (115 patients overall) [199].

“Far East” Mindfulness Methods Yoga (different varieties), Baduanjin exercise, Tai Chi, and Qi Gong were all addressed in a number of SR/MAs of RCTs (yoga predominantly in India, Tai Chi and Qi Gong in China) but practically exclusively for “depressive difficulties” in a variety of conditions. Generally, these trials are of poor quality and not of primary interest for this review [200–203]. For yoga, two small RCTs vs. usual care (e.g., antidepressants or similar) (total of 79 patients) in patients with depressive disorders indicated “no difference,” while comparisons vs. “relaxation” indicated a greater symptom reduction (3 trials, 99 patients) [201].

20.6 Dance Movement and Music Therapy

A Cochrane review on dance movement therapy identified only two small RCTs in MDD/dysthymia one with a wait list control and one vs. standard care (total of 107 patients), indicating greater reduction of symptoms with dance therapy, but uncertainty is extreme (bias, imprecision) [204]. Similar is the case with music therapy added to standard of care or antidepressants [205].

20.7 Exercise

Various forms of exercise have been evaluated in a large number of RCTs but almost exclusively related to postpartum depression. We mention two more recent SR/MAs (e.g., [206], [207]) as an example: no trials included specifically women with postpartum depression – trials were aimed at reduction of depressive difficulties postpartum.

20.8 Conclusion

Cumulatively, CAM interventions have been evaluated in a large number of RCTs for treatment of depressive disorders but considerably less than for “reduction of depressive difficulties.” Generally, existing trials, even for the most extensively evaluated interventions, are rather limited in extent and quality resulting in a high uncertainty about (a) whether the effect exists, (b) its size, and (c) a setting in which it is the most relevant.

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Chapter 21

Psychopharmacology Algorithms for Major Depressive Disorder: Current Status



Marsal Sanches, João Quevedo, and Jair C. Soares

Abstract Major depressive disorder (MDD) is one of the leading causes of disability worldwide, and a considerable portion of depressed patients does not respond well to available treatment strategies. Algorithm-based treatment may contribute to improving the MDD outcomes and have the potential to homogenize the pharmacological treatment of MDD patients, facilitating outcome research and cost-effectiveness analysis. This chapter provides a critical review of the available literature on the use of treatment algorithms for the management of MDD. The main available algorithms, their effectiveness, and challenges and limitations associated with their development are discussed. Finally, we provide a discussion of the future direction of algorithm-based treatments for MDD.

Keywords Major depressive disorder · Treatment · Algorithms · Antidepressants · Guidelines

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21.1 Introduction

Major depressive disorder (MDD) is one of the leading causes of disability worldwide and has a lifetime prevalence of 16% [1, 2]. In addition to the considerable degree of psychological suffering associated with that condition, the association between MDD and increased risk/worsening prognosis of medical conditions, such as stroke, heart disease, and diabetes, is well established. Furthermore, there is a strong association between MDD and suicide, with an almost 20-fold increase in the risk of death by suicide among MDD patients [3].

Moreover, the burden associated with MDD is aggravated by the fact that, despite the countless advances in the treatment of that condition, a considerable portion of depressed patients does not respond well to available treatment strategies. According to the findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, regarded by many as the largest and most significant antidepressant study ever conducted, only 33% of depressed patients achieved remission after one treatment step, with a cumulative remission rate of 70% after four steps [4]. Despite some methodological issues, which may have impacted the validity of the conclusions [5], these results point to an urgent need for novel strategies aiming at optimizing the treatment response in MDD.

While antidepressants continue to be some of the most prescribed medications in the world, the process of choosing a particular pharmacological agent instead of another is complex. Clinicians usually base their choice of therapeutic strategies in several different factors, including (but not limited to) the mechanism of action and side effect profile of different medications, patient's previous history of response to certain agents, sociodemographical data, family history information, risk of drug interactions, presence of medical comorbidities, and, more recently, results of pharmacogenetic testing [6]. Despite the existence of proposed treatment guidelines, the clinician's own judgment and his/her previous experience become the main determinants when it comes to the initial treatment of patients with MDD and, especially, to subsequent therapeutic recommendations in case of partial or nonresponse.

Not surprisingly, evidence indicates considerable variations involving antidepressant choice in clinical practice, with hundreds of different treatment sequences adopted by prescribers worldwide [7]. Nevertheless, the response to antidepressants seems to progressively decrease after several unsuccessful medication trials [4, 8], and clinical experience per se does not seem to be enough to achieve higher remission rates. Several cognitive biases may affect clinicians' choices of antidepressants, including selective memory towards positive response associated with specific agents in detriment of non-response. Moreover, the high rates of placebo response to antidepressants (as demonstrated in clinical trials) may affect clinicians' decision-making process. Available literature points to a strong relationship between early placebo response and subsequent relapse among depressed patients.

Algorithm-based treatment may offer several advantages in the treatment of MDD. Algorithms are easy to implement in clinical practice and may be utilized not only by psychiatrists but also by non-specialists. In addition to contributing to

improving patient outcomes, they have the potential to homogenize the pharmacological treatment of MDD patients, facilitating outcome research and cost-effectiveness analysis.

The present chapter provides a review of available literature on the use of therapeutic algorithms in the management of MDD. The main available algorithms, their effectiveness, and the challenges and limitations associated with their development are discussed. Finally, we provide a critical discussion on the future direction of algorithm-based treatments for MDD.

21.2 Rationale and Challenges in the Creation of Algorithms for Major Depressive Disorder

Given the large number of options for the treatment of MDD, the idea of a standardized step-by-step approach to guide clinicians across the different available therapeutic strategies sounds like an attractive and cost-effective approach. Nevertheless, some issues and limitations involved in the development of algorithms for the management of MDD have been discussed over the last several years [9–12]. Those include:

- a) Algorithms take a long time to develop. Given the rapid pace at which new treatments for depression are approved and delays involved in the preparation of an algorithm and in its subsequent publication, algorithms may be outdated/obsolete by the time they are available to clinicians.
- b) Lack of a standardized approach to create algorithms. Given the limited evidence regarding the superiority of certain antidepressant agents over others, algorithms for the treatment of depression are often based on consensus, anecdotal reports, and expert opinions instead of sound scientific evidence.
- c) Emphasis in monotherapy. Many algorithms still emphasize monotherapy among the initial strategies, in marked contrast with clinical practice, where the early combination of different pharmacological agents to optimize treatment response seems to be the rule instead of the exception. There is a paucity of studies specifically addressing combination strategies as second-step options, limiting the amount of evidence that could support augmentation strategies during the elaboration of an algorithm.
- d) Non-incorporation of residual symptoms, such as memory impairment and attentional problems, in the algorithm-based strategies. Evidence indicates that residual symptoms are of great importance from a functional standpoint, and are sometimes dissociated from the expected response associated with antidepressant treatment. As a rule, algorithms fail to incorporate residual symptoms in their sequential approaches.
- e) Disregard for specific features associated with depressive episodes in the elaboration of the algorithm. MDD episodes may present with different symptom profiles, with a predominance of certain types of symptoms over others. Evidence suggests that different antidepressants vary in terms of effectiveness according to the main characteristics of the depressive episode in question. For example, bupropion seems to be more effective in the treatment of depressive episodes associated with low energy/apathy than in anxious depressive states. These differences are not usually taken into account when an algorithm is created.
- f) Limited attention to non-pharmacological strategies. The role and the timing of psychotherapeutic interventions and non-pharmacological somatic therapies (with exception of electroconvulsive therapy) are often poorly explored in MDD treatment algorithms.

In summary, algorithms for the treatment of MDD may lack ecological validity, as their recommended sequential treatments often do not contemplate or address the clinical challenges and peculiarities commonly faced during daily clinical practice. Some exceptions to that rule will be discussed in the next section of the present chapter.

21.3 Algorithms for the Treatment of Major Depressive Disorder: Current Status

Although discussions about the potential benefits of an algorithmic approach for the treatment of MDD go back to the early 1980s [13], the development of algorithms became widespread only in the 1990s. There are currently several different available algorithms addressing the management of MDD, and some of them are discussed below. It is important to emphasize that a comprehensive review of each one of them falls beyond the scope of the present chapter, and more detailed information on the algorithms in question can be found in their respective original publications.

Furthermore, despite their importance, we are not contemplating, in the present chapter, algorithms developed as part of broader collaborative care studies, such as the Prevention of Suicide in Primary Care Elderly Collaborative Trial (PROSPECT) [14] and the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) [15]. Similarly, we did not include real-life clinical trials such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) [4], since its primary focus was not on the development of an algorithm but on the assessment of the efficacy and response (or lack of response) of depressed patients to different therapeutic interventions proposed in a sequential, step-by-step approach. A detailed description of the methods and results of the STAR*D trial falls beyond the scope of the present chapter.

21.3.1 The Texas Medication Algorithm Project

One of the first proposed MDD treatment algorithms, the Texas Medication Algorithm Project (TMAP), was developed to encourage evidence-based treatment of psychiatric disorders (including MDD) in the state mental health system [16]. It was specifically designed to allow a best-practices approach for the treatment of MDD while allowing some flexibility based on the clinician's judgment. The algorithm specifically states that any stages can be skipped or modified by the clinician at any point during the management of a patient, as long as the rationale behind that deviation is documented and justified [17].

In the TMAP (Fig. 21.1), first-line options for the treatment of depression include monotherapy with selective serotonin reuptake inhibitors (SSRIs), nefazodone, bupropion SR, venlafaxine XR, and mirtazapine. In the case of nonresponse, options

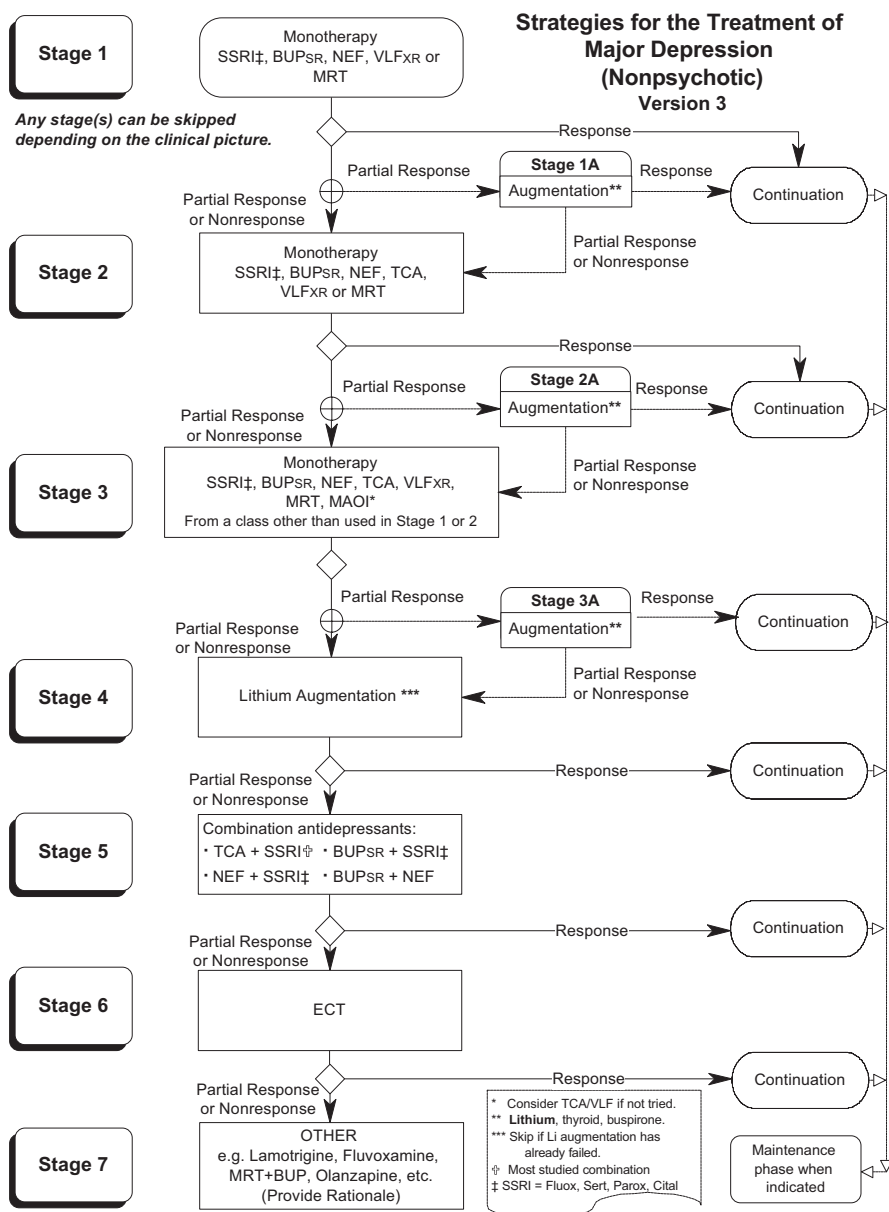


Fig. 21.1 The Texas Medication Algorithm for the treatment of major depressive disorder without psychotic features

Reproduced from the Texas Medication algorithm website (content in public domain, available at: <https://web.archive.org/web/20041013172939/http://www.dshs.state.tx.us/mhprograms/TMAPtoc.shtml>). SSRI selective serotonin reuptake inhibitor, BUP_{SR} bupropion SR, NEF nefazodone, VLF_{XR} venlafaxine XR, MRT mirtazapine, TCA tricyclic antidepressant, MAOI monoamine oxidase inhibitor, ECT electroconvulsive therapy

include switching to a different drug (preferably from a different class, unless in case of intolerance), augmentation with lithium or thyroid hormone, antidepressant combinations, a different class of medications (among the options above), electroconvulsive therapy (ECT) (stage 6), and other strategies, such as lamotrigine, fluoxetine, olanzapine, and others (stage 7). A separated algorithm is provided for the treatment of MDD with psychotic features (Fig. 21.2).

The TMAPP was initially implemented in a paper-and-pencil version, and analysis comparing the outcome of patients who received algorithm-based treatment and treatment as usual (TAU) indicated statistically significant differences, with better outcomes observed among the former (see next section) [18]. A computerized version of the TMAPP (CompTMAPP) was later developed and tested in a small parallel designed clinical trial, targeting its implementation and efficacy in primary care settings [19]. The results again indicated the superiority of the algorithm over TAU.

Despite its historical value and innovative approach at the time of its initial conceptualization, the TMAP for MDD was never updated, limiting its utilization in the current clinical scenario, more than 20 years later. Nevertheless, the principles utilized in its development inspired most of subsequently created algorithms, as discussed in the following sections.

21.3.2 The Psychopharmacology Algorithm Project at the Harvard South Shore Program

The Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS) has issued evidence-based algorithms for the treatment of depression since the early 1990s, and the most recent version of the algorithm for the management of nonpsychotic unipolar depression was released in 2019 [8].

The methodology utilized in the development of the algorithm simulates a curbside pharmacological consultation, where information on a hypothetical clinical situation (including previous treatment history) is provided and recommendations are made by the authors based on available evidence, including randomized clinical trials. Treatments are prioritized taking into account efficacy, tolerability, safety, and cost. The PAPHSS flowchart is comprised by a sequence of “nodes”, each one corresponding to a clinical situation warranting a decision involving treatment choices.

The algorithm places great emphasis on comorbidities and other clinical features of the depressive state, including an early recommendation for electroconvulsive therapy (ECT) in case of inpatient, severe melancholic depression with acute risk of suicide, catatonia, insufficient oral intake, or medical conditions that would limit the use of medications. Ketamine appears as a second option in those cases where ECT is refused or found to be ineffective, followed by venlafaxine, mirtazapine, or a

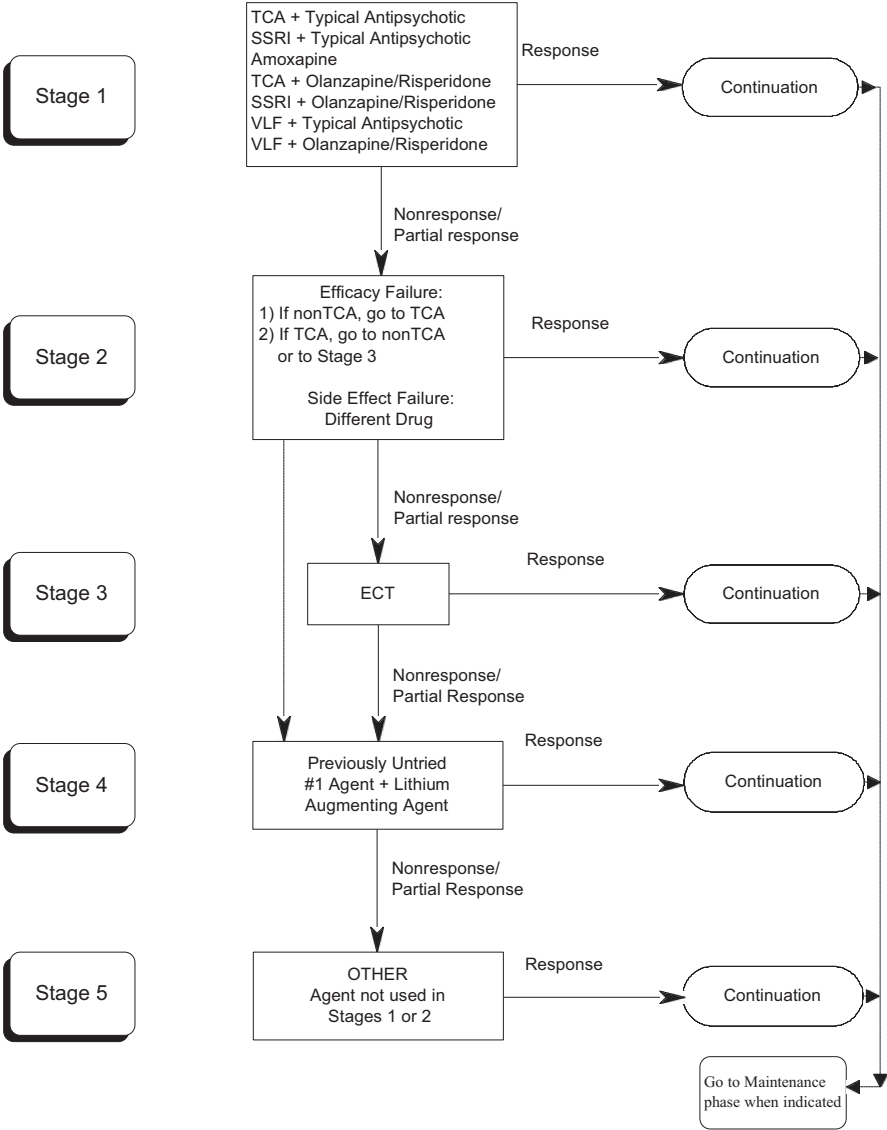


Fig. 21.2 The Texas Medication Algorithm for the treatment of major depressive disorder with psychotic features
Reproduced from the Texas Medication algorithm website (content in public domain, available at: <https://web.archive.org/web/20041013172939/http://www.dshs.state.tx.us/mhprograms/TMAPtoc.shtml>. SSRI selective serotonin reuptake inhibitor, VLF_{XR} venlafaxine XR, TCA tricyclic antidepressant, ECT electroconvulsive therapy

tricyclic antidepressant. For patients who do not fall into the inpatient, severe melancholic depression category, initial pharmacological strategies include sertraline, escitalopram, or bupropion. That is followed by several different options in terms of switching or augmentation strategies, including atypical antipsychotics, antidepressant combinations, lithium, T3, light therapy, nutraceutical agents, and transcranial magnetic stimulation (TMS). Patients who do not respond to the initially proposed trials are considered to have treatment-resistant depression, and different steps for the management of those patients are proposed, taking into account the presence or not of comorbidities and of atypical features.

Last, patients who do not show satisfactory response to the treatment-resistant depression management steps (usually including at least four or more medication trials, as well as ECT) are classified as having “highly treatment-resistant depression”. The evidence involving therapeutic options for these patients is very limited and includes novel pharmacological interventions as well as invasive neurostimulation techniques, such as vagus nerve stimulation (VNS). The PAPHSS does not include systematic recommendations for the management of this group of patients, given the multiple peculiarities involved in their management and their unfitness for inclusion in a general algorithm.

A separate algorithm (last updated in 2018) addresses the treatment of MDD with psychotic features. Both MDD algorithms can be consulted at a publicly available website (website (www.psychopharm.mobi)).

21.3.3 The Korean Medication Algorithm for Major Depressive Disorder (KMA-MDD)

The Korean Medication Algorithm for Major Depressive Disorder (KMA-MDD) was created by the Korean Society of Depressive and Bipolar Disorder, utilizing an evidence-based approach and a consensus panel, comprised by 21 Korean experts [20]. Of notice, it was specifically designed to reflect specific characteristics of depressive disorders and their treatment in Korea. Available evidence was categorized into three levels, with level A comprising only placebo-controlled, randomized, double-blinded clinical trials, level B including open trials and retrospective studies, and Level C corresponding to case reports and expert opinions. The algorithm was developed between 2001 and 2003 (but published only in 2006) and offers two separate stepwise sequences for the management of MDD patients with and without psychotic features. In the case of MDD without psychotic features, the initially recommended antidepressant monotherapy (Stage 1) includes paroxetine, fluoxetine, sertraline, venlafaxine, or mirtazapine. Stages 2 and 3 continue to emphasize antidepressant monotherapy, including SSRIs, venlafaxine, mirtazapine, bupropion, milnacipran, moclobemide, TCAs, tianeptine, trazodone, and St. John’s wort. Stage 4 includes augmentation with lithium, valproic acid, or carbamazepine, as well as several possible antidepressant combination strategies. ECT appears as a stage 5 strategy.

Finally, several additional strategies (such as augmentation with buspirone, thyroid hormone, risperidone, and stimulants) are listed as stage 6 options. The sequence for treatment on MDD with psychotic features differs significantly from the one targeting patients without psychotic features and preconizes the combination of antidepressants and antipsychotics as the core treatment strategy, with different alternatives in terms of treatment combinations, as well as several additional augmentation strategies. It also includes the possibility of amoxapine as a possible stage 2 strategy, as well as early use of ECT (also as a stage 2 option).

The KMA-MDD is very simple and easy to implement in clinical practice. However, it is outdated and does not reflect the several new strategies currently available for the treatment of MDD.

21.3.4 The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders was updated in 2013 [21]. It provides recommendations for the management of depressive disorders based on available evidence, ranked from category A (full evidence from controlled studies) to F (lack of evidence). Those are subsequently translated into five different types of recommendation grades (ranging from 1 to 5), which take into consideration not only the category of available evidence but also the risk-benefit ration. For example, recommendation grade 1 is based on the availability of category A evidence and a good risk-benefit ratio. A stepped-care model, considering different levels of care, with respective focuses and interventions (according to the severity of the depressive states), is also included.

The algorithm included in the WFSBP guidelines includes recommendations for initial choice of antidepressants (recommendations grades 1 to 5), which should be based on different factors, such as previous treatment history, severity, comorbid psychiatric and medical conditions, safety/side-effect profile, and the patient's preference, among others.

In the case of poor response within 2–4 weeks, the next step recommendation is for dose optimization, as long as the medication is being tolerated. Adding mirtazapine (in case the initial antidepressant is an SSRI) is listed as a second step, followed by different augmentation options, including first-line augmentation strategies (quetiapine, aripiprazole, and lithium), and second-line strategies (thyroid hormone and olanzapine in combination with fluoxetine). Psychotherapy is recommended to be considered as an add-on therapy at any time during treatment. Adding ECT appears as the final step in case augmentation and switching medication strategies fail, although the guidelines emphasize it can be considered a first-line treatment in certain circumstances, included but not limited to severe MDD with

psychotic features, severe MDD with psychomotor retardation, other situations where rapid relief of depression is required (e.g., refusal of food intake), situations where medications might be contraindicated (e.g., pregnancy), and previous positive response to ECT.

Overall, the guidelines and the included algorithm are comprehensive yet succinct, and their straightforwardness makes it user-friendly and of easy implementation in clinical practice. However, they have not been updated since 2013, and some treatment modalities already incorporated into some of the newer algorithms (e.g., TMS) are not properly contemplated in WFSBP guidelines.

21.3.5 The Florida Best Practice Psychotherapeutic Medication Guidelines for Adults with Major Depressive Disorder

The Florida Best Practice Psychotherapeutic Medication Guidelines (FPG) for Adults with Major Depressive Disorder were based solely on randomized, placebo-controlled trials, as well as pooled, meta-analysis, and network analysis, and the expert panel responsible for the consensus included not academicians but also multiple stakeholders, such as advocacy and public health policy experts [22]. The algorithm is organized hierarchically, at different levels, based on the available evidence regarding efficacy, tolerability, and safety of the different agents. It also takes into account patients' preferences, prior response history, and comorbidities, among other clinical features, but does not provide different recommendations for outpatients versus inpatients.

Of notice, the FPG for MDD is the only available algorithm to address MDD with mixed features and is comprised by three different subsections: one addressing MDD without mixed features or psychotic features, one focusing on MDD with mixed features but no psychotic features, and a third one targeting MDD with psychotic features. For MDD without mixed features or psychosis, step 1 recommendations include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, bupropion, mirtazapine, or vortioxetine. Level 2 includes mentions to dose optimization and adherence, as well as switching and augmentation strategies, adjunct and aerobic exercise, and evidence-based psychotherapies, such as cognitive-behavioral therapy and interpersonal therapy. Level 3 includes different augmentation strategies, in addition to tricyclic antidepressants, monoaminoxidase inhibitors, ECT, and TMS. Finally, level 4 introduces L-methylfolate combination, triple drug combinations, MAOI augmentation, and other neuromodulatory techniques, including VNS. The algorithm for management of MDD with psychosis emphasizes the need for the combination of an antidepressant and a second-generation antipsychotic, with considerations about ECT, which can be considered as initial treatment in case of concerns about patient welfare.

Finally, the recommendations for treatment of MDD with mixed features highlight the role of second-generation antipsychotics and mood stabilizers and, although allowing the possibility of monotherapy with antidepressants, warns about the risk of limited response associated with that strategy. The different subsections of the FPG algorithm are in the public domain and can be freely accessed at a publicly available website (www.medicaidmentalhealth.org).

21.3.6 The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder

One of the most comprehensive MDD management guidelines available, the CANMAT 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder is based on the review of studies published between 2009 and 2015, as well as the review of other guidelines and major reports [23]. The different lines of treatment (first, second, and third-line) are established according to the available level of evidence, ranked from 1 to 4. The guidelines emphasize that, despite the multiple factors involved in the selection of an antidepressant, the available evidence is still inconsistent with respect to the ability of many of these factors to predict the antidepressant response (e.g., in the case of age, gender, or ethnicity). Moreover, the guidelines highlight that, with regard to DSM depressive episode specifiers, most of the large trials have not found differences in treatment response involving different antidepressant agents, although older studies seemed to indicate a superior response of MAOIs in the treatment of those patients. They also emphasize that, based on available literature, the combination of an antidepressant with an antipsychotic is superior to monotherapy with either of those agents in the treatment of MDD with psychotic features.

The guidelines include an algorithm for the management of inadequate response to antidepressants, which is based on the initial selection of a first-line antidepressant (an SSRI, an SNRI, bupropion, mirtazapine, mianserin, milnacipran, vortioxetine, or agomelatine), while further steps taking into account the presence or absence of early response to treatment (2–4 weeks), different factor involved in the decision of switching medications versus utilizing an augmentation strategy, the presence of symptom remission, and risk factors for recurrence. Risperidone, aripiprazole, and quetiapine are listed as first-line augmenters, while brexpiprazole, bupropion, lithium, mirtazapine/mianserin, modafinil, olanzapine, and thyroid hormone are considered second-line augmentation strategies. Of notice, augmentation with ketamine is listed as an acute experimental treatment strategy in the CANMAT 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder, while stimulants, tricyclic antidepressants, and ziprasidone are considered third-line augmentation strategies.

Each decision refers the reader to different tables, where the level of evidence and the factors to be considered at each clinical decision are listed. Despite the fact that the algorithm in question is extremely comprehensive and based on sound literature findings, it is our opinion that its complexity makes it difficult to implement in regular clinical settings.

21.4 Are Algorithms for the Treatment of Major Depressive Disorder Superior to Treatment as Usual?

One of the earliest studies to address the question of superiority of algorithm-based treatment compared to treatment as usual (TAU), Adli et al. [24] looked into the impact of a standardized stepwise approach for inpatients with depression admitted to an academic center. The algorithm utilized was comprised by a sequential therapeutic process, which included antidepressant monotherapy, sleep deprivation, augmentation with lithium, monoamine oxidase inhibitors, and ECT. There was no control group, and the Bech Rafaelsen Melancholia Scale (BRMS) was adopted as the primary outcome measure. Of notice, just 48% (119 out of 248) of the depressed inpatients admitted to the service in question during the study timeframe were enrolled, due to issues related to relatively low acceptance rates of the algorithm by clinicians. The intention-to-treat analysis indicated remission rates of 38%, while 34% of the subjects showed a decrease equal to or higher than 50% in the BRMS. The open nature of the study and the absence of a control group limit the interpretation of the findings. In fact, the results in question were considered preliminary findings of a more comprehensive, multistep project aiming at analyzing the impact of antidepressant treatment algorithms, the German Algorithm Project. The subsequent, randomized portion of the study included a small, single-centered trial, and a nationwide, randomized controlled study to evaluate the efficacy of algorithms compared with TAU.

Trivedi et al [18] carried out a prospective trial, analyzing the effectiveness of the TMA on the treatment of MDD in the public mental health system in Texas. A total of ten prematched mental health clinics were included in the study, with four providing algorithm-based treatment and six offering TAU. The primary goal of the study was to look into differences between both approaches with respect to early improvements and overall clinical outcomes over a 1-year period. The Depressive Symptomatology–Clinician-Rated Scale, the Medical Outcomes Study 12-item Short-Form Health Survey (SF-12), and the Depressive Symptomatology–Self-Report Scale were adopted as outcome measures. Improvements were observed in both groups, but the patients who received algorithm-based treatment displayed greater decreases in the depression scales and greater improvements in the SF-12 compared to the TAU group.

Furthermore, Bauer et al. [25], published the second-wave of results of the German Algorithm Project, represented by a randomized, prospective, single-center study, in the management of inpatients with depression. The algorithm-based treatment group and the TAU group were comprised by 74 patients each. Time to

remission was shorter among the patients assigned to algorithm-based treatment, while medication changes and the number of psychotropic medications were greater in the TAU group. The study has several methodological limitations, including the lack of blindness of patients and clinicians with respect to the group assignment and the fact that patients in both treatment groups were treated by the same group of clinicians, raising issues about possible cross-contamination.

Another group [26] compared the efficacy of algorithm-guided treatment (composed of four treatment strategy steps) with TAU in the management of outpatients with mild and moderate MDD without psychotic features. A total of 240 patients were enrolled in the study, with 83 assigned to the algorithm-based treatment group and 127 participants assigned to TAU. The method utilized for group assignment is not described and only three patients in the algorithm group entered the third step of the 4-phase utilized algorithm, while no patients entered the fourth step.

Finally, in 2017, the results of the third phase of the German Algorithm Project were published [27]. This was a multicenter study, carried out in 10 different psychiatric departments in Germany. The participants were randomized into five different arms; three of them consisted of algorithm-based treatment, one proposing medications and less specific recommendations, based on a computerized documentation and expert-based system, and the last one consisted of TAU. The three algorithm-based approaches differed with respect to the proposed second-step strategies, with one recommending lithium augmentation, the second one offering antidepressant dose escalation, and the third one preconizing switching to a different antidepressant. The results favored the algorithm-based treatments, with higher rates of remission at discharge observed in the antidepressant dose escalation algorithm group, while the TAU group showed the lowest remission rates (89.2% versus 66.2%). Time to remission was also shorter among the former compared to both TAU and the computerized documentation and expert system.

Another group [28] looked into the impact of a three-phase stepwise treatment algorithm on the outcome of hospitalized patients with depression. The algorithm utilized consisted of 3 phases, the first one comprising monotherapy antidepressant with either venlafaxine or imipramine, the second one augmentation with lithium, and the third one ECT. Patients were initially randomized to either venlafaxine or imipramine, with the two subsequent steps offered to all patients with no satisfactory response to the antidepressant monotherapy. A total of 85 patients participated in the three-phase algorithm, with a dropout rate of 28%. The modified intention-to-treat analysis revealed a response rate of 71% by the end of the third phase, with a remission rate of 46%. There was no control group and, since the study was embedded within a randomized antidepressant clinical trial (which corresponded to the first phase of the proposed algorithm), the results of this study need to be interpreted with caution. Remission rates were lower in the algorithm-based treatment group, while the median number of treatment days to remission was higher in the TAU group. On the other hand, dropout rates secondary to intolerance were significantly higher in the algorithm-based group, probably due to a higher degree of physician's flexibility as for continuing versus switching medications due to intolerance in the TAU group.

Last, in a recent study, the cost-utility of stepped-care algorithms in the treatment of depression was analyzed [29]. The economic evaluation utilized a state-transition model, combining evidence on clinical effectiveness and costs from different sources, including clinical data, expert opinion, and effect sizes from meta-analyses. The cost-utility analysis revealed, for mild MDD, better health outcomes against lower costs associated with guideline-congruent stepped care. For moderate and severe MDD, the model indicated a 67% likelihood of health gains at higher costs associated with the stepped-care approach. The findings in question support the hypothesis that cost-effective health gains can be reached following guideline-based, stepped-care algorithms.

In summary, available literature findings support the notion that evidence-based algorithm-based treatment is effective in optimizing the treatment of depression. The use of algorithms seems to contribute to better patient outcomes when compared to treatment as usual, likely in a cost-effective way. Furthermore, there is limited evidence on the cross-comparison of different algorithms, making it difficult for clinicians to choose one algorithm over other in light of the available data.

21.5 Obstacles to the Implementation of Algorithms in Clinical Practice

Even though available evidence highlights the potential benefits of the use of algorithms in clinical practice, several issues can be raised with regard to their implementation. Those include resistance from clinicians and administrative obstacles related to the frequency and duration of clinical encounters and to the availability of medications and other therapeutic modalities incorporated into the algorithm [11, 30].

In addition, risks involved in the development and implementation of treatment algorithms have been previously discussed [10]. Potential problems include incorrect algorithm formulation (based on lack of evidence or mistakenly interpretation of available literature findings) and inappropriate application of algorithms by clinicians and administrators. Limited education as for how the algorithm should be utilized may lead physicians to question their own clinical judgment and to deny the need to deviate from an established algorithm in certain circumstances.

21.6 Perspectives in the Use of Algorithms in Major Depressive Disorder

Future directions in the development of algorithms include the need to incorporate the growing amount of evidence on the treatment of MDD in a timely way. For example, the last several years have witnessed the conceptualization of different

forms of neurostimulation, including invasive (e.g., VNS and deep brain stimulation) and noninvasive ones (TMS, ECT, magnetic seizure therapy, among others). Many of them are still at an experimental stage, making their assimilation into a treatment algorithm difficult but, as the evidence on their efficacy continues to grow, their inclusion in algorithms targeting specifically treatment-resistant MDD will be of high interest.

In addition, the advances observed in the field of pharmacogenomics over the last several years have enabled the creation of pharmacogenomic-based MDD treatment algorithms. Although some initiatives (e.g., Hall-Flavin et al) [31] have identified positive results associated with the use of pharmacogenomic algorithms, it is not yet possible to affirm that the systematic genotyping of patients with MDD as a way to optimize medication choices and dosages is associated with superior outcomes when compared with treatment as usual [6]. Ideally, evidence will eventually allow the integration of pharmacogenomic data into broader MDD treatment algorithms, providing clinicians with additional guidance regarding the different therapeutic choices available, especially in dilemma situations involving resistant cases.

Last, a considerable amount of research has focused on the possible role of proposed mood disorder biomarkers (e.g., neuroimaging findings) as predictors of response to certain therapeutic interventions. Despite some promising findings and their potentially revolutionary impact on the treatment of MDD, the current status of biomarker research does not yet allow or contemplate the inclusion of biomarkers in treatment algorithms.

21.7 Conclusions

The role of algorithms in the treatment of MDD has been an extensive source of discussion. Despite its demonstrated efficacy and promising role in improving outcomes in MDD, algorithms still seem to be subutilized. Clinicians' education as for the potential benefits associated with algorithm implementation, as well as its actual role, represents a promising area for research. Similarly, the conceptualization of an ongoing system allowing the quick and continuous update of algorithms would be of high interest.

Moreover, most of the currently available algorithms do not contemplate more recently developed treatment interventions, including ketamine and vagal nerve stimulation. Other neurostimulation approaches, such as deep brain stimulation and magnetic seizure therapy, are currently under investigation and seem to correspond to promising approaches in the treatment of severe, resistant MDD.

Finally, the incorporation of pharmacogenetic and biomarker data into MDD treatment algorithms would have the potential to revolutionize the practice of psychopharmacology as we know it, allowing a more precise approach for the treatment of depression and, by default, optimizing response rates.

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Part IV
Promising Future Treatments for
Depression

Chapter 22

“Novel Psychopharmacology for Depressive Disorders”



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and Andrea Fusco

Abstract Major depressive disorder carries a significant burden and a high risk for suicide. The need for more effective, safer, and faster-acting drugs is, therefore, compelling. The present chapter briefly assesses the most promising agents, focusing on non-monoamine-targeting compounds, namely, the glutamate antagonist ketamine and its enantiomer esketamine. A critical overview of the evidence and the pitfalls associated with current antidepressant drug development is likewise provided in the following text.

Keywords Major depressive disorder · Ketamine · Esketamine · Novel antidepressant · Treatment resistance

22.1 Introduction

Major depressive disorder (MDD) represents the second leading contributor to chronic disease burden as measured by “years lived with disability” among all medical conditions [1]. MDD also inflates the risk for subsequent cardio- [2] and cerebrovascular diseases [3] and suicidal behavior [4]. Psychotherapy and

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neuromodulatory interventions represent common therapeutic strategies for MDD, although pharmacotherapy remains the cornerstone treatment of modern management of depression [5]. However, despite the recent advances in the understanding of the neurobiology of MDD [6, 7], the efficacy and tolerability rates of common antidepressants significantly vary across active- and placebo-controlled trials [8], as the adopted methods likewise do [9]. For example, the remission rate seen in phase 1 treatment with a standard antidepressant drug in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial approximates 27.5% based on the Hamilton depression rating scale (HDRS) [10] score [11]. Subsequent treatment phases of the STAR*D trial – the most extensive and most consequential antidepressant study ever conducted to date – lead to a negligible increase in remission or response rates [12]. Large-scale randomized clinical trials such as the “Combining Medications to Enhance Depression Outcomes” study documented similar outcomes [13]. Also, the operational definitions for treatment-resistant depression (TRD) and related phenomena [14] vary across different literature sources and different presentations of MDD [15].

Besides the aforementioned methodological issues, novel pharmacological interventions for depression are therefore warranted, especially considering that, with the notable exception of ketamine, the market is “running dry” on novel antidepressants for several reasons [16].

Therefore, the present chapter aims to succinctly appraise the most promising novel pharmacological opportunities in the treatment of major depression, alongside a critical appraisal of the boundaries toward the discovery of novel antidepressant drugs.

22.2 Monoamine-Targeting Antidepressants

The monoamine neurotransmitters serotonin (5-hydroxytryptamine or 5-HT), norepinephrine (NE), and dopamine (DA) had initially been implicated in the pathophysiology of MDD following the acknowledgment that compounds such as the antihypertensive drug reserpine reduce their levels and that some patients taking these drugs lead to the development of MDD [17]. The monoamine theory of depression had a tremendous impact on the regulatory affairs and the standard clinical practice, with monoamine-based drugs still dominating the field of modern psychopharmacology of MDD [18], with a few exceptions such as the melatonin-modulator antidepressant agomelatine [19]. Nonetheless, many studies measuring plasma, urine, and cerebrospinal fluid concentrations of 5-HT and NE metabolites, as well as postmortem studies, yielded inconsistent results [20]. Besides, monoamine-targeting drugs affect these systems in a matter of hours after administration, whereas the antidepressant effect could usually be achieved after several weeks, if ever [21]. Changes in the brain gene expression that occur after uninterrupted treatment with drugs targeting the monoamines might underlie their therapeutic effects [22], rendering the monoamine theory of depression too simplistic [20]. Therefore, even the usefulness of the standard classification of

antidepressant drugs, based on the specific effects on individual monoamine neurotransmitters, has been challenged in favor of the so-called *Neuroscience-based Nomenclature Second Edition* (NbN2) [22] as well as more sensible, neurobiologically-grounded classification frameworks, such as the Research Domain Criteria (RDoC) [23].

Quite new monoamine-modulating antidepressants include the multimodal agent vortioxetine [24] and the serotonin partial agonist reuptake inhibitor (SPARI) vilazodone [25]. Vortioxetine acts as 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} partial agonist, and 5-HT_{1A} agonist, and a 5-HT transporter inhibitor. Inhibition of the serotonin transporter (SERT) with stimulation of 5HT-1A presynaptic receptors associated with a blockade or partial blockade of presynaptic 5HT-1B and 5HT-1D and postsynaptic 5HT-7 receptors concurs to raise 5-HT levels at multiple nodes within neural networks across the brain [26]. Vilazodone could rapidly increase the levels of 5-HT, which may theoretically reduce the lag phase of antidepressant effect. However, such an assumption has been debated [27], whereas a rapid increase in 5-HT levels may result in poor tolerability, especially at the gastrointestinal tract. Besides, dose titration must be slowed down in order to attain full dosing, which would also slow down any potential rapid antidepressant onset [27]. Finally, SPARI actions could theoretically lead to lesser sexual dysfunction due to lesser degrees of SERT inhibition than selective serotonin reuptake inhibitors (SSRIs) [25]. However, head-to-head randomized controlled trials (RCTs) comparing vilazodone efficacy and tolerability with established antidepressants are warranted. Overall, while most recently introduced monoamine-targeting antidepressants would represent an advance in the management of MDD, especially from a tolerability perspective concerning the selective serotonin reuptake inhibitors (SSRIs) and other established drugs [28] – yet not that harmful as historically claimed [29] – novel antidepressants acting on different pathways, ideally addressing further therapeutic unmet needs, are nonetheless warranted, as recently reviewed elsewhere, taking into account a broad range of potential non-serotonergic novel antidepressant compounds [30].

22.3 Ketamine as a Novel Antidepressant

Rapid onset of action and improved efficacy for TRD cases and those with prominent suicidal ideation/attempt(s) are among the compelling needs to be addressed by novel antidepressant drugs, including those targeting glutamate or other non-monoaminergic pathways [30, 31].

Recent studies on the pathophysiology of MDD found abnormalities in glutamate, along with dendritic and synaptic atrophy in neural circuits [32]. Glutamate, which is by a wide margin the most abundant excitatory neurotransmitter in the central nervous system (CNS), and glutamatergic *N*-methyl-D-aspartate (NMDA) receptor modulators, in particular, represent essential targets toward the exploration on novel antidepressant drugs [32, 33], especially for MDD cases at high risk for suicidal behaviors [34], as postulated for bipolar disorder (BD) too [34]. The NMDA

receptor antagonist ketamine may contribute to fast excitatory glutamate transmission, enhanced release of brain-derived neurotrophic factor (BDNF), and synaptogenesis [35].

Several open-label studies [36–38], RCTs [39–42], and meta-analyses [43, 44] found that subanesthetic doses of ketamine have rapid antidepressant – typically, “a matter of hours or a few days” in contrast to 7 days or longer or even “several weeks” as for standard monoamine-based antidepressants [45] – and anti-suicidal effects [46]. Nevertheless, the intravenous administration route required by ketamine reduces its applicability in the clinical practice, especially in the outpatient setting [47].

Esketamine, an enantiomer of ketamine that also modulates glutamatergic transmission [48], has been used in the treatment of patients with TRD [49] as an intranasal formulation [50]. Intravenous administration of esketamine resulted in a rapid antidepressant effect in TRD patients [51]. However, the RCTs assessing the efficacy and tolerability of intranasal esketamine in the treatment of depression pointed toward mixed results [52, 47, 53, 54]. A recent meta-analysis covering 4 RCTs fetching 7 active arms encompassing 708 MDD patient total did, however, suggested an overall effect of esketamine adjunctive to standard antidepressants [46]. Specifically, adjunctive intranasal esketamine outperformed placebo in terms of study-defined response (usually 50% or more reduction in the total scale of a given rating scale for depression at study endpoint vs. baseline record) (risk ratio [RR]=1.39, 95% confidence interval [C.I.]=1.18–1.64, $p<.0001$) and rates of remission (a reduction below an absolute value at a given standard rating scale for depression) (RR=1.42, 95% C.I.=1.17–1.72, $p=.0004$) at endpoint assessment. Adjunctive intranasal esketamine had greater study-defined response starting at 2 h (RR=2.77, 95% C.I.=1.62–4.76, $p=.0002$), peaking at 24 h (RR=5.42, 95% C.I.=1.38–21.20, $p=.02$), and lasting at least 28 consecutive days (RR=1.36, 95% C.I.=1.16–1.58, $p=.0001$). Intranasal esketamine resulted in greater study-defined remission starting at 2 h (RR=7.71, 95% C.I.=2.16–27.55, $p=.002$), peaking at 24 h (RR=6.87, 95% C.I.=1.55–30.35, $p=.01$), and lasting by 28 days (RR=1.38, 95% C.I.=1.11–1.72, $p=.004$). However, intranasal esketamine leads to higher discontinuation rates due to poor tolerability (RR=3.50, 95% C.I.=1.38–8.86, $p=.008$), albeit acceptability (discontinuation due to any cause) and lack of efficacy did not differ versus placebo [46].

Even though the scarcity of controlled trials about intranasal esketamine as an augmentation to standard antidepressants, such therapy maintains a high degree of momentum worldwide [55]. Please refer to the editorial by Bahr R. et al. 2019 for a critical essay about the roadmap of the pivotal trials leading to the US Food and Drug Administration (FDA) approval of esketamine nasal spray adjunctive to standard antidepressants for TRD – Janssen® Spravato™ [56]. Without doubt, the “breakthrough,” “novel” antidepressant esketamine was accompanied by both enthusiasm [57] and concerns about the actual efficacy, safety, and even its regulatory process [58] of the compound in the treatment of depression [59]. Among other concerns raised about esketamine nasal spray for TRD, the fact that phase 3 program leading to the FDA approval included three pivotal trials and that in only one study by Popova et al. [53] there was a statistically significant separation from

placebo on the primary endpoint. The effect size documented by Popova et al. was 0.30, which is quite a small one. Besides apparent efficacy concerns, the control condition appears more tolerated, except for a few individuals experiencing dissociation even with placebo. Finally, the response seen with intranasal esketamine was recorded early and sustained over the trial, but there was no further gain in advantage beyond the initial separation from placebo so that the actual benefit from prolonged maintenance appeared uncertain to Dr. Schatzberg [60]. While continued use of esketamine in rodents extends its acute neuronal spine-producing effects to produce stronger interneuron communication [61], how much and for how long esketamine should be maintained in TRD humans remain uncertain. The current package insert for the drug in refractory depression does, however, recommend twice-weekly administration for 4 weeks, once weekly for 4 weeks and then beyond 8 weeks, and once weekly or once every 2 weeks, aiming for the least frequent dosing to maintain response or remission – please refer to the most current FDA webpage or the manufacturer for additional information or elsewhere [56]. Besides, it has been reported that the acute antidepressant effects of esketamine are blocked when the patient undergoes pretreatment with the μ -opioid receptor competitive antagonist naltrexone (also blocking κ -opioid receptor and, to a far lesser extent, the δ -opioid receptors), leading to the suggestion that μ -antagonism may be responsible for the antidepressant effects of esketamine, even if the NMDA antagonist effect a core antidepressant mechanism of esketamine could not be ruled out, especially for sustaining response after acute administration [62]. In response to commentary by Schatzberg 2019 [60] and his 2014 editorial calling for prudence about the potential of abuse for ketamine injection [63] – yet reinforced by the briefing documented released by the FDA in the year 2019 [64] – several authors, including some involved in the pivotal registration trials for esketamine, remarked that a critical point in interpreting the $RR=0.30$ is the fact that the saline placebo comparator was not administered alone but in combination with a newly initiated oral antidepressant, selected for each participant as one that had not previously failed [65]. The use of an active control arm likely decreased the difference in improvement, and thus even an effect size of 0.30 is remarkable in this context (almost every registration trial needs to outperform placebo alone). Also, the attenuation of the pretreatment with oral naltrexone, essentially a μ - and κ -opioid receptors antagonist, may suggest that the initial antidepressant effect seen with esketamine may at least in part depend upon release of endogenous opioid receptors, albeit the standard 0.5mg/kg i.v. ketamine used for antidepressant effect may be too low to produce direct activation of μ -opioid receptors [65]. At writing time, it remains debated whether opioid antagonism is needed to promote the antidepressant effect of ketamine [66]. Similarly, the claimed abuse potential due to the dissociative effects carried by ketamine and its derivatives seems unlikely at the subanesthetic dose used for TRD [65]. Overall, caution in overinterpreting opiate receptor stimulation as mediating antidepressant effects of ketamine is nonetheless warranted [67], and clinical predictors of ketamine response in TRD (including studies involving the often rapid-acting electroconvulsive therapy and psychotherapy control subjects) should be further explored alongside with additional acquisitions about the complex molecular mechanisms involved in its antidepressant and anti-suicidal efficacy [68], especially for

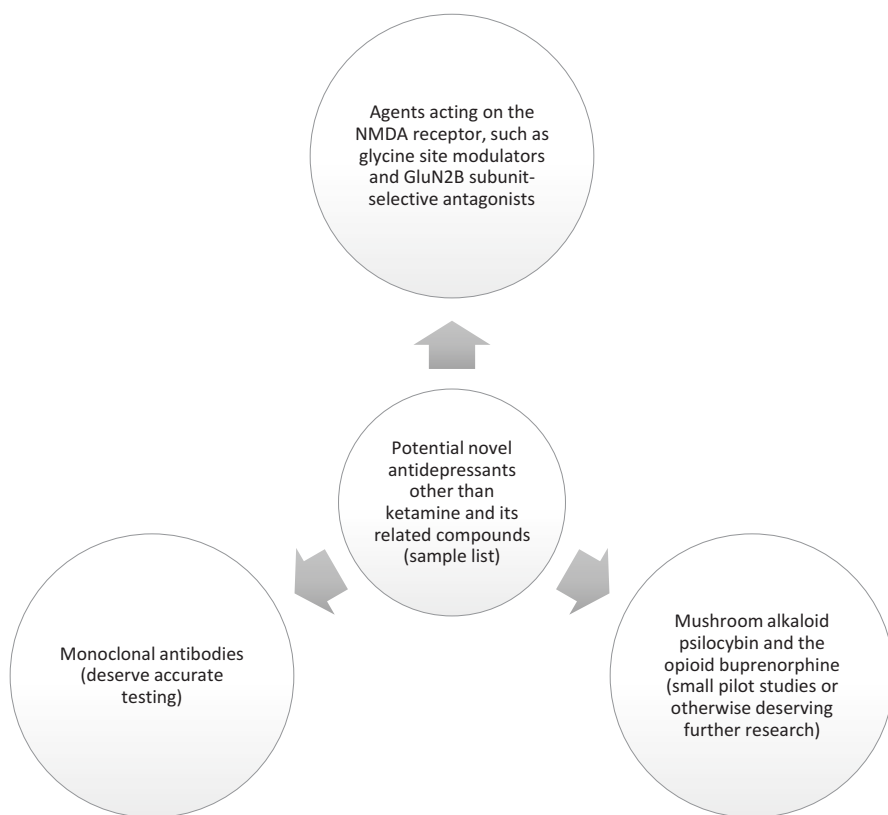


Fig. 22.1 This is just an overview of some of the potential novel compounds. Additional drugs are currently in their Phase-II or Phase-III testing, as documented elsewhere. (Please refer to Refs. [70, 71] in particular)

long-term use of the drug [69]. Additional non-ketamine alike approaches for depression warrant controlled investigation; however the final reader is encouraged to refer to Fig. 22.1 for an essay and to the work by Chaki S., 2017 for details [70] and Garay R.P. (2017) for TRD in particular [71].

22.4 Boundaries Toward “Novel Psychopharmacology” and Future Perspectives

Low productivity, rising research and development (R&D) costs, dissipating proprietary products, and dwindling pipelines are driving the pharmaceutical industry toward unprecedented challenges [72]. The field of psychopharmacology makes no exception. Large pharma companies generate maximal revenues and spend the most on R&D activities. However, many large pharmaceutical brands avoid investing in

products with lower or moderate market size potential (usually below \$300 million potential). The “annus horribilis” suffered by European neuroscience in 2010 as the result of the GlaxoSmithKline®, AstraZeneca®, Pfizer®, Merck®, and Sanofi® all announcing significant reductions in their research efforts into traditional drug discovery for the treatment of neuropsychiatric drug disorders has been well documented [73]. Globally, about 4.4% of the general population suffer from MDD, thus representing a relevant “market” for the pharmaceutical industry [74]. However, most pharmaceutical companies are increasingly reluctant to invest in new antidepressant drug development despite most monoamine-targeting antidepressant drugs’ patents expired. Data from the center of medical research suggest that phase 2 clinical trials account for over 70% failures and attrition rates overall (read no revenue) [72]. The development of new antidepressant drugs has reached a plateau [75]. Attempts to reduce the side effects of the antidepressants, improve effectiveness, and address concerns over the delayed onset of action have also led to a small number of newer antidepressants reaching the market [76]. As placebo-response rates rise, effect sizes shrink, and more studies fail or are negative [77, 78]. On the contrary, whenever the antidepressants outperform a placebo at improving depression, this does not necessarily mean they treat the total disorder [79].

The antidepressant drug discovery process locked into an iterative loop able to produce only variations (“drug repurposing”) of established psychotropic drugs [80], prompting for more valid animal models of depression supported by deeper neurobiological insights about MDD and subsequent pharmacological biosignature [81, 82]. However, drug repurposing in psychiatry may still be worth in some cases, as exemplified by the anesthetic drug ketamine and its enantiomers for TRD [83].

While several proposals have been made in order to improve the development of novel antidepressants [84], what seems clear is that monoamine-targeting antidepressants should not be the sole avenue to pursue in the development of novel antidepressants; in this regard, ketamine, a rapid-acting antidepressant, stood out as a breakthrough innovation.

In the year 2012, the FDA Safety and Innovation Act created the “breakthrough therapy” designation, and its subsequent amendments, to expedite the development of promising drugs intended to treat severe or life-threatening conditions. This provides for more intensive feedback and expedited review than the earlier “fast track” designation [85]. The FDA also issued guidance that reflects their current perspective on drug development, biomarker qualification for a specific context of use, and trial designs in psychiatry [86]. While at present there are still no surrogate markers for the assessment of antidepressant effectiveness, the FDA urges on the matter; those sponsors seeking to include a biomarker in their clinical trial are encouraged to arrange a meeting with the appointed FDA division, still, in its early development phase [87]; a gradual rejuvenation of interest of the pharmaceutical companies involved in drug discovery for depression resulted in two antidepressants being approved by the FDA on March 2019: the aforementioned intranasal spray esketamine for TRD adjunctive to standard antidepressants and intravenous brexanolone for postpartum depression (now referred to as “peripartum” depression).

Intranasal spray esketamine was granted FDA fast track and breakthrough therapy designation to Janssen Pharmaceuticals®, Inc. for intranasal esketamine adjunctive to standard antidepressants in the year 2013 TRD and in 2016 for the treatment of MDD with an imminent risk of suicide [49]. However, even recent qualitative synthesis of the evidence solicits further studies to ascertain the term efficacy and safety of intranasal esketamine [55].

Besides, additional insights about the actual mechanism of action responsible for rapid antidepressant effect are likewise needed [88]. Even the drug development process needs to take full advantage of novel methods to quantify target engagement in living subjects such as positron emission tomography (PET) tracers to assess molecular interactions, as well as high-density electroencephalography and functional magnetic resonance imaging (fMRI) to measure effects of drugs on brain circuits [86].

In the meanwhile, current antidepressant drugs should be ideally prescribed in a “novel” way too, taking advantage of augmentation therapy with latest antipsychotics, as exemplified by most recently released atypical antipsychotics [89], and recent [90] insights from pharmacogenomics to promote precision medicine concerning antidepressant drug prescription [91]. More accurate [92, 93], prompter recognition and adequate management of subthreshold bipolarity among *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5) [94] cases of MDD should also aid toward the development of novel antidepressant drugs [95] and better outcomes in the clinical settings, even for the otherwise-labeled cases of TRD [96].

Finally, while esketamine represents an intriguing opportunity for the management of TRD cases, especially in case of imminent and severe risk for suicidality, the authors believe that real innovation in the development of future antidepressant drugs should be much more grounded on comprehensive understanding of the whole putative mechanisms of action, with a particular emphasis toward the molecular basis of the effects seen in the clinical practice. It is also our firm belief that precision medicine and implementation of reliable biomarkers would be the key toward effective novel antidepressant discovery, paralleled by a deeper understanding of the complex phenomena associated to depression and suicidality and treatment-resistance phenomena in general, especially considering that TRD and/or at high suicidal risk are those excluded per protocol by current trials potentially leading to the registration of “novel” antidepressant drugs.

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Chapter 23

Creative, Person-Centered Narrative Psychopharmacotherapy of Depression



Miro Jakovljevic

Abstract Depression as a multifactorial, polygenic mental disorder with thousands of faces, poorly defined endophenotypes and characterized with high rate of morbidity, comorbidity, disability, mortality, and treatment failures, remains a relentless illness with heavy burden on patients, their families, and society. Therapeutic outcome of depression needs to be significantly improved and overcome the 65% barrier. The best treatments are those that utilize and integrate multiple modalities. The time is ripe for psychiatry to find its transdisciplinary integrative soul and increase treatment effectiveness. Creation and fostering hope, meaning, personal responsibility, spirit of optimism, and commitment can significantly contribute to overall positive response to pharmacotherapy, but in the other way round drug treatment can also contribute to creation and fostering hope, meaning, personal responsibility, spirit of optimism, and commitment. This chapter addresses the concept of creative person-centered narrative psychopharmacotherapy (CP-CNP) as a transdisciplinary integrative strategy for improvement of the therapeutic effectiveness in patients with depression.

Keywords Depression · Resilience · Creative psychopharmacotherapy · Person-centered narrative medicine · Personal recovery

23.1 Introduction

“If there is hell on earth, it is to be found in the heart of a melancholy man” – Robert Burton (1577–1640): “The Anatomy of Melancholy”

“I am now the most miserable man living. If what I feel were equally distributed to the whole human family, there would not be one cheerful face on earth” – Abraham Lincoln (1809–1865)

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Depression as a multifactorial, polygenic mental disorder with thousands faces, poorly defined endophenotypes and characterized with high rate of morbidity, comorbidity, disability, mortality, and treatment failures, remains a relentless illness with heavy burden on patients, their families, and society. Pharmacotherapy of depression today is a hot topic with very controversial views on it related to its glorification and vilification, as well as to underdiagnose and undertreating of depression, but also to antidepressant overmedicalization. This hot topic has been looking from time to time like a real war of viewpoints about the usefulness and effectiveness of antidepressant medication. In 1992 Cassano [1] cautioned that “depression is one of the great scandals of medicine” because “it is an underdiagnosed and undertreated disorder because only a small percentage of depression is recognized, a limited number of patients receive antidepressant treatment, and many of those who are treated receive inadequate dosages of antidepressant drugs”. Two decades later Stahl [2] also cautioned that “the true scandal lies in the treatment of the depressive disorders. A third of patients in a real life never fill their first antidepressant prescription, and for those who do, perhaps less than half get a second month of treatment and maybe less than a quarter get an adequate trial of 3 months or longer”. Despite the overall increase in number of depressed people seeking help, only half of them receive any form of treatment, and only about half of these receive adequate treatment [3–5]. For time being, unfortunately, there is still no consensus as to which all depressed patients get clear optimal benefit from antidepressant medications generally and from specific ones particularly [6]. According to some authors, there has not been much success in pharmacotherapy of depressive disorders in the last 50 years [7] while others even deny their usefulness [8]. According to Kirsch [8, 9], the patients treated by antidepressants showed considerable improvement in the clinical trials submitted to the FDA by the manufactures, but so did the patients given placebo, and the difference in outcome between drug and placebo was below the criterion for clinical meaningfulness. Mechanistic, formistic, fragmentary, and binary categorical thinking have produced many oversimplifications, false beliefs, and myths (see Table 23.1) preventing their creative and rational application and leading to failed treatment outcome (see [10, 11]). It is widespread opinion that antidepressants are lacking in efficacy and even more in effectiveness and that better treatment options for depression are needed. According to some authors antidepressant treatment can help some 30–40% depressed patients (see [12]), although the number of antidepressants was increasing, particularly during the 1990s decade of the brain and the first decade of twenty-first century. Sorry to say, for patients with full or partial remission, most medications needs 3 or more weeks to months to exert positive effect and commonly that may be after multiple medication trials associated with undesirable adverse events (see [12]). Quite a number of authors claim that the magnitude of therapeutic effect of antidepressants compared to placebo in double-blind clinical trials (the golden standard for treatment efficacy and comparisons) increases with severity of depression and may be minimal or nonexistent in patients with mild and moderate depressive episodes [7].

Etiopathogenesis and related diagnostic and prognostic biomarkers of depression have been pursued from the beginning of modern psychopharmacology

Table 23.1 Harmful myths about antidepressant medications that prevent their creative application

Myth 1. Antidepressant medications are ineffective—Fact: Antidepressant medications are effective if used properly.
Myth 2. Antidepressant medications represent symptomatic, cosmetic treatment, and psychotherapy is etiological/causative treatment—Fact: Antidepressant medications stimulate neurogenesis and improve neuroplasticity underlying positive thinking, mood improving, and appropriate behavior.
Myth 3. Antidepressant medications are for morally weak people—Fact: Antidepressant medications are for individuals suffering from depressive illness.
Myth 4. Antidepressant medications are addictive because after the sudden stopping (e.g., paroxetine) appears abstinence syndrome and illness exacerbation—Fact: Antidepressant medications are generally not addictive, but the sudden stopping may be followed by the syndrome of sudden medication withdrawal as some nonpsychiatric medications.
Myth 5. Antidepressant medications change personality and self-disorders—Fact: Untreated depression change personality and self-disorders as well as depression may reflect personality and self-disorders
Myth 6. Antidepressant medications are toxic and dangerous drugs—Fact: Antidepressant medications are relatively safe and nontoxic if used properly.
Myth 7. Antidepressant medications should be stopped as soon as possible—Fact: Antidepressant medications should be stopped when personal recovery is achieved in agreement with the patient.
Myth 8. Antidepressant medications are the cause of violent, autodestructive, or suicidal ideation and behavior—Fact: Antidepressant medications are unlikely to create new autodestructive, suicidal, or violent ideation and behavior.
Myth 9. There are no significant differences between antidepressant medications belonging to the same class, for example, between selective serotonin reuptake inhibitors (SSRIs)—Fact: Global effectiveness of the same class antidepressant medications, for example, SSRIs, is similar, but they have also specific effectiveness.
Myth 10. Antidepressant medications with many mechanisms, for example, nonselective monoamine reuptake inhibitors known as tricyclic antidepressants are “dirty drugs”—Fact: There are no dirty antidepressant medications; there is only wrong selection and use of antidepressants.
Myth 11. Antidepressant medication monotherapy is generally recommended as good clinical practice compared to polypharmacotherapy that is implicitly or explicitly considered as bad clinical practice—Fact: Creative polypharmacotherapy covering more pathological mechanisms and increasing therapeutic effectiveness should be the rule rather than exception.
Myth 12. Antidepressant medications should be used only in for treatment of severe forms of depression—Fact: Appropriate use antidepressant medication in mild depressive episodes may prevent developing severe forms of depression.

without success. The Holy Grail regarding the treatment of depression has been to create a novel antidepressant with a high rate of the fast efficacy, high level of safety and tolerability, high power of relapse/recurrence prevention, and without withdrawal syndrome (see [7]). Unfortunately, for the time being antidepressant drug discovery by pharmaceutical industry seems to be hampered by many factors. While waiting for magic antidepressant bullets, psychiatrists and other mental health workers try to overcome the gap between relatively poor treatment results in practice and significantly higher therapeutic possibilities in theory. What is needed at the first place is creative systems thinking and transdisciplinary integrative approach in

understanding and treating depression using both tacit (hardwired in persons) and explicit (codified and documented) knowledge. The aim of this chapter is to present theory and practice of the creative, person-centered narrative psychopharmacotherapy (CP-CNP) of depression which opposite to directive telling and medication prescribing approach to the patients represents learning organization to maximize personal recovery and well-being, personal mastery, resilience, and antifragility of patients.

23.2 Creative, Person-Centered Narrative Psychopharmacotherapy of Depression as Transdisciplinary Integrative Learning Organization

Creativity refers to any idea, product, or practice that significantly changes an existing domain, or transforms an existing domain into a new one in a meaningful and useful way (see [13]). Psychopharmacotherapy of depression is expected to be practiced in normative, evidence-based way according to rules of official guidelines. However, in clinical practice treatment approach is commonly too dogmatic, not rarely pseudoscientific and misguided by official treatment guidelines, and followed by poor treatment outcomes. Fortunately, initiatives known as personalized medicine, person-centered medicine, and precise medicine have tried to find optimal treatment options for each patient and so improve general treatment successfulness. The terms personalized medicine, person-centered medicine, and precise medicine are often used interchangeable although they refer to the three similar, but different concepts [14]. The objective of precision medicine is to improve choosing antidepressant medication with best possible therapeutic effects and without or with minimal adverse effects using objective biomarkers. This is still wishful thinking in psychiatry despite of the extensive research in this field during the last four decades. For an example, we [15] investigated dexamethasone suppression test that had previously claimed to be a specific marker for major depression, as an aid for avoiding errors in the choice of antidepressant treatment. Personalized medicine promotes selecting antidepressant medications based on taking into consideration age, sex, core-symptoms of depression (psychotic vs non-psychotic, agitated vs inhibited episode, sleep and appetite disturbances, etc.), comorbid disorders and diseases, comedications, and patients' preferences with regard to choosing antidepressants. Person-centered medicine promotes partnership with patients as persons with specific life scripts who are responsible for their life and health as well as personal recovery and well-being as the treatment goal. CP-CNP represents an art and practice of learning organization based on systems, critical, and creative thinking; building joint visions with patients of the meaning of depression and defining treatment goals; learning together with patients and their families how to get optimal treatment results; and supporting patients to change their mental models and life scripts and increase personal mastery in order to achieve personal recovery and

post-depression growth. This concept includes creative synergism between pharmacology and positive psychology: (1) multitargeted treatment and synergistic drug combinations based on person-centric approach; (2) building therapeutic relationship and alliance through therapeutic communication; (3) increasing resilience and antifragility and decreasing fragility and vulnerability; (4) increasing placebo and decreasing nocebo response; (5) changing old illness narrative and creating new therapeutic narrative; (6) enhancing creativity and supporting self-actualization; (7) creating personal recovery and new life story.

23.2.1 Evidence Based Versus Evidence Biased Psychopharmacotherapy and Debunking Myths on Antidepressants

There are many misbeliefs and pseudoscientific myths about antidepressants and their use in clinical practice (see Table 23.1) that may have negative impact on the treatment of depressed patients [10]. Some of these myths apply to all mental health medications, some relate to antidepressants only, some are by their nature completely misbeliefs and untrue, some may hold some grains of the true. Unfortunately, even well-educated patients and member of their families as well as some physicians may be under influence of these misconceptions and myths.

Antidepressants are among the most widely prescribed medications all over the world, but they are accused to be “little more than a deceptive product of greedy, lying pharmaceutical companies that sell hope to the hopeless” and one of the major medicalization of living problems in modern society. Patients may be significantly affected in different harmful ways by negative views on antidepressants and evidence-biased and marketing-based stories and myths through public media. As antidepressant medications work not only by pharmacodynamic mechanisms, but also on the account of the meaning they have for the patients, debunking these myths of the psychiatric glorification and antipsychiatric vilification is of the great importance.

23.2.2 Person-Centered Approach: Each Patient is a Unique, Responsive, and Responsible Subject

The more effective psychopharmacotherapy means the more is selective, specific, and person-centered. Person-centered approach represents a shift of paradigm from seeing parts to seeing wholes, from seeing patients with depression as helpless reactors to seeing them as active participants and partners in therapy and shaping their reality from reacting to the present to creating the future predicated on the joint vision of treatment goals (see Table 23.2).

Table 23.2 Treatment goals from seven perspectives

Perspectives	Treatment goal
Disease/illness or medical perspective	Clinical remission/recovery
Person-centered perspective	Personal recovery
Cognitive-axiological perspective	Positive thinking and circulus virtuous
Behavioral perspective	Assertive and creative behavior
Spiritual/transpersonal perspective	Life mission and spiritual values
Narrative perspective	Reconstructing narratives and life story
Systematic integrative perspective	Positive mental health and well-being

The specific psychiatrist–patient relationship is the foundation on which science-based psychopharmacological knowledge can result in success or failure. The absence of therapeutic relationship and alliance leads commonly to treatment non-adherence and consequently to treatment failure. Numerable different personalized factors need to be considered when making selection of antidepressant treatment (see Table 23.3). It is very important to identify the characteristics by which the patient is unique. Specific clinical manifestations, for example, presence of anxiety, psychomotor agitation or inhibition, crying, insomnia or hypersomnia, loss of appetite and anorexia or hyperphagia, delusions, suicidality need problem-solving psychopharmacology approach (see [16]) and selection of antidepressant medication with specific characteristics.

Rational and reliable choice of antidepressants has been limited by a lack of reliable biomarkers to distinguish categories of depression, relying instead upon self-report symptoms, and clinical signs. For this reason, it is important to use different perspectives (see Table 23.2) in deeper understanding of depression and therapeutic mechanisms in a holodigmatic and transdisciplinary way (see [17]).

23.2.3 *Transdisciplinary Integrative Model of Depression and Multilevel Integrative and Comprehensive Treatment*

Depression is a complex heterogeneous disorder with many different neurobiological, psychological, social, and even spiritual theories about its roots in epi/genetics, neurophysiology, psychotraumatology, family psychopathology, false learning, and conceptions of the self, the world and life, etc. The biological theories have mainly focused on genetic predisposition and epigenetic misregulations, stress-related neurotransmitters dysregulation, disruption of biological rhythms, low-intensity neuroinflammation, oxidative stress and neuroendocrine disbalance, neuroplasticity dysregulations, etc. Psychological theories emphasize unconscious conflicts between love and hate, rage and guilt, between ideals and self-perception, or suppressed negative emotions, problems in the early mother–child relationship and insecure attachment, learned helplessness and hopelessness, punishing experiences

Table 23.3 Antidepressant medications selecting triangle

Patient’s characteristic
- Depression type, first or recurrent episode, and clinical picture
- Patient’s narrative
- Previous experience with treatment
- Pharmacophylic or pharmacophobic features
- Placebo or nocebo proneness
- Age of patient
- Comorbid somatic/neurologic diseases
- Comorbid psychiatric disorders
- Other medications prescribed
Pharmacodynamic and pharmacokinetic medication specifics
- Risk-benefit profile
- Pharmacodynamics profile (therapeutic mechanisms)
- Pharmacokinetic profile
- Type of formulation
- Dosing
- Side-effects and adverse events
- Safety in overdose
- Cost
Treatment goals and therapeutic alliance
- Acute phase, stabilization phase, or maintenance phase of treatment
- Symptoms remission as soon as possible
- Patients as proactive partners, not as objects of treatment
- Inducing placebo, preventing nocebo response
- Enhancing resilience and antifragility
- Promoting and fostering patients’ creativity
- Creating appropriate illness and therapeutic narrative
- Personal recovery, post-depression growth, new life story, and mental health

and lack of positive reinforcement, faulty information processing and maladaptive beliefs, and so on [18]. Consistently to existence of many theories of depression, there are many treatment approaches. However, as none of the multiple theories provides an adequate explanation for all aspects and types of depression, so none of the fragmentary treatments is successful. CP-CNP is predicated on the circular feed-back biopsychosociospiritual model of depression from seven perspectives and multitargeted integrative and comprehensive treatment.

23.3 Multitargeted Treatment of Depression and Synergistic Therapeutic Medication Effects

Antidepressant CP-CNP is a neuroscience-based and multilevel process focused treatment in order to reset self-esteem (related to mood, social status—isolation, reactivity to novelty), hedonic capacity, mental agility; alter risky personality; normalize sleep; modify stress response; improve impulse control and behavior; foster resilience and lifestyle modification; and enhance functioning of healthy mind. It involves integrative multimodal use of mental health medications together with other modes of treatment like psychotherapy, family therapy, narrative therapy, risk management strategies, complementary supplementations (vitamins, omega-3 fatty acids, amino acids, S-adenosyl-L-methionine (SAME), Saint John's wort, ginkgo biloba, etc.). What is optimal treatment for one depressed patient may not be appropriate for another because diagnostic, pharmacodynamic, pharmacokinetic and individual and family psychodynamic, and life narrative considerations.

23.3.1 *Medications with Antidepressant Effects*

Quite a number of the medications with antidepressant actions are available (see Table 23.4). The treatment selection (see also [19]) should be based on drug specific pharmacodynamics and pharmacokinetics and on patient specific characteristics (see Table 23.3).

According to Cipriani et al. [20] in head-to-head studies agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were statistically more effective than other antidepressants, whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were statistically the least efficacious drugs. For acceptability agomelatine, citalopram, fluoxetine, sertraline, and vortioxetine were statistically more tolerable than other antidepressants, whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropout rates [20]. However, statistical and clinical relevance are commonly different issues, and the aim of precise, personalized, and person-centric medicine is to make the best choice for the concrete patient. Emphasizing nomothetic knowledge promotes a technical rationality in the treatment of depression that significantly contributes to the 65% barrier in antidepressant successfulness (see [21]). Clinicians in everyday practice treat individuals not groups, real depressed patients not statistical ones, so in antidepressant CP-CNP both nomothetic and idiographic knowledge are respected as necessary evidence components (see [17]).

Table 23.4 Drugs with antidepressant effects and other biological forms of treatment

- RIMA (reversible type A monoamine oxidase inhibitors): Moclobemide
- RIMA/SSRI. Brofaromine
- Phosphodiesterase inhibitors: Rolipram
- Nonselective monoamine reuptake inhibitors (so-called tricyclic antidepressants): Imipramine (SNRI, mild D2, 5-HT2, moderate musc. AcH, H1, strong alfa1), amitriptyline (SNRI, mild D2, moderate 5-HT2, strong musc. AcH, H1, alfa1-NA), doxepin
- Selective serotonin reuptake inhibitors (SSRIs): Fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram, escitalopram
- Selective noradrenaline reuptake inhibitors (SNaRI): Maprotiline, reboxetine
- Serotonin noradrenaline reuptake inhibitors (SNRIs): Venlafaxine, duloxetine
- Noradrenaline dopamine reuptake inhibitors (NDRIs): Bupropion
- Noradrenaline specific serotonin antidepressants (NaSSA): Mirtazapine
- 5-HT2/alpha2NA receptors antagonists: Mianserin
- Serotonin antagonist and reuptake inhibitor (SARI) weak serotonin reuptake inhibitors/5-HT2A antagonist: Trazodone, nefazodone
- Selective serotonin reuptake enhancers (SSRE): Tianeptine
- Melatonergic (M1, M2 receptors) agonist/5-HT2C antagonist—Chronotherapeutics: Agomelatine
- Multimodal (5-HT1A agonist, 5-HT1D partial agonist and antagonist of 5-HT3, 5-HT1D, and 5-HT7 receptors): Vortioxetine
- Other medications and supplements: MAO-B inhibitors (selegiline), NMDA receptors inhibitors (ketamine, es-ketamine), SAMe, agonists 5-HT1A receptors (buspirone), Hypericum extract (St. John’s worth), amino-acid precursors (L-tryptophan, phenylalanine, tyrosine), Omega-3 fatty acids
- Other biological therapies: Electrostimulative therapy (EST), transcranial magnetic stimulation (TSM), magnetic seizure therapy (MST), vagus nerve stimulation (VNS), deep brain stimulation (DBS), light therapy (phototherapy), sleep deprivation

23.3.2 Neurobiological Targets of Antidepressant Pharmacotherapy

Despite our increasing knowledge about the presumed pharmacodynamics and pharmacokinetics of antidepressant medications, it is disappointing that we are still ignorant about what is going on in the brain and mind of many patients with depression. We have several theories but few proven facts about neurobiology of depression and therapeutic mechanisms. However, fortunately the up-to-date knowledge enables us to increase the successfulness of antidepressant treatment by transdisciplinary integrative person-centered approach. Antidepressant pharmacotherapy is overlapping multitargeted treatment, correcting complex neurotransmitters disbalance and hyperactivity of hypothalamic–pituitary–adrenal (HPA) axis, stimulating neurogenesis and decreasing apoptosis signaling, decreasing oxidative stress and neuroinflammation, and correcting desynchronosis of circadian pacemakers [22].

Neural Circuits and Neurotransmission Modulation and Balancing Imbalance or dysbalance of neurotransmitters triggers depression, and extent of their imbalance

decides combinations of symptoms and severity of depressive episodes. Depression is related to the imbalance of serotonin, dopamine, noradrenaline, acetylcholine, GABA, and glutamate, and majority of antidepressants act by enhancing directly or indirectly the monoamine neurotransmission. Antidepressants can alter brain chemistry, and chemistry of brain modulates our thoughts, emotions, and behaviors. Our increasing understanding of the brain chemistry in regulation of mental functions provides to some extent knowledge for the rational use of antidepressant medications. Ketamine, an N-methyl-D-aspartate receptor antagonist, has become the prototype for novel potential rapid-acting glutamate-based antidepressants such as traxoprodil, rislenemdaz, and riluzole. [23]. Some evidence indicates that endogenous glutamatergic modulators like agmatine, creatine, guanosine, and vitamin C may be able to regulate mood and to elicit rapid antidepressant effects [23].

Neurons in the brain are organized in systems or functional networks that synthesize and release specific chemical neurotransmitters. The neural circuits/networks framework enables better understanding of neurobiological, psychological, social, cultural, and spiritual processes in patients with depression. Understanding of multimodal brain neurocircuitry with complex brain neurochemistry can increase rationality and effectiveness of selecting an antidepressant and its combination with other medications. Depression reflects brain/neuronal dysfunctions at different levels inducing negative affectivity, negative cognitions, negative motivations, dysfunctional behavior, and vegetative changes (see Table 23.5).

Antidepressants may have multiple discrete effects on functions and interactions between neurons, glial cells, and astrocytes resulting in correction of depression-associated miscommunication between neuronal networks such as, for an example, the default mode network (DMN), the salience network (SN), and the central executive network (CEN) that regulate emotion, thinking, behavior, and stress response [24]. According to the response styles theory of depression, rumination represents repetitive and passive thinking about symptoms of depression and their possible causes and consequences, and so exacerbates and prolongs depression (see [18]). The DMN (the ventromedial prefrontal cortex, the posterior cingulate cortex, the inferior parietal cortex, and the middle temporal lobe) mediates introspection and rumination, the SN (the anterior cingulate cortex, the insula, and the ventromedial

Table 23.5 Signs and symptoms of depression

- Negative affectivity: low or dysphoric mood, loss of pleasure, feelings of guilt, nervousness, irritability, and boredom
- Negative cognitions: negative view of the self, the world and the future; indecisiveness, self-blame and feelings of worthlessness, helplessness and hopelessness, suicidal thoughts
- Negative motivations: loss of interest and amotivation, suicidal ideation, social withdrawal, and neglected appearance and hygiene
- Dysfunctional behavior: reduction in activities or psychomotor retardation, psychomotor agitation, and suicidal behavior
- Vegetative changes: insomnia, loss of appetite and weight, reduced libido, vague aches, and pains

prefrontal cortex) mediates processing of salient information from the external world, and the CEN (the dorsolateral prefrontal cortex) mediates working memory and attention. In a 10-week double-blind clinical study, duloxetine but not placebo reduced the excessive connectivity of the DMN with the SN and CEN, and this correction was correlated with an antidepressant effect; while in other study, a rapid antidepressant response to ketamine was associated with an equally rapid improvement of connectivity between the SN and DMN (see [24]).

HPA Axis Modulation There is significant evidence that HPA axis (FKBP5/GR/HPA axis signaling) is implicated in depression and other stress-related disorders. Stress inducing activation of the HPA axis causes the brain to be overwhelmed with corticosteroids in depression [25–27], affecting psycho-neurophysiological functions with a down-regulation of hippocampal neurogenesis [28]. The HPA axis is considered as a suitable target for specific antidepressant medications, but up to date there is no specific antidepressant targeting HPA axis components that is approved for depression treatment [29]. However, antidepressant drugs regulating monoamines may indirectly modulate HPA axis activity. The sensitivity of glucocorticoid receptors (GR) is substantially regulated by FKBP5, encoding the FK 506 binding protein 51 or FKBP51, a co-chaperone of heat-shock protein 80—hsp90 (see [29]). FKBP5 has been reported to be important in depression and other stress-related disorders, and aggressive and suicidal behavior [29]. Some studies suggest that FKBP51, a protein chaperone important for the regulation of the glucocorticoid receptors in stress responses, is essential for therapeutic effect of paroxetine (see [30]). GR antagonists such as mifepristone seem to be promising for the treatment of psychotic depression (see [29]). Dexamethasone-induced gene expression test may be a promising tool to assess the GR sensitivity and FKBP5 function [29].

Decreasing Oxidative Stress Oxidative stress can damage the cell through lipid peroxidation, DNA or protein oxidation, and mitochondrial damage, and has important role in the pathogenesis of different disorders and illnesses. Due to mitochondrial lowered antioxidant capacity and an imbalance between oxidative and antioxidative systems in favor of the former, oxidative stress is supposed to be involved primarily or secondarily in the pathogenesis of depression [31]. Sarandol et al. 2007). Reactive oxygen and nitrogen species have been reported to modulate levels of NA, 5-HT, DA, Glu, and neurotransmitters that play an important role in depression and its treatment [32]. Data about effects of antidepressants on mitochondria and oxidative stress are contradictory. According to some research, fluoxetine may act as a radical scavenger showing selectivity for HO and CH₃O, but without the effect on peroxy radicals [33].

Decreasing Neuroinflammation Depression may be associated with inflammatory responses of the organism and consequent increase of proinflammatory cytokines such as IL1, IL6 and TNF and lipid peroxidation, acute phase proteins, and kynurenine pathway metabolites [28, 34]. Microglial activation is linked to neuroinflammation, increased metabolic demands, and brain neurons damage (see [35]).

Low-grade inflammation may be important not only in the pathogenesis of depression but also in the therapeutic responsiveness to antidepressants [36]. Increased serum levels of CRP and IL-6 are associated with poor responsiveness to predominantly serotonergic antidepressants but a better responsiveness to antidepressants with noradrenergic, dopaminergic, or glutaminergic actions, and anti-inflammatory agents like minocycline and infliximab [36]. In addition to the effects on neurotransmission in the brain, some antidepressants possess antineuroinflammatory properties and can also influence activity and number of immune cells, and modulate the immune processes and thus contribute to clinical improvements. Curcumin may contribute to the reduction of depressive symptoms when supplemented with standard antidepressants [37].

Neuroprotective and Antiapoptotic Effects Different experimental and clinical studies indicate neuronal death associated with high levels of reactive oxygen species in depression and neuroprotective, and anti-apoptosis effects have been suggested for different antidepressant medications. An interesting study indicates that mirtazapine and imipramine have neuroprotective effect against H₂O₂-induced cell death in human neuroblastoma [38]. The potential of antidepressants such as fluoxetine to have a neuroprotective effect for patients with multiple sclerosis by correcting common mechanisms in depression and multiple sclerosis such as serotonin, noradrenaline, glutamate and brain-derived neurotrophic factor (BDNF) disruption, HPA axis dysregulation, and neuroinflammation is challenging [39].

Neurogenesis Stimulation and Neuroplasticity Improvement Neurogenesis during adulthood is proved in two specific neurogenic niches, the dentate gyrus of the hippocampus and the subventricular zone adjunct to lateral ventricles, where new neurons are generated throughout life from stem cells (see [40]). Depression may be associated with impairments of neuroplasticity (cellular resilience, axon branching, dendritogenesis and synaptogenesis, and glial cell loss) in specific areas of the CNS, particularly in the hippocampus due to BDNF decrease [28, 41]. Antidepressants have been shown to increase the ability of brain to form new neural connections and increase neuroplasticity (see Table 23.6).

Antidepressants treatment with SSRIs and EST increases BDNF levels, stimulates neurogenesis and improves neuroplasticity, and reverses the inhibitory effects of stress that is usually evident only after 3–4 weeks of treatment (see [7, 41]). It is considered that the time course for maturation of new neurons is about 3–4 weeks.

Restoring Circadian Rhythms Depression is commonly associated with alteration in circadian rhythms of rest–activity and sleep–wakefulness cycles, core body temperature, cardiac rhythms, blood pressure, the secretion of melatonin, cortisol, growth hormone, thyrotropin, and other hormones, as well as inflammatory cytokines and neurotransmitters (see [42]). There is growing evidence that some antidepressants and mood stabilizers may restore circadian rhythms. Understanding of chronobiological mechanisms of cell resilience and resistance to stress enables development of more specific and successful treatment of depression such as chrono-therapeutics. Antidepressant agomelatine with its resynchronizing effects is

Table 23.6 Antidepressants, depression, and neuroplasticity [7]

- Phosphodiesterase inhibitors: increased levels of pCREB
- MAP kinase modulators increase the expression of the major neurotrophic protein Bcl-2
- mGluR II/III agonists modulate release of excessive levels of glutamate
- Drugs such as lamotrigine and riluzole act on Na+ channels to attenuate glutamate release
- AMPA potentiators upregulate the expression of BDNF
- NMDA antagonists like ketamine, esketamine, and memantine enhance plasticity and cell survival
- Novel drugs to enhance glial release of trophic factors and clear excessive glutamate may have utility for the treatment of depressive disorders
- CRF antagonists and glucocorticoid antagonists attenuate the deleterious effects of hypercortisolemia, and CRF antagonists may exert other beneficial effects in the treatment of depression via non-HPA mechanisms
- Agents that upregulate Bcl-2 like pramipexole are effective in bipolar depression
- GABA-A positive allosteric agonist like (PAM) brexanolone—SAGE-547 is effective in postpartum depression

Table 23.7 Antidepressants exerts epigenetic changes (see [45, 46])

- Imipramine reduces <i>Crf</i> mRNA level and increases DNA methylation at the <i>Crf</i> promoter in socially defeated mice.
- Amitriptyline reduces DNA methylation, but not by HDAC inhibition.
- Fluoxetine increases the level of miRNA-16 that targets serotonin transporter (SERT) transcript in 5-HT neurons and decreases SERT expression.
- Escitalopram reduces elevated DNA methylation at the P11 promoter leading to an increase in P11 and a decrease in DNMTs in prefrontal cortex.

considered as pharmacological chrono-therapeutics. Chronobiology studies indicate when some antidepressants, for example, clomipramine 150 mg/d, are given in a single dose at noon are superior in comparison when they are given three times a day (see [42]). Some antidepressants such trazodone and agomelatine belong to the group of so-called night antidepressants and reboxetine to the morning antidepressants.

Modulating Epigenetic Mechanisms The interplay between genome, epigenome, and environment shapes a phenotype of human health or illness such as depression (see [43]). Some studies indicated that individuals with the short variant of the serotonin transporter gene (5-HTTLPR) experienced higher levels of depression and suicidality following recent life stressors, and hyperactivity of the amygdala in the short 5-HTTLPR carriers was related to increased sensitivity to negative stimuli and negative bias in the processing or interpretation of emotional stimuli [44]. Depression is polygenic in nature with both genetic and epigenetic components related to transcription, neurogenesis and functional neuroplasticity, and cellular and personal resilience. Epigenetic mechanisms may moderate or mediate therapeutic effects of antidepressant medications (see Table 23.7) creating a “window of synaptic plasticity” (see [11]), and targeting selective epigenetic mechanisms is being suggested as a possible new avenue for finding novel antidepressant medications.

Furthermore, the epigenome is supposed to be of predictive utility and treatment monitoring (see [11]). Some studies suggested that antidepressant efficacy may be related to the increase of peripheral BDNF levels and that a decrease of BDNF plasma levels within the first week of treatment could predict treatment nonresponse with high sensitivity [47]. It is interesting that lower pretreatment average 5-HTT1B promoter methylation may be associated with increased functional recovery after fluoxetine treatment (see [11]).

Mitochondrial Functioning Because the brain uses about 20 times more energy than the rest of the body, and anergia or decreased energy is one of the fundamental signs of depression, while research evidence shows that mitochondrial diseases are related to depression, mitochondrial functioning is suggested as a target in the development of novel antidepressants, and specific forms of mitochondrial dysfunction as biomarkers to personalized treatment and an aid in early diagnosis by differentiating between specific types of depression (see [48]). Although the data on antidepressant medications' effect on mitochondrial functions are contradictory, this issue is intriguing and warrants further investigation because it may give an expanded model of the neurobiology of depression and its treatment. In mitochondrial dysfunction model of depression and its treatment, at present prevailing hypotheses of altered neurotransmission (5-HT, DA, NA, Glu, GABA) and stress-induced decreases in hippocampal neurogenesis can be connected with hypotheses about neuroinflammation, oxidative, and altered epigenetic mechanisms. Understanding how all these processes influence each other could lead to new therapeutic vistas and approaches.

23.3.3 *Selecting Antidepressant Medications, Types of Depression, and Treatment Strategies*

Depression is associated with different genotypes/phenotypes, life stories, and comorbidities. Successful type or subgroup identification, and the ability to apply this information in clinical settings, is essential for improving treatment paradigms and strategies [14, 35]. Antidepressant treatment response can be influenced by (1) what a patient «has» (depressive illness including comorbidities); (2) how a patient suffers (illness); (3) how a patient is defined by diagnosis and how community respond to his behavior (sickness, stigma, and social role); (4) what a patient «is» (personality, narrative self, and human being in the world); (5) what a patient «does» (behaviors and morality); (6) what a patient believes in (life philosophy and spirituality); (7) what a patient feels (life satisfaction and well-being); (8) what a patient «encounters» (life stories) and what a patient tends to be (life management, life script and mission, and self-actualization).

Selecting treatment strategies (see Table 23.8) and choosing preferable antidepressant medications depend on the patient's characteristics, pharmacodynamic and

Table 23.8 Basic treatment strategies in clinical practice

<i>Serial monopharmacy and switching strategies:</i> Stopping the medication to which the patient is not responding and prescribing another medicine, usually from an another group of the same class
<i>Augmentation strategies:</i> Adding another agent to an ongoing medication that has been insufficient
<i>Combination strategies:</i> Starting with two or more compounds with a well-established efficacy as a single agent for the treatment of the mental disorder

Table 23.9 Preferable antidepressants selection depends on types of depressive illness and clinical features of depressive episode

*Mild depressive episode: St. John’s wort, tryptophan, Omega-3, alprazolam,
*Moderate depressive episode: SSRI, venlafaxine or duloxetine, mirtazapine, tianeptine
*Severe depressive episode: SSRI, venlafaxine or duloxetine, maprotiline, mirtazapine, TMS,
*Psychotic episode of depression: fluvoxamine, amitriptyline, sulpiride, olanzapine, quetiapine, EST
*Typical depression
- Insomniac: trazodone, mianserin, agomelatine
- Anorectic: sulpiride, paroxetine
*Atypical depression:
- Hypersomnia: reboxetine, tianeptine
- Hyperphagic: fluoxetine, bupropion,
*Agitated depression: maprotiline, quetiapine, olanzapine, clonazepam
*Inhibited depression: reboxetine, bupropion
*Wet/crying depression: sulpiride, fluvoxamine, maprotiline, trazodone,
*Suicidal depression: lithium, olanzapine, clozapine, EST
*Seasonal depression: moclobemide
*Bipolar depression: lamotrigine, lithium, aripiprazole, quetiapine, olanzapine,

pharmacokinetic medication features, therapeutic context, and treatment phase and goals (Tables 23.3 and 23.9).

There is an interesting attempt of Kraus et al. [35] to create an algorithm-based sequential treatment optimization scheme for recommended treatments (see Table 23.10). First and second line treatments are recommended sequentially during the first episode and within 3 months [35].

Selecting antidepressant medications also depends on actual psychiatric (generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, PTSD, and personality disorder) and somatic (cardiovascular diseases, diabetes, thyroid disorders, and chronic pulmonary disease) comorbidities because they may significantly influence the treatment outcome. Very important observation is that depression and comorbidities have bidirectional effects on diseases trajectory (see also [35]).

Table 23.10 Sequential treatment optimization scheme [35]

Stage 1—Monotherapy and dose escalation
* Reuptake inhibitor (SERT, NET, DAT)—multiple substances
* Receptor antagonist (NE alpha2, 5-HT2, 5-HT3)—mirtazapine
* Reuptake inhibitor (SERT and NET, receptor antagonist (5-HT2)—amitriptyline
* Reuptake inhibitor (SERT, receptor partial agonist (5-HT1A), receptor antagonist (5-HT3)—vortioxetine
*
Reuptake inhibitor (SERT, receptor agonist (5-HT1A), receptor antagonist (5-HT2)—trazodone
* Receptor antagonist (5-HT2 and D2)—trimipramine
* Receptor agonist (Mel1, Mel2), receptor antagonist (5-HT2B, 5-HT2C)—agomelatine
Stage 2—Augmentation and switch
* Augmentation
- Receptor antagonist (D2, 5-HT2)—quetiapine, olanzapine
- Receptor partial agonist (D2, 5-HT1A)—aripiprazole
- Enzyme interactions—lithium
* Combining two classes with complementary mechanisms
* Switch—within class of reuptake inhibitors
* EST/ketamine in recurrent (severe episodes, suicidal ideation
* rTMS, TBS
Stage 3
* Enzyme inhibitor (MAO-A and MAO-B), releaser (DA, NE)—tranylcypromine
* EST
* Ketamine
* rTMS, TBS
* Vagus nerve stimulation
Stage 4
* Repetition of previous stages
* Experimental treatments (DBS)
* Augmentation (buprenorphine)
* Consider clinical trials for novel substances

23.3.4 *Phases of Treatment and Antidepressant Medications Selection*

Theoretical concept of the therapeutic journey through three phases: (1) acute phase—clinical or symptoms remission; (2) continuation (stabilization) phase—functional/social recovery; (3) maintenance (relapse prevention) personal recovery phase is searching for very high “therapeutic to side effect ratio” in efficient way in order to reach wanted destination of breaking the patterns of depression and personal recovery and positive mental health as soon as possible.

23.3.4.1 Acute Phase of Treatment: Are Antidepressants First Choice or Last Resort?

It is evidence-based claim that all registered antidepressants work, but individual therapeutic response on them may vary significantly. As duration of untreated depression is correlated with worse later treatment outcome, early diagnose and properly selected medications are essential for positive outcome. Inverse correlation between shorter duration of symptoms, no matter of the first or the recurrent episode, and treatment response underlines the importance of early antidepressant treatment. The goal of treatment of acute phase of depression is to achieve as complete as possible symptoms remission as well as soon as possible. Duration of this phase treatment is usually about 2–4 weeks. According to many guidelines, antidepressants are effective for many of the symptom dimensions of depression, and are therefore typically prescribed as monotherapy [35, 49]. Should an antidepressant medication prove ineffective or poorly tolerated, switching to a different antidepressant is recommended what means switching from one SSRI to another SSRI, or from the SSRI to NARI [49]. Here is an important question when to switch and when to augment. According to the aforementioned authors, switch is recommended when there is no response or response is partial to the first trial; the switch or augment if there is a partial response to a second trial, and to augment when there is no response to a third trial. The use of monotherapy with single antidepressant medication, either with single-action or multiple action, is always the simplest and the most wishful treatment. However, the fact is that in too many cases antidepressant monotherapy, both by single-action and multiple-action antidepressant, is unsuccessful or only partially effective. As successive trials of monotherapy are commonly followed by treatment resistance, according to CP-CNP concept starting monotherapy is indicated only for mild depressive episode. Antidepressant medication differ significantly in their energizing, anxiolytic, sedative, and hypnotic effects making some of them more or less effective for different typical and atypical, agitated, and inhibited types of depressive episodes. In moderate and severe depression, an additive, synergic effect between two or more medications with antidepressant effects produces the greater overall therapeutic benefit than that achieved by either medication alone. According to majority of international guidelines, different combinations of medications with different actions are recommended for treatment-resistant depression. However, many so called treatment-resistant depression could be prevented by appropriate intelligent, balanced, and rational synergic combination (syn-combos). The ideal treatment is to apply the least number in least doses needed to achieve optimal remission.

When selecting antidepressants for resolution of an acute episode of depression, clinicians should prioritize (1) specific efficacy (percentage of responders with specific clinical type and picture of depression and degree of improvement); (2) specific tolerability profiles and comorbid states; (3) speed of onset and time interval until euthymia; (4) effectiveness and risk–benefit ratio, drug–drug interactions; (5)

subjective preferences of the patient; (6) cost-effectiveness; and (7) rules of insurance and reimbursing agencies. Psychotic episode of depression is always indication for antipsychotics with antidepressant mechanisms such as olanzapine, quetiapine, aripiprazole, and paliperidone. Seasonal depression usually appears in the fall or early winter when there is less sunlight, mainly at the same time each year, commonly with atypical symptoms like hypersomnia, overeating, craving for carbohydrates, and lethargy. Antidepressants with dopamine and noradrenaline enhancing effects such as bupropion and reboxetine are drugs of first choice in combination with light therapy. SSRIs with NRI effects such as fluoxetine or DRI effects may also be effective. It is of great importance from the very beginning to cover all key symptoms and aspects of depressive episode with rational synergic combinations (see Table 23.11). If the first-choice medication treatment appears to have had partial benefit then new medication/s can be added or replace some of the previously prescribed. In the case of the failure of the first or previous medication treatment, there are options to a switch to the second-choice combination or augmentation with agents that are not considered as official or primary antidepressant drugs [6, 35].

Therapeutic communication and creating alliance and partnership with depressed patients may be as important as the prescribing medication. When patients are respected, empathized with, included in medication decisions they are feeling better and are more ready to cooperate in the treatment. In addition to appropriate

Table 23.11 Good or rational synergic combinations (SynComb)

- SSRI in the morning + maprotiline in the evening
- SSRI in the morning + agomelatine in the evening
- SSRI in the morning + NaSSA (mirtazapine) in the evening
- SSRI in the morning + trazodone or mianserin in the evening
- SSRI + sulpiride + benzodiazepine
- SSRI + DRI (bupropion)
- SSRI + NRI (reboxetine)
- SSRs in the morning + olanzapine/quetiapine in the evening
- SSRIs + aripiprazole in the morning + quetiapine/olanzapine in the evening
- SSRI/SNRI +NDRI (Triple-action or heroic combo—see [2])
- SNRI + modafinil (Arousal combo—see [2])
- SNRI + mirtazapine (California rocket fuel—see [2])
- NRI (reboxetine) in the morning + olanzapine/quetiapine in the evening

medications prescription inducing placebo and reducing nocebo responses is very important from the very beginning.

23.3.4.2 Treatment in Stabilization/Continuation Phase

Major shift in treatment philosophy has happened over the past 10 years. In clinical practice in many patients, treatment is started with multiple medications because polypharmacy regimen with different antidepressant medications may be essential to achieving and maintaining full remission. Both taking too much and taking too little antidepressant medications are not good. The right medication for the right patient at the right time for an appropriate long time with appropriate psychosocial and spiritual support is the motto of CP-CNP. Successful treatment of an acute episode of depression as soon as possible is a commendable accomplishment, but it is just the first of the three goals of treatment. Stabilization and maintenance of euthymia require psychotherapeutic communication skills more and more in addition to pharmacotherapy. Therapeutic alliance is more than compliance. Well-established therapeutic relationship and partnership with patients are crucial in this treatment phase. The goal of stabilization phase treatment is to preserve clinical improvement and stabilize remission and prevent worsening or relapse of depressive episode and to achieve at least 6 month long complete remission. Antidepressants should be used for an appropriate period of time as well as at an appropriate dose to sustain euthymia. Dosage adjustment or augmentation is important to achieve optimal treatment outcome. Instigating and supporting patients to stay on stabilizing antidepressant medications is crucial because many patients do not take all their prescribed antidepressants or commonly miss doses. Specific communication approach is needed to the so called “difficult” medication patients such as the patients preoccupied with side effects, the “naturalists”, the nonadherent patients, the information overload patient, the patients who need to be in charge, and so on (see [50]).

23.3.4.3 Treatment in Maintenance Phase

Depression for most patients is recurrent episodic disorder and with each new episode the illness severity tends to worsen, and treatment responsivity may lessen [51]. Mechanisms of recurrences are related to brain sensitization, fragility, and kindling. Prevention of new episode and supporting personal growth and well-being, resilience, antifragility, and personal recovery is the final goal of the treatment. Duration of maintenance prophylactic treatment is very individual and varies from case to case. According to some recommendations depressed patients with three episodes, including the index episode or two episodes where one was very severe or with family predisposition should receive long-term treatment for at least 5 years (see [49]) or for indefinite extended or lifetime period [51]. It is to be noted that numeric precepts for number of episodes or length of extended maintenance

treatment serve only as a flexible guideline. Patients with a history of severe depressive episodes and serious suicidality or strong family history of mental disorders or psychotic episodes are considered for extended or lifetime treatment even if they have less than three episodes. Risk–benefit ratio is crucial when considering the length of maintenance treatment. If each new episode increases risk for long-term deleterious consequences, suicide, job loss, marital discord, divorce, psychophysical deterioration, medical comorbidities, and so on, extended treatment is recommended to be done as long time as it is possible. Although discontinuation of antidepressant medication is generally associated with increased risk of appearance of new depressive episode, intermittent medication maintenance treatment may be successful option in many cooperative patients. In such cases, the taper or dosage decreasing should be slow and cautious during at least 6 months, because rapid discontinuation may result with exacerbation or appearing new severe episode. In the case of the reappearance of mild depressive symptoms medication treatment should be restarted promptly, before a fully exacerbation and developing serious depressive state. In general, whenever medications by the time passing become unnecessary, they are recommended to be reduced in number and dosage slowly and discontinued carefully. In order to achieve the final goal of the treatment “patients need to learn the specific skills of positive psychology: how to have more positive emotion, more engagement, more meaning, more accomplishment and better human relations” [52]. If not, when antidepressant treatment stops, depression could appear again.

23.4 Personal Recovery, Increasing Resilience and Antifragility—How to Overcome the 65% Barrier?

“Drawn by the future, not driven by the past”—Martin E.P. Seligman

First to be noted is a fact that depression is a result of interplay between hereditary and environmental factors, tied together by epigenetic mechanisms. Generally speaking depression is a stress-related disorder associated with fragility and decreased resilience, while depressive episodes may be defined as vicious circles of negative affect, cognition, and behavior based on negative experience and definition about the self, the world, and the future, impervious to positive stimuli. CP-CNP is an art and practice of rapport and changing destructive narratives, beliefs, and meanings into creative and salutogenic ones combined with rational application of mental health medications. Psychotherapy, unfortunately, has been traditionally competed with psychopharmacotherapy [2] and that competition is still present in clinical practice. Some studies showed a 65% relief rate in patients treated with cognitive therapy for depression or SSRIs such as Prozac, Zoloft, or Lexapro accompanied by a placebo effect that ranges from 45% to 55% (see [52]). In order to overcome the 65% barrier, CP-CNP has been created as an integrative concept involving rational psychopharmacology and positive psychology with therapeutic communications, collaborative-thinking, reframing, rethinking, and empathizing based on

understanding of neuroplasticity and how the mind–body systems function. Neuroplasticity related to the therapeutic communication deletes old neuronal connections with “the negative cognitive triad” brain maps and creates new ones through neural networking or synaptic pruning.

23.4.1 Practicing Therapeutic Communication and Establishing Therapeutic Treatment Context

“To say something doesn’t mean it is heard.
To hear it doesn’t mean it is understood.
To understand doesn’t mean to agree.
To agree doesn’t mean to do.
To do doesn’t mean to keep doing it”.
Konrad Lorenz

In addition to pharmacodynamics and pharmacokinetics antidepressant treatment outcome is determined significantly at the psychological and communicational level as well. Helping patients decide to start and continue taking appropriate antidepressant medications, associated with therapeutic narratives and communication, is one of the essentials of CP-CNP. Motivational interview, therapeutic communication, and therapeutic alliance represent important initial part of the creating therapeutic context. Balint’s metaphor of the doctor as medication came from the notion that patients respond to the personal interaction, authenticity, nonpossessive warmth, acceptance, respect, accurate empathy, supportive stance, and curiosity. Creating therapeutic relationship and therapeutic context is a central part of the CP-CNP of depression. Strategies for establishing therapeutic doctor–patient relationship involve (1) understanding depressive illness and life story of the patient; (2) complementary salutogenic communication; (3) increasing reflexivity and empathy; (4) treating illness and disease; (5) respecting diversity in interpreting depression; (6) respecting family and social context of treatment; (7) personal recovery, antifragility, and well-being orientation. A patient without a proper therapeutic alliance will probably not stay in the treatment or not be adherent to the prescribed antidepressant medication. Without therapeutic communication the ever-helpful placebo response is less likely and nocebo response is more likely to happen. Motivational interview is a skillful clinical method of meeting patients in their model of the world for eliciting their own good motivations for treatment success. Cooperative and collaborative partnership honoring patients’ autonomy is not only offering patients what they lack, be it medicines, knowledge, insight, or skills, but also activating their own motivation and resource for change and treatment success in connection with their personal goals, values, aspirations, and dreams. Making diagnosis with the patient as part of therapeutic alliance is more effective than making diagnosis on the patient. Rapport is based on taking a genuine interest in the patient as a person, on being curious about who he/she is and how he/she thinks, feels and behave, and on being willing to see the world from their point of view.

23.4.2 *Restoring Psychobiological Basis of Resilience and Antifragility—Enhancing Optimism and Overcoming Pessimism and Learned Helplessness*

“Our greatest glory is not in never falling but in rising up every time we fall”—Confucius

Resilience is a complex psychobiological and multidimensional process, very important for understanding the pathogenesis of depression, and salutogenesis, therapeutic, and healing mechanisms. Causes of depressive disorders are the same stresses that affect all people, but result in cognitive or affective symptoms because of their negative life position, pessimism and negative views of themselves, of the world and of the future. According to the model of learned helplessness and hopelessness repeated exposure to uncontrollable events with faulty learning due to negative attribution style leads to (1) *negative affectivity* (low mood, loss of pleasure, feelings of guilt, irritability, and anxiety); (2) *negative cognitions* (negative view of the self, the world and the future, indecisiveness, self-devaluation, self-blame, and hopelessness); (3) *negative motivations* (loss of interest, suicidal drive, social withdrawal, and neglect of appearance and hygiene); (4) *behavioral changes* (agitation, hypoactivity, and psychomotor retardation); and (5) *vegetative changes* (reduced libido, loss of appetite and weight, vague aches, and pains). According to evolutionary theory depression serves the triple purpose: (1) to signal submission to dominant figures in a hierarchy conflict and internally communicate defeat; (2) to signal helplessness and communicate a need for help to potential caregivers; and (3) to disengage from commitments to futile or dangerous goals [53].

Some studies indicated that learned helplessness and hopelessness related to decreased resilience may be prevented by facilitation of serotonergic transmission in the dorsal hippocampus (see [54]). Decreased 5-HT_{1A} receptors binding in the cerebral cortex, the hippocampus, the amygdala, and the raphe nucleus have been reported in patients with major depressive disorder [54]. Resilience is the ability to reframe the things, most notably moving from feeling disappointment to seeing opportunities and new possibilities. Resilience-enhancing psychological intervention such as redefining depression, positive mood induction and creating pleasant states of mind, relaxation exercises, breaking ruminative patterns, reframing and cognitive restructuring, ego-strengthening, improving social skills, etc. Pleasant mental state involves feelings of love, hope, agency, purpose, positive goals, communion, and gratitude joy can be induced in many different ways, not waiting for pharmacodynamics effects of antidepressants in 3–4 weeks. An interesting brief clinical intervention for dealing with acute symptoms of depression, known as First Aid for Depression involves ventilation, education, adopting antidepressive posture, forcing a smile, imaging a “funny face,” playing a “happy mental tape and conditioning to a cue” (see [18]). This method can ameliorate symptoms of acute depression quite dramatically under certain circumstances [18]. When we see an attractive smiling face, the orbitofrontal cortex responsible for processing sensory rewards is activated. Some research showed that one smile can generate the same level of brain reward stimulation as up to 2000 bars of chocolate.

23.4.3 *Increasing Placebo and Decreasing Nocebo Response*

“He cures most successfully in whom the people have the most confidence”—Galen

“Many wanted to get appointment with Hector, not only because he looked like a true psychiatrist, but also because he knew a secret which all good doctors know, and which is not learned in school: he was sincerely interested in people”—Francois Lelord: *Hector and the Search for Happiness*

As the difference between therapeutic response rates to antidepressant and placebo treatment in double blind controlled clinical is still relatively very low, it is of utmost importance to practice therapeutic communication inducing and enhancing placebo response in everyday clinical practice [55]. Placebo reaction is a pleasant subjective feeling and positive response to a real or sham/dummy treatment while nocebo reaction is an unpleasant subjective feeling or negative response to the application of real or sham treatment. Placebo and nocebo phenomena are integral to everyday clinical practice and may significantly influence on treatment outcome. Therefore, all psychiatrists should be familiar with these phenomena and be educated to manage them. Anxiety disorders and depressive disorders are classified among stress-related disorders because causal factors of depression are linked to adverse life experiences and negative beliefs, views, and expectations. As depression may be provoked by negative expectations, it can be described in some way as a nocebo response to stressful and important life events. Depressed patients are characteristically engaged in a negative view of themselves, in a negative view of the world, and in a negative view of their future. The concept of depression as a nocebo reaction to stressful life events may explain high rates of placebo reaction in patients with depression. For depressed patients, the prescription of antidepressants may have different meanings and results in feelings of punishment, confirmation of self-blaming beliefs, reinforcement of masochist trends, or ambivalence and resignation regarding the painful feeling of loneliness and isolation, and imply as if the medications could replace the human relationship. In antidepressant trials for adults, the placebo rate is 30–50%, compared with a medication response rate of 45–70%, and it has risen at a rate of 7% per decade over the past 30 years [56, 57]. According to the “Dodo bird verdict” in psychotherapy 40% of change comes from patients’ personal resources, both psychological and environmental, 30% from common features of therapists such as empathy, warmth, acceptance, and encouragement of risk taking, 15% from patients’ trust and expectation, sometimes called placebo, and 15% from the therapist’s specific techniques and theoretical models [58]. Some authors, on the basis of meta-analyses, claimed that 50% of clinical improvement in patients with depression is an effect of placebo, 25% is due to pharmacodynamic effects, and 25% to spontaneous remission [8, 9, 59].

Placebo can be understood from different angles (see Table 23.12) as a way of the pleasing the patient, resilience and antifragility activation, resetting the brain, natural healing activation, the power of positive thinking/faith, and as a game that people play. Depression is a vicious circle in which pessimistic thinking, negative

Table 23.12 Placebo and nocebo from seven perspectives

- Disease (depression) perspective: symptoms fluctuation, spontaneous remission
- Personal perspective: pharmacophilic and pharmacophobic personality traits, treatment motivation and desire for symptoms relief; optimism vs pessimism
- Cognitive perspective: power of positive and negative, self-defeating thinking; trustworthiness or untrustworthiness activation
- Behavioral perspective: positive and negative conditioning; social learning by observation; habituation vs sensitization; placebo and nocebo games
- Narrative perspective: positive and negative narratives, winner’s and loser’s scripts
- Spiritual perspective: behind the drive for survive there is faith; nocebo lack of faith
- Systems perspective: positive and negative synchronicity

expectations, and negative emotions feed on each other. Placebo response is related to positive expectations that can set in motion a positive cycle, in which positive fluctuations in mood and well-being are interpreted as evidence of treatment effect instilling a sense of hope. In addition to their pharmacodynamics effects, antidepressant medications work also on account of meanings, expectations, and relationships. Patients are always subjects who give meanings and respond more or less actively to meanings that disease, illness, and treatment have for them and psychiatrists. Inducing positive emotions and optimism during motivational interview or when creating therapeutic narrative is commonly followed by patient’s placebo response. Having pleased patients taking antidepressant medications can be achieved by numerable well-being interventions.

23.4.4 *Changing Old Ill Narrative and Creating New Therapeutic Narrative*

Depression and suffering that bring patients to psychiatrists derive in significant measure from the ways they interpret and give meaning to the events of their life in the form of self-defeating narratives. A life story is an internalized and evolving narrative of the self that incorporates the reconstructed past, perceived present, and anticipated future in order to provide a life with a sense of unity and purpose [17]. Life script is a person’s unconscious life plan, an ongoing program for a life drama that dictates where the person is compulsively going with her/his life and the path that will lead there. Some patients with depression grew up with self-denying interpretations and meanings and became hostage to toxic life scripts that adversely define and constrain their identity, self-image, and future. The manifestation and outcome of depression may be very different within different life scripts. Narrative psychiatry, established on the logic of narrative, life stories and narrative self, help patients to transform psychological suffering and experience depression into an active process of self-reflection, a source of meaning, and an opportunity for psychological and spiritual growth. Patients come to the clinics with intensely personal life stories of suffering, despair, and failure to tell [58, 60] as well as with their

losing and sorrowful unconscious life scripts, life plans made in childhood. Patients with depression focus on negative thoughts as well as on negative imagery and so enter the state of negative auto-hypnosis: (1) depressive rumination is a common response to negative moods; (2) rumination interferes with effective problem-solving by promoting pessimistic and fatalistic thinking; (3) persistent and recyclic negative thinking enhances the effects of low mood on cognitive distortions, thus potentiating negative appraisal of the current circumstances; (4) rumination interferes with instrumental behavior; and (5) people who chronically ruminate lose social support.

Reframing techniques help patients to create new meanings and find different ways of making sense of events and their experiences. Deconstructing narratives that fuel depression, helplessness, low self-esteem and developing stories of strength and meaning can be cultivated and nurtured into narratives that are resources for personal recovery. While restitution story “yesterday I was healthy, today I am sick, but tomorrow I’ll be healthy again” may work for some illness experience, it can be problematic in the context of some other mental disorders for which cure, or return to previous health as it was once, may not be forthcoming [17].

CP-CNP is meaning centered and forgiveness-oriented therapy. Depression is fundamentally about tragic and self-defeating narrative and its reconstruction to one that is hopeful and empowering the patient to construct or co-author a new life story with new values or identity. Throw the reconstructed or new narrative the patient defines the significance of depression, what it means to them or those around them, how it has changed them, how it might empower them, etc. Through illness narratives patients form their own explanations about the causes of their illnesses. Therapeutic narrative refers to explanations how mental health medications work as well as in decisions about using them all the way through therapeutic journey. The restitution narrative presumes the illness to be cured or overcome so that the patient becomes the same or healthy again. The quest narrative is characterized by the patient’s search for meaning and the idea that something can be learned or gained from the illness experience. Treatment relies on the reinterpretation, reframing, and reconstruction of a life narrative that will give new meaning and direction to the patient’s life regarding love, freedom, power, joy, and purpose (narrative therapy).

23.4.5 Fostering Creativity and Supporting Self-Actualization

The huge gap between achieving high treatment effectiveness and poor results in clinical practice may be stitched by more scientific creativity and less dogmatism. Creativity, both on the sides of psychiatrists and patients, is fundamental to CP-CNP of depression. Life success in general, and success in depression treatment in particular, depends on levels of the motivation, learning, self-regulation, and creativity (see [13]). Creativity is a universal quality that exists in all people, but varies from person to person, and usually we differ every day, ordinary or “little c” creativity and eminent, genius or “big C” creativity. Creativity is an enriching and

empowering process that improves motivation, self-esteem, self-actualization, and achievement. Integrative good clinical practice opens the door of creative cooperation to pharmacotherapy and psychosocial and spiritual therapies, in order to achieve optimal therapeutic outcome.

The idea that creative expression can significantly contribute to the healing process has been old one in medicine. In general treatments can be divided into creativity-promoting and creativity-killing ones. The CP-CNP concept promotes prescribing antidepressants as a part of creative life reorganization “with a little help of our medication friends.” Stimulating antidepressants are more helpful in fostering creativity in inhibited patients, while sedating ones are better in agitated patients. The important role of dopaminergic neurotransmission in creative thinking and behavior is explained by its impact on motivation, mental imagery including hallucinations, visions and vivid metaphors, curiosity and novelty-seeking behavior, epistemophilia, and reward-based actions (see [12, 61]). Quite a number of studies conformed the strong connection between DA system, reward, and creativity [61]. Creative drive and novelty seeking are influenced by mesolimbic DA while self-transcendence is the foundation for creativity and integrity [62]. Eliminating depression SSRIs can foster creative activity, but in some patients they may decrease motivation, libido, and curiosity and cause apathy or amotivational syndrome. Adding dopaminergic antidepressant, for example, bupropion may eliminate SSRI-induced amotivational syndrome. Agomelatine by blocking 5-HT_{2C} receptors can stimulate DA release and induce pro-cognitive effects [2].

Creativity is a multidimensional construct in which different moods influence distinct components of creative thinking. Relationship between creativity and mood disorders differs according to the study approach [63].

Consistent with their negatives self-schemas depressed patients have a negative self-perception of their creativity and coping-adequacy. There are many creativity stimulating techniques and methods nurturing the therapeutic alliance: (1) asking at least five times daily “why is that like that?” and “how to get what I want” establishing purpose and goals; (2) building motivation, particularly intrinsic, and self-esteem; (3) stimulating and rewarding curiosity and exploration and seeing things through others’ eyes; (4) encouraging confidence and a willingness for self-change; (5) promoting supportable beliefs about creativity; (6) building basic skills; (7) providing opportunities for choice and discovery; and (8) focusing on personal mastery and self-competition.

23.4.6 Achieving Personal Recovery and Modeling New Life Story

Depression is commonly very suffering and painful experience, a period of unhappy withdrawal and hibernation where patients should realize that something has gone wrong with their life and that something needs to be change. According to the

evolutionary model depression serves the triple purpose: (1) to signal submission to dominant figures in a hierarchy conflict and internally communicate defeat; (2) to signal helplessness and communicate a need for help to potential care givers; and (3) to disengage from commitments to futile or dangerous goals [53]. Some patients going through depression really discover new dimension in their life and put important things right, but too many of them go on and on, again and again through the dark nights of the soul. For some patients, depression is some kind of a psychological prison in which they put themselves unconsciously. In addition, depression can be compared with looking at life through very dark sunglasses, everything looks black and ominous with hopelessness and feeling of being lost and patients cannot see the right way and the lights at the end of tunnel. Antidepressant medication can help patients to remove the dark glasses that life and future may be seen in light, what to change, which life values to follow, which way to continue life journey...

Personal recovery is defined as the extent to which a patient with depression regains or attains a fulfilled and meaningful life, with or without depressive episodes or symptoms. Personal recovery focused psychopharmacotherapy is supported by creating and fostering hope, meaning, personal responsibility, spirit of optimism, changing the helpless and hopeless victim mentality [5], and commitment to building new life scenario that can significantly contribute to overall positive response to pharmacotherapy, but in the other way round antidepressant medication can contribute to creation and fostering hope, meaning, personal responsibility, spirit of optimism, and commitment to new life story.

23.5 Conclusions

Transdisciplinary integrative theory of depression applied in an art and practice of clinical psychopharmacology may help to overcome gap between academic and clinical psychiatry and significantly improve treatment success of contemporary pharmacotherapy of depression. The concept of CP-CNP has been a distillation of the 40 years of clinical practice and of the personal experience of principal investigator in many international double-blind clinical trials with psychiatric drugs including antidepressant medications. The CP-NCP model has been presented at many regional psychiatric congresses during the last two decades and promoted through International School of the CP-CNP from 2018 at Department of Psychiatry, Clinical Hospital Centre, Tuzla, Bosnia, and Herzegovina.

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Chapter 24

Induced Pluripotent Stem Cells (iPSCs) Technology: Potential Targets for Depression



Gabriela D. Colpo and Antonio L. Teixeira

Abstract Major depressive disorder (MDD) is a heterogeneous condition with complex pathophysiology resulting from the interaction between genetic and environmental factors. Despite a reasonable array of therapeutic options, the management of MDD has been marked by an increasing number of treatment resistant cases. Identifying the multiple pathways involved in the pathogenesis of MDD is fundamental to move the field forward and to define novel and more effective therapeutic targets. The current disease models are not able to recapitulate the complexity of this condition. In the last years, induced pluripotent stem cells (iPSCs) have emerged as a unique tool to help the elucidation of the pathophysiology of psychiatric disorders through disease modeling. In addition, the iPSCs may play an important role in the validation of new therapeutic targets.

Keywords Depression · iPSCs · Disease modeling · Drug screening · Cell therapy

24.1 Introduction

Psychiatric disorders are a leading cause of morbidity worldwide, and major depressive disorder (MDD) is the most prevalent psychiatric disorder, affecting approximately 15 million adults every year in the United States [1, 2]. The pathophysiology of MDD has not been elucidated yet, but studies have provided consistent evidence that genetic and environmental factors are implicated in its pathogenesis [3–5]. Even with the great progress in recent decades, our knowledge about the pathophysiology of many psychiatric disorders, including MDD, remains incomplete. Identifying the

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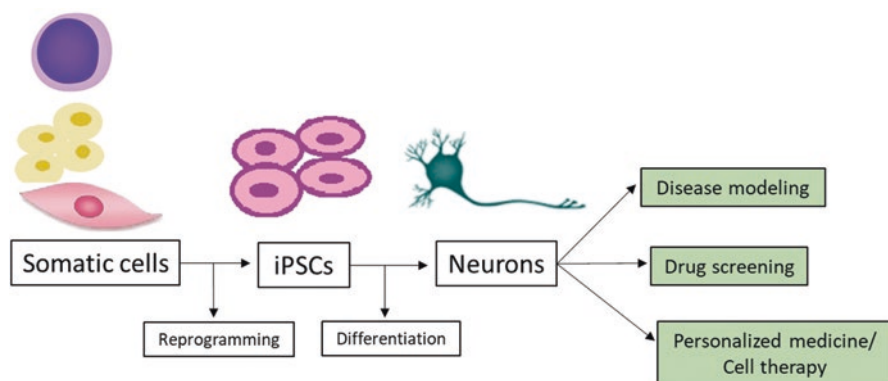


Fig. 24.1 Scheme showing the different possibilities of the use of iPSCs

mechanisms and/or pathways underlying each condition is fundamental to discover novel and more effective therapeutic targets. Despite multiple therapeutic options, the management of MDD is challenging due to side effects and variable degree of response, with a growing frequency of treatment resistant depression. In this context, there is a critical need to identify more effective strategies for the biological treatment of MDD beyond the modulation of monoamine systems [6, 7].

In the last years, the emergence of cellular reprogramming technologies has led to an exciting period for the stem cell biology and regenerative medicine fields, as well as disease modeling and drug discovery. Since 2007, adult somatic cells can be reprogrammed into induced pluripotent stem cells (iPSCs) by the induction of key transcription factors that define the embryonic stem cell state [8–10]. The iPSCs have already been generated from humans' fibroblasts, keratinocytes, hair follicles, peripheral blood, and many other cell types [11], while a variety of cells has been generated from iPSCs, including myocardial, liver, retinal pigment epithelial and neuronal cells [12]. These recent advances hold enormous potential in psychiatry, especially for disease modeling, drug screening, and stem cells therapies [13] (Fig. 24.1).

24.2 iPSCs for Disease Modeling

Identifying pathological mechanisms underlying human diseases plays a key role in discovering novel therapeutic targets. The incomplete understanding of the human brain and the complex interaction between genetic and environmental factors are some of the difficulties that hamper the advance of research in psychiatry. In addition, there is the lack of consistent and valid models able to recapitulate the heterogeneity and complexity of psychiatric disorders.

Animal models have provided valuable tools for modeling human diseases, allowing the identification of pathological mechanisms. However, modeling “mental” disorders in animals is challenging because of the subjective nature of most symptoms, and the lack of biomarkers and reliable tests [14]. Moreover, it is difficult to assess complex phenotypes in animals, such as the melancholic and psychotic experiences. Another valuable source for examining pathological changes in patients is postmortem human brains. Nevertheless, these tissues only represent the disease endpoint while the changes that lead to the progression of these disorders usually occur early in development. Postmortem brain tissues are also limited in their ability to study dynamic cellular changes usually implicated in the physiopathology of psychiatric disorders [15]. Based on those facts, there is a need to establish human disease modeling platforms to study psychiatric disorders. iPSCs technology is a promising method in this context.

One of the greatest benefits of the iPSC technology for modeling human diseases is that iPSCs contain the complete genetic background of the donor, making it particularly suitable for the study of diseases with strong genetic basis. These cells are appropriate to identify molecular alterations, examine gene expression, and identify and test novel signaling pathways. Unfortunately, epigenetic changes are lost during the reprogramming process. For conditions like MDD, in which environmental factors play a major role and are able to induce epigenetic modifications, this is a matter of concern [11].

One advantage of iPSCs in comparison to embryonic stem cells (ESCs) is their availability as any adult individual can donate somatic cells. Another advantage is the more limited ethical concerns compared to the multiple issues associated with human ESCs [16]. Besides that, due to their inherent properties of self-renewal and potential to differentiate into any cell types, patient-specific iPSCs could provide great quantities of disease-relevant cells and a variety of cell types that were previously inaccessible, such as neurons and cardiomyocytes [13].

A challenge in disease modeling with iPSC technology is to generate region-specific disease-relevant cell types [17]. There is a great diversity of cell subtypes in the central nervous system (CNS), and distinct psychiatric disorders seem to be associated with different groups of neurons. In order to model MDD pathogenesis with iPSC technology, it will be necessary to generate specific sets of neuronal cells that are more directly involved in its pathophysiology. Due to the complex nature of depression, involving multiple symptoms and behavioral domains, different subtypes of neuronal cells and glial cells, or even neural circuits, must be taken into account for meaningful in vitro modeling [18].

To deeper study depression modeling, two independent groups proposed protocols for generating serotonergic neurons from iPSCs. Xu et al. described that human primary fibroblasts were directly converted to induced-serotonergic (i5HT) neurons by the expression of *Ascl1*, *Foxa2*, *Lmx1b*, and *FEV*. They observed that i5HT neurons expressing markers for mature serotonergic neurons had Ca^{2+} -dependent serotonin release and selective serotonin uptake, and exhibited spontaneous action potentials and excitatory postsynaptic currents [19]. The second group showed that

overexpressing the transcription factors NKX2.2, FEV, GATA2, and LMX1B together with ASCL1 (Achaete-scute homolog 1) and NGN2 (Neurogenin-2) directly and efficiently generated serotonergic neurons from human fibroblasts. Induced serotonergic neurons had high expression of specific serotonergic genes known to be expressed in raphe nuclei. These neurons exhibited spontaneous action potentials, releasing serotonin *in vitro* and functionally responding to selective serotonin reuptake inhibitors (SSRIs) [20]. Serotonergic neurons are dysregulated in depression and are the target of commonly used antidepressants such as the SSRIs. The same group generated iPSCs from a large cohort of well-characterized MDD patients with SSRI-remitters and SSRI-non-remitters. They studied serotonergic neurotransmission in forebrain neurons *in vitro* and observed that non-remitter patient-derived neurons displayed serotonin-induced hyperactivity downstream of upregulated excitatory serotonergic receptors, contrasting with the normal activity from healthy subject- and remitter patient-derived neurons. Their data suggest that postsynaptic forebrain hyperactivity downstream of SSRI treatment may play a role in SSRI resistance in MDD [21]. Apart from the understanding of the involvement of serotonergic neurons in MDD and the related therapeutic response, iPSCs may help the study of other pathways (e.g., glutamatergic), possibly contributing to dissecting the biological underpinnings of depression clinical heterogeneity.

It is also worth mentioning some studies in bipolar disorder (BD). Mertens et al. created iPSCs from fibroblasts of patients with BD, and these iPSC model neurons were hyperexcitable, firing action potentials at a higher frequency than control neurons. In line with this neurophysiological finding, these neurons showed different expression of calcium signaling and mitochondrial genes [22]. Interestingly, the hyperexcitability exhibited by the neurons was selectively reversed by lithium treatment only in neurons derived from patients who also responded to lithium treatment, but not in neurons derived from non-lithium responder patients. Later, the same group generated hippocampal dentate gyrus (DG) neurons from iPSC-derived fibroblasts of BD patients. They wanted to verify that the hyperexcitability of DG-like neurons could be reproduced in this different cohort of patients and cells. Electrophysiological analysis showed that intrinsic cell parameters were very different between the cells derived from lithium-responsive patients and those derived from lithium-non-responsive patients. They confirmed that these two subpopulations of cells are so intrinsically different from each other that it is possible to predict the response to lithium of a patient based on electrophysiological results [23].

Although the use of iPSCs to study psychiatric disorders has provided exceptional insights to the field and has demonstrated great potentials to bridge the clinical features with cellular phenotypes that can be studied in the lab, there are a number of obstacles to overcome. For example, there is a great amount of variability in the reprogramming of iPSCs from somatic cells and in the generation of brain cells from the iPSCs. These variations may occur in any steps from reprogramming to differentiation.

24.3 iPSCs for Drug Screening

Traditional high-throughput screenings for drug usually use immortalized cell lines or rodent primary cells which have debatable validity due to methodological artifacts and/or their nonhuman nature with poor track record for predicting results in therapeutic clinical studies [24, 25].

iPSCs have become an important tool for drug screening as a more tailored model to mimic human conditions. iPSCs are also a valuable source of primary cells with reasonably stable genomes that can be cultured, expanded, and differentiated into different types of tissue. In addition, its intrinsic ability to self-renew allows the growth of stem cell colonies for high throughput assays and drug screening purposes. Conversely, the confirmation of the link between genotype and disease can be misleading due to the complexity of the individual's genetic composition and the potential influence of epigenetic changes on disease manifestation and progression. These limitations can increase exponentially when studying complex disorders as depression in which multiple genes and environmental factors seem to play a role [26].

iPSC-based drug screening has been used to evaluate compounds for multiple diseases [27, 28], and some candidates have been identified [29–31]. So far no study using iPSCs for drug screening for depression has been published. This reflects at least in part the complexity and heterogeneity of this disorder.

Another related application of disease-specific iPSCs is in drug repurposing, in which current drugs already approved for specific diseases are tested to find new applications. For example, the anti-epileptic drug ezogabine demonstrated efficacy in an iPSC model of amyotrophic lateral sclerosis and is now undergoing clinical evaluation for this indication [32].

Although significant progress has been made with iPSCs technology and drug discovery platforms, there are issues that must be addressed. First, cell-type heterogeneity reduces the chances of identifying a positive hit, illustrating the need for better differentiation protocols. Second, the culture conditions and protocols require to be controlled and standardized. Third, the cell type must be robust and disease-relevant. Finally, animal models are still required for the validation of positive hits from iPSC-based screening platforms. Despite these challenges, this technology holds great promise as a new translational platform for drug testing using human neurons [26].

24.4 Clinical Applications Using Human iPSC Products

Human iPSCs are a promising prospect for cell therapy for several diseases that do not have cure or effective therapies, including psychiatric disorders and neurodegenerative diseases. The standard use of iPSCs for cell therapy purposes involves

their differentiation into the desired cell types of interest for their later transplant as cell suspensions or more complex tissue constructs into patients. The differentiation step is essential because if undifferentiated iPSCs are directly injected, they could form tumors called teratomas due to their highly proliferative nature and extensive differentiation potential. Although the cells differentiated from iPSCs have not been shown to generate teratomas, it is critical to confirm that the final cells do not contain any undifferentiated cells that have the potential to generate teratomas [13]. However, protocols for differentiating human iPSCs into desired cell types with specific identity and cellular functions need to improve. Some small molecule inhibitors have been identified that shown to induce selective and complete cell death of undifferentiated human pluripotent stem cells without affecting their differentiated derivatives [33, 34]. Treatment of the iPSC-derived cellular products with these inhibitors may reduce the potential tumorigenicity. Another potential solution is to sort the iPSC-derived cells before transplantation through positive selection for desired cell types and negative selection against human ESC markers using fluorescence-activated cell sorting (FACS). The risk of tumorigenicity can also be tested in animal models prior to transplant, although this approach may not be applicable to patients with rapid disease progression due to the long period of time associated with animal testing.

Up to date there is no study using iPSCs to treat depression; however, several iPSC-based clinical trials have recently been underway to treat macular degeneration, Parkinson's and heart disease, highlighting the rapid progress in this area [13, 35]. For depression treatment, there are only studies using mesenchymal stem cells (MSCs), that is, a type of multipotent progenitor cells that have the capacity to differentiating into all lineages of mesodermal origin. MSCs also have the ability to promote neurogenesis and improve survival of neuronal cells by expressing soluble factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1) [36]. Tfilin et al. showed that the intracerebroventricular administration of MSCs improved depressive-like behavior and increased hippocampal neurogenesis in a genetic rat model of depression (Flinders sensitive line) [37]. In contrast to MSCs, iPSCs can be generated from more accessible tissues such as skin and blood, and are pluripotent instead of multipotent stem cells. iPSCs can also be produced from the same patient and be used in autologous transplantation, avoiding complications of rejection by the host immune system [16].

There are several obstacles associated with iPSC-based therapy that will need to be addressed before routine clinical applications can begin [38]. Ethical, legal, and safety considerations for the use of these cells should be taken into account before starting any clinical trial. One concern is the risk of tumorigenicity iPSCs [39]. Because pluripotent cells are maintained in culture for prolonged periods of time, they can accumulate karyotypic abnormalities, copy number variants, and loss of heterozygosity [40]. Prior to clinical use, iPSC-derived products need to be carefully screened for the lack of potentially risky genetic alterations [40] and rigorously tested to ensure their purity, quality, and sterility. Increased knowledge on the

basic biology of pluripotency induction and maintenance will also help us to reduce the risk of mutation development and genetic instability associated with human iPSC derivation and maintenance.

24.5 Conclusion

In the 12 years since the first iPSC report, great progress has been made and iPSCs have opened up a new avenue for stem cell research and unique opportunities for disease modeling for complex disorders, such as depression. In addition, iPSCs constitute a new possibility to treat diseases that still have no cure or effective therapies. However, there are several issues that must be addressed in the methodology to ensure the safety of patients. Reprogramming technology also has its own ethical and social issues that must be carefully considered. Laws and standards must be put in place to ensure the integrity of iPSC production/application and to simultaneously remove unnecessary barriers in the research and therapy with iPSCs.

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Chapter 25

Vaccination and Immunotherapy for Major Depression



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Abstract Depression is a very common disease with increasing incidence resulting from complex interactions of genetic, environmental, and immunological processes. To this day, the etiopathogenesis and treatment of depression unfortunately seem to be stuck in the synaptic gap. Despite highly potent antidepressants, the treatment rate cannot reach 100%, the treatment resistant group cannot be eliminated, and relapse cannot be prevented. These problems lead researchers to further and different research to understand and treat psychopathology. Immune dysfunction and neuroinflammation have been one of the main issues that psychiatry has focused on in recent years and helps us to understand depression. Extraneuronal components of all neuropsychiatric disorders, especially depression, have begun to be revealed in detail thanks to a better understanding of the immune system and an increase in experimental and technological possibilities. There is increasing evidence of a causal relationship between the etiopathogenesis of major depression and low-level chronic neuroinflammation. In this article, the role of neuroinflammation in the etiopathogenesis of depression and the possibilities of vaccination and immunotherapy are discussed.

Keywords Depression · Neuroinflammation · Vaccination · Immunotherapy

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25.1 Introduction

Homo sapiens co-evolved with microorganisms according to the view firstly presented as “hygiene hypothesis,” then expanded as “old friends hypothesis.” This process has come out of its natural course in the twenty-first century due to modern living conditions (excessive and unnecessary use of disinfectants, antibiotics, vaccination, urban life, etc.) and has played an important role in the etiopathogenesis of many physical and mental diseases [1].

The next ring of this view suggested by Rook et al. and related to the cause of neuropsychiatric disorders, especially depression contains recommendations for treatment. If depression is a neuroinflammatory disease, can't we treat it by modulating the immune system? In other words, “Can we vaccinate against depression?” [2].

Since the 1950s, with the discovery of psychotropics, antidepressants have found wide use in the treatment of depression. However, both remission rates are not satisfactory and there is a high risk of relapse in antidepressant treatments. Therefore, both central nervous system researchers and extraneuronal (internal diseases, infectious diseases, microbiology, pharmacology, etc.) clinicians have been in search of alternatives to antidepressants in the treatment of some types of depression during the last two to three decades. Examples include fecal microbiota transplantation and psychobiotics [3, 4].

As an extension of this search, the recently proposed vaccination and immunotherapy options can go beyond being science fiction. Since the hypothesis has been present for a short period of time and perhaps appears to be a bit speculative, little information has yet been accumulated in this area. Nevertheless, this article will focus primarily on the inflammatory hypothesis of depression, and then discuss the immunomodulation options in the treatment of depression in the light of the limited information available.

25.2 Immunopsychiatry

In fact, the immune hypothesis of depression dates back to much older times [5]. According to this view, the level of proinflammatory cytokines and immune mediators in the circulation of many depression patients increases while the number of anti-inflammatory cytokines and mediators decreases. Although this may be described as a coincidence, recent evidence points to the causal role of proinflammatory cytokines in the etiology of depression [6]. Where this inflammation came from has long been a question of interest [7]? The possible source of this endogenous inflammation may be the intestinal microbiota [8]. In response to systemic endotoxemia caused by dysbiosis and leakage in the intestinal microbiota, immune system activation occurs and thus may provide a basis for neuroinflammation [9].

The immune interaction between the brain and the body functions in two ways. While the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic/parasympathetic nervous system connects the brain to the body, the messages of the immune system reach from the body to the brain through the cytokines and vagus nerve [6]. Inflammation is the classic response of the immune system to cell damage. This cell damage may be the result of infectious agents or physical injury. Sometimes, autoantibodies trigger physical injury. In addition, one of the immune activators is psychological stress.

Four classical signs of inflammation are heat (calor), redness (rubor), pain (dolor), and swelling (tumor). However, these cardinal symptoms are not observed in neuroinflammation. Even so, the cellular response occurred in brain tissue is similar to that of other tissues. Microglia, immune system cells in the brain, are activated and cause cytokine, chemokine, and prostaglandins to be secreted between neurons [9].

25.3 Depression As a Neuroinflammatory Disease

Depression is frequently observed in people with chronic inflammatory disease (e.g., rheumatoid arthritis, Crohn's disease) [10, 11]. Besides, depression develops in about half of the patients receiving interferon (an immune mediator that induces proinflammatory cytokines) for the treatment of hepatitis C virus [12]. Elevated proinflammatory cytokine interleukin-6 (IL-6) following typhoid vaccination causes depression in healthy subjects [13]. In addition, recent meta-analysis studies have shown that proinflammatory cytokine (IL-6, IL1 β , tumor necrosis factor alpha, and C-reactive protein) levels increase in depression patients and decrease with antidepressant treatments [14, 15]. Evidence showing that autoimmunity increases is accumulating [16]. These and similar observations suggest that immune processes and inflammation may play a role in the etiopathogenesis of depression.

Although controversy continues as to whether this is the cause or consequence of depression, some recent cohort studies have revealed data about the fact that proinflammatory cytokines may be the cause of depression [17, 18]. However, it is still useful to focus on specific symptoms to clarify the role of inflammation in depression. Since, for example, elevated CRP levels in patients with depression are more related to physical symptoms (anergy, sleep, and appetite problems) than psychological symptoms (unhappiness, pessimism, etc.) [19]. These results are similar to those of cancer patients who developed depression due to interferon treatment [20]. In the light of evaluations taking into account all confounding factors, the available evidence suggests that an inflammatory process is likely to function before the development of depression and may be a causal risk factor for depression.

One of the important areas that has become a research topic in the etiopathogenesis of depression in recent years is the immune-kynurenine pathway [21]. Tryptophan is the precursor of serotonin and kynurenine [22]. More than 90% of tryptophan is converted to kynurenine by indoleamine-2,3-dioxygenase (IDO,

found in all cells) and tryptophan-2,3-dioxygenase (TDO, found only in the liver) enzymes [23, 24]. IDO has two different structures as IDO1 and IDO2 [25]. Systemic inflammation plays an important role in the activity rate of IDO1 and TDO. Proinflammatory cytokines strongly activate the IDO1 pathway while glucocorticoids strongly activate the TDO pathway [24]. The metabolites of kynurenine (kynurenic acid and quinolinic acid) show stimulant effect by stimulating *N*-methyl D-aspartate (NMDA) and alpha-7 nicotinic receptors [26]. Kynurenic acid has anti-inflammatory and neuroprotective properties, while quinolinic acid has excitotoxic properties [27, 28]. When the composition of the intestinal microbiota is disrupted (dysbiosis), the synthesis of serotonin from tryptophan in the intestine decreases [8]. In addition, lipopolysaccharides involved in the systemic circulation due to leaky gut can stimulate the immune system and cause low-grade inflammation [8]. With extra inflammation added to the cycle, serotonin production from tryptophan is further reduced and tryptophan catabolism shifts to the kynurenine pathway. This cyclic system may be involved in the etiopathogenesis of depression [4].

25.4 Effect of Cytokines on Neurotransmitter Systems

There are many clinical and preclinical studies showing that cytokines have an effect on neurotransmitter levels and functions. The majority of these studies are undoubtedly related to serotonin (5-HT). Acute 5-HT turnover has been shown to increase in the brains of experimental animals exposed to proinflammatory cytokines [29, 30]. It has been shown that IDO activity increases with low-level chronic inflammation and inflammatory cytokine administration, and as a result, metabolism of kynurenine from tryptophan is increased [31–33]. IDO activity rapidly increases and peaks on the second day in the experimental animal brain after hours of lipopolysaccharide (LPS) administration [34, 35]. This evidence becomes even more significant when LPS administration is considered a model of depression in animal experiments. These findings have been interpreted to suggest that the reduction of 5-HT synthesis via IDO in the brain plays an important role in cytokine-induced depression. Because a correlation was found between cytokine-induced depression and decreased plasma tryptophan, increased kynurenine level, increased kynurenine/tryptophan ratio [32, 36].

Fatigue is an important symptom of depression caused by cytokines and may mean the reflection of cytokines on dopamine (DA) functions (especially in basal ganglia) [37, 38]. Changes in basal ganglia activity and DA metabolism in cytokine-induced depression may be the cause of symptoms such as psychomotor retardation and anhedonia [39]. In a functional magnetic resonance imaging (MRI) study, decreased basal ganglia glucose metabolism was found in motivational tests following IFN-alpha administration [40].

Cytokine exposure causes an increase in locus coeruleus activity and norepinephrine (NE) levels in the hippocampus. This increase is thought to result from activation of the HPA axis associated with immune stimulation [41]. Although 5-HT

metabolites in CSF were correlated with depressive symptoms and DA metabolites were correlated with psychomotor slowing, levels of 3-methoxy-4-hydroxyphenylglycol, the major metabolite of NE, were not associated with behavioral symptoms in patients treated with IFN- α [39, 42]. However, no correlation was found between DA beta-hydroxylase (enzyme converting DA to NE) gene polymorphism and depression development in hepatitis C virus (HCV) patients treated with IFN- α [43]. Further studies are needed to better understand the relationship between the highly complex functions of neurotransmitter systems and cytokines.

25.5 Can Depression Be a Side Effect of Vaccination?

Information on the relationship between depression and the immune system is increasing in the literature of psychoneuroimmunology. In addition, views about that the immune system triggered by vaccines may be associated with depression are also being expressed. Vaccination for infections may have some very surprising results. One of these is that flu-vaccine virus in mice adversely affects normal bacterial colonization according to a study published by the American Society for Microbiology [44]. It was found in another study that live, attenuated, viral vaccines may also have an effect on the levels of microbiota microorganisms (e.g., probiotic bacteria) which are not targeted by the vaccine [45]. A correlation was found between vaccine response (antibody levels) and mood symptoms in adolescents (11 years of age) followed up for 6 months following meningococcal vaccination in a large sample study [46]. The literature of the last 50 years was reviewed in a recent review by Kuppli et al. on the interrelation between psychiatric disorders and vaccination. However, there was no study showing a relationship between vaccination and depression [47].

25.6 Antidepressant Efficacy of Anti-Inflammatories

Today, selective serotonin reuptake inhibitor (SSRI) antidepressants are the first line drugs for the treatment of depression [48]. The ancestor of these drugs is iproniazid (an anti-tubercular drug) [49]. It came out by the discovery of spectrophotofluorometer (SPF) that iproniazid caused MAO inhibition [50]. The electrical and chemical activity in the synaptic gap was observed and the neurotransmitters we know today were identified thanks to SPF [51]. A similar situation to iproniazid applies to minocycline, which is a tetracycline antibiotic [52]. If an antimicrobial molecule can produce an antidepressant effect by affecting synaptic transmission at the same time, can anti-inflammatory drugs also show antidepressant activity with various mechanisms of action? Bai et al. responds positively to this question [53].

Non-steroidal anti-inflammatory drugs (NSAIDs, e.g., acetylsalicylic acid: aspirin) are the family of drugs whose antidepressant efficacy has been most studied among the anti-inflammatory drugs. These drugs show anti-inflammatory activity by inhibiting cyclooxygenase (COX) enzymes, an important step in the inflammation pathway. No correlation was found between the two conditions in a retrospective study on the relationship of long-term (5 years) use of aspirin on depressive symptoms [54]. In another retrospective study conducted in the same year, the rate of depression in aspirin and statin users was found to be approximately 7 times lower compared to the control group [55]. However, the use of statins in addition to aspirin in this study may have significantly affected the outcome. Because statins are thought to have anti-inflammatory activity [56]. No significant difference was found between the three groups receiving daily celecoxib (400 mg/day), naproxen sodium (440 mg/day), and placebo in terms of depression scores in a 5-year prospective study [57].

In addition to the studies in which NSAIDs were examined as monotherapy for the treatment of depression, studies have also been conducted in which they are used as augmentation therapy to antidepressants. Addition of celecoxib to fluoxetine was found to be more effective than use of fluoxetine alone in one of the randomized, placebo-controlled, double-blind trials [58]. In another study with similar design, celecoxib was combined with sertraline and compared with the group receiving sertraline monotherapy. Significant correlation was found between serum IL-6 rates and decrease in depression scores after 6 weeks [59]. In addition to the efficacy of NSAIDs, its reliability in terms of various side effects (intracranial or gastric bleeding) needs to be considered [60].

Minocycline is thought to have both antidepressant and neuroprotective effects by stimulating anti-inflammatory cytokine release from astrocytes and inhibiting proinflammatory cytokine release from microglia [52]. In a study evaluating the efficacy of minocycline as monotherapy on depressive symptoms, the minocycline group was found to be significantly effective and reliable compared to the placebo group [61]. It was found that minocycline augmentation had a significantly reducing effect on psychotic properties and depression level in an open-label study comparing patients with and without minocycline added to their standard SSRI antidepressant treatments in cases with psychotic major depression [62].

25.7 Vaccination As an Antidepressant Treatment Tool

We should start by repeating the question we asked at the beginning of this article: “Can we vaccinate against depression?” [2]. This idea, which was suggested by Rook et al. in 2012, seems to be met with indifference as in any innovative thought. Because a vaccine being searched for the treatment of depression has not been found in the literature [63]. In fact, considering the low rates of treatment with standard antidepressant drugs and the high relapse rates, it should be said that vaccination possibilities should be available, especially in order to prevent recurrent

depression. The immune component is quite clearly evident in depression according to the rapidly growing literature.

Vaccines are the treatments generally developed for a specific infectious disease and are used to produce immunization against the pathogenic microorganism that causes the disease [64]. In other words, the agent/pathogen causing the disease must be determined first in order to develop the vaccine. It is clear that the same route should be followed to develop a vaccine against depression.

In this respect, the target microorganisms should be the ones in the intestinal microbiota. Because there is an avalanche of literature on gut-brain axis in recent years [4, 65]. The most important development emphasized by this literature is leaky gut in depression patients. As a result of this, Ig A and Ig M levels for LPS of gram-negative enterococci (Proteobacteria) increase [66]. According to the results of another study, fecal microbiota analysis of depression patients showed an increase in Bacteroidete levels [67]. However, there are two studies showing that it is possible to transfer depression. The “depression microbiota” obtained from depression patients was transferred to mice in one and to rats in the other one of these two germ-free animal experiments, which were designed and performed independently and published in the same year. Depressive symptoms were observed in experimental animals in both studies [68, 69]. If depression is a disease caused by some microorganisms, we may be hopeful to develop a vaccine against depression after their clear identification in the future.

25.8 Conclusion

Since the 1950s, much has been learned in favor of the pathophysiology and treatment of depression. However, all this information is just the tip of the iceberg and it may be a long way to go. The monoamine hypothesis provides a very consistent basis for the explanation of depression at synaptic level, and depression has now become readily curable due to the effective and safe antidepressant drugs put into use by modern psychopharmacology. Nevertheless, the success rates of antidepressants are not satisfactory due to late treatment effect, remission rates of around 70%, high relapse percentage, and side effects that disrupt treatment compliance of the patients (weight gain, sedation, sexual dysfunction, etc.).

Information from clinical and preclinical studies in recent years suggests that there may be low-level inflammation on the basis of depression. It is known that antidepressant drugs have some roles beyond synaptic transmission both by creating antimicrobial effect on the intestinal microbiota and as the mediator of the immune system. At this point, the question “*If depression is a neuroinflammatory disease caused by some microorganisms, can’t it be prevented by vaccination?*” will make sense. There is no significant improvement in response to this question yet. However, light may be seen at the end of the tunnel if all the scattered information at hand can be put together.

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Chapter 26

Psychedelic Medicines in Major Depression: Progress and Future Challenges



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Abstract The volume of research on the therapeutic use of psychedelic drugs has been increasing during the last decades. Partly because of the need of innovative treatments in psychiatry, several studies have assessed the safety and efficacy of drugs like psilocybin or ayahuasca for a wide range of mental disorders, including major depression. The first section of this chapter will offer an introduction to psychedelic research, including a brief historical overview and discussions about appropriate terminology. In the second section, the recently published clinical trials in which psychedelic drugs were administered to patients will be analysed in detail. Then, in the third section, the main neurobiological mechanisms of these drugs will be described, noting that while some of these mechanisms could be potentially associated with their therapeutic properties, they are commonly used as adjuvants in psychotherapeutic processes. The last section suggests future challenges for this groundbreaking field of research and therapy.

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26.1 Introduction to Psychedelic Therapy

Psychedelics are a series of compounds, active principles, plants, fungi and animal secretions that induce dramatic altered states of consciousness that have central roles in the worldviews and ontologies of many indigenous cultures around the globe. The term ‘psychedelic’ is derived from the Greek words *ψυχή* (*psyche*, ‘soul, mind’) and *δελείν* (*delein*, ‘to manifest’), hence ‘mind-manifesting’. The word describes a state of consciousness in which human potentialities can be manifested. The term was coined by the English psychiatrist Humphry Osmond in 1957 as an alternative to ‘hallucinogen’ [from the combination of the Latin word *alucinor*, ‘to wander in mind’, with the Greek word *gen*, ‘producing’]. Although the term ‘hallucinogen’ is commonly used in the scientific literature, some authors consider the term pejorative because it refers to something that is pathological and that is not a main effect of these drugs (i.e. hallucinations). In that sense, the so-called psychedelic experience is ‘real’ and not a hallucination and indeed may have psychological benefits if it is properly conducted. However, it could be argued that the term ‘psychedelic’ is too related to the counterculture of the 1960s and would not be adequate to describe the ritual and religious uses of some of these compounds. Therefore, both terms have their limitations, and both are the ones currently mostly used in the scientific literature.

The terminology for referring to those active principles and plants is challenging because of the unspecific nature of their effects, which are often ineffable and context- and cultural-dependent. For indigenous people, for example, which have the larger (probably millenary) historic use of psychedelic compounds and plants, the terms psychedelic and hallucinogens do not reflect the meaning that they attribute to those practices. For them, the use of psychoactive plants goes beyond the effects over the single person but are conceived as the main spiritual tool that connect the individual with the community, as well as with their environment and with the geographical and spiritual territory. In that sense, psychoactive plants for the indigenous cultures are considered sacred because they operate in their spiritual world, where all the above-mentioned connections take place. Every single culture has a specific name for their traditional plants, being psychedelic (or hallucinogen) the term used by our Western scientific culture, that does not necessarily mean the same for members of other cultures.

The early Western psychedelic researcher Leo Hollister characterized the effects of psychedelics as follows: (1) a small dose produces great effects; (2) compared to other effects, the changes in thought, perception and humour predominate; (3) intellectual or memory deterioration must be minimum with high-medium dose; they

can be produced with large doses; (4) sedation or stimulation should not be an integral part of the action; (5) the side effects on the nervous system must not be incapacitating or severally disturbing; (6) the addiction potential must be minimum. According to these categories, the prototype of psychedelic drug is lysergic acid diethylamide (LSD) [1]. Nowadays the term psychedelic is mainly used to refer to substances that act as agonists or partial agonists on cortical 5-HT_{2A} serotonin receptors, such as LSD, psilocybin, mescaline and dimethyltryptamine (DMT). Thus, these drugs are also known as serotonergic psychedelics or hallucinogens, and all of them fulfil Hollister's criteria [2].

The history of use of psychedelic drugs is probably millenary. The oldest archaeological evidence corresponds to a post-Palaeolithic rock paint in Spain where supposedly *Psilocybe* mushrooms (containing psilocybin) are represented, indicating the first direct evidence for possible ritual use of psychedelics [3]. Other Neolithic paintings of *Psilocybe* mushrooms have been found in the Sahara Desert, in South Africa and in Australia, and numerous anthropomorphic sculptures representing *Psilocybe* mushrooms have been found in Mexico and Guatemala. The ritual use of *Psilocybe* mushrooms survives in remote mountains of Mexico, as well as the use of iboga roots (*Tabernanthe iboga*) in tropical Africa, peyote and San Pedro cactuses (containing mescaline) in areas of Canada, the United States, Mexico, Peru, Ecuador, Bolivia, Chile and Argentina, ayahuasca (an Amazonian decoction containing DMT) along all the Amazonia and DMT-containing snuffs (yopo or epená) in Venezuela and Brazil, among others.

Western culture has also a long history and tradition of psychedelic drug uses for psychospiritual and social integration purposes. The main example is the Eleusis ritual in ancient Greece, where for 2000 years a ritual using a drink with eventual LSD-like properties ('kykeon') was used with spiritual and self-transformative purposes. Philosophers like Plato, Aristotle or Seneca participated in the rituals until the temple of Eleusis was destroyed by the Christians and the rites were forbidden [4]. But similar rituals survived in different parts of Europe over the centuries.

With the advances of modern chemistry, the active principles of different psychedelic plants were isolated. The first isolated compound was mescaline in 1897 from the peyote cactus. In 1938 LSD was first synthesized by the eminent chemist Albert Hofmann. In 1955 DMT was identified in *Viola peregrina*, and in 1958 Albert Hofmann isolated psilocybin from *Psilocybe* mushrooms, publishing its synthesis process in 1969. The isolation of mescaline and the discovery of LSD and psilocybin inaugurated the modern era of psychedelic psychotherapy in the 1950s. The Sandoz pharmaceutical company marketed LSD and psilocybin for the following uses: (1) in analytical psychotherapy, to elicit repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses, and (2) in experimental studies on the nature of psychoses. In that sense, above all Europe, psychedelics were used in psychotherapy to boost the therapeutic process, using relatively low doses, in what is known as the 'psycholytic' ('to decompose the mind') paradigm. Psychedelics were used in disorders like anxiety, depression, alcoholism, autism, schizophrenia and even in survivor syndrome in holocaust survivors. At the

same time, these drugs were self-administered by psychiatrists and psychiatry students under training in order to better understand the process of psychosis in what is known as the ‘psychotomimetic’ paradigm.

In the United States, although psychiatrists also used psychedelics under the psycholytic paradigm, Dr. Humphry Osmond, working with alcoholic patients, discovered that high doses of psychedelics could induce a spiritual experience that could lead patients to withdraw from alcohol. The paradigm of administering high doses to induce spiritual experiences was named the ‘psychedelic’ paradigm. This method was predominant in the United States and was used for all kinds of diseases and psychological disturbances, mainly depression, obsessive-compulsive disorders, anxiety and depression in end-of-life diseases, cancer-related pain and drug dependence, among others [5].

Scientific research with psychedelics was interrupted for some decades because of technical and political reasons [6]. But in the early 1990s, psychotherapeutic and neuropharmacological research with these drugs started again, in what some authors call the ‘Psychedelic Renaissance’. Since then, several studies have been conducted, and the main compounds being currently investigated are LSD, psilocybin and ayahuasca/DMT for the treatment of depressive and anxiety disorders and drug dependence [7].

The general assumption is that psychedelics enhance the psychotherapeutic process instead of having intrinsic therapeutic properties, although there are some biological mechanisms of action that can explain their therapeutic properties and in particular their antidepressant effects (see below). In that sense, the term often used to describe this intervention is ‘psychedelic-assisted psychotherapy’.

26.2 Clinical Trials Assessing the Antidepressant Effects of LSD, Psilocybin and Ayahuasca/DMT

In the late 1960s and early 1970s, psychedelics were investigated in the treatment of mood disorders [5] and existential anxiety and depression associated with cancer and other life-threatening diseases [8]. Since 2011, four randomized, double-blind, placebo-controlled, crossover trials using LSD (one trial) or psilocybin (three trials) were published investigating the effects of these drugs on anxiety and depressive symptoms in this clinical population [9–12]. Regarding depressive symptoms specifically, the three trials with psilocybin [9, 10, 12], assessed these symptoms, while the LSD study only assessed anxiety symptoms [11]. The main characteristics and results of these trials are presented in Table 26.1.

These trials included samples of 12–51 patients and administered oral psilocybin doses of 14–30 mg/70 kg in a supportive environment. Depressive symptoms were assessed using the Beck Depression Inventory (BDI) in all three studies, and two studies [9, 12] also used the Hospital Anxiety and Depression Scale (HADS). All studies found a significant reduction in BDI scores 6 months after psilocybin

Table 26.1 Completed clinical trials of LSD, psilocybin and ayahuasca assessing depressive symptoms published in the last decade^a

References	Study design/sample	Main results
Grob et al. [10]	Double-blind, randomized, crossover, with active control (250 mg niacin) 12 patients with advanced-stage cancer and depression and anxiety 0.2 mg/kg oral psilocybin	Significant reductions in BDI scores at 6-month follow-up ($p = 0.03$)
Carhart-Harris et al. [16, 17]	Open-label trial 12 patients with TRD (+8 patients included in the 6-month follow-up) 10 mg oral psilocybin followed by 25 mg 7 days apart	Significant reductions in BDI, QIDS and SHAPS scores at 1-week and 3-month follow-up and in QIDS and SHAPS scores at 6-month follow-up ($p < 0.001$)
Griffiths et al. [9]	Double-blind, randomized, crossover, with active control (1 or 3 mg/70 kg oral psilocybin) 51 patients with life-threatening cancer with depression and anxiety 22 or 30 mg/70 kg oral psilocybin	Significant reductions in GRID, BDI, HADS (total) and POMS scores at 5-week ($p < 0.05$) and 6-month follow-up ($p < 0.001$)
Ross et al. [12]	Double-blind, randomized, crossover, with active control (250 mg niacin) 29 patients with life-threatening cancer with depression and anxiety 0.3 mg/kg oral psilocybin	Significant reductions in BDI and HADS (total/depression) scores at day 1; week 2, 6, 7 and 26; and 6.5-month follow-up ($p < 0.05$)
Osório et al. [14] and Sanches et al. [15]	Open-label trial 6 patients with TRD (+11 patients included in the final sample) 2.2 mL/kg oral ayahuasca (0.8 mg/mL DMT)	Significant reductions in HAM-D, MADRS and BPRS scores at 1-, 7- and 21-day follow-ups ($p < 0.05$)

(continued)

Table 26.1 (continued)

References	Study design/sample	Main results
Palhano-Fontes et al. [13]	Double-blind, randomized, parallel-arm, placebo-controlled 29 patients with TRD 1 mL/kg oral ayahuasca (0.36 mg/mL DMT)	Significant reductions in MADRS scores at 1-, 2- and 7-day follow-ups and at HAM-D scores at 7-day follow-up ($p < 0.05$)
Griffiths et al. [18]	Andomized, waitlist (immediate vs. delayed treatment), controlled trial 21 patients with MDD 20 mg/70 kg oral psilocybin followed by 30 mg/70 kg	Significantly higher reductions in GRID scores between immediate vs. delayed treatments at 1- and 4-week follow-ups ($p < 0.05$) No patients showed clinically significant response or remission in the delayed condition, while in the immediate condition 62% presented response ($p < 0.01$) and 39% presented remission ($p < 0.05$) at 1- and 4-week follow-ups

BDI Beck Depression Inventory, *BPRS* Brief Psychiatric Rating Scale (anxiety-depression subscale), *DMT* dimethyltryptamine, *GRID* GRID-Hamilton Depression Rating Scale, *HADS* Hospital Anxiety and Depression Scale, *HAM-D* Hamilton Rating Scale for Depression, *MADRS* Montgomery-Asberg Depression Rating Scale, *MDD* major depressive disorder, *POMS* Profile of Mood States, *QIDS* Quick Inventory of Depressive Symptomatology, *SHAPS* Snaith-Hamilton Pleasure Scale, *STAI-T* State-Trait Anxiety Inventory (Trait scale), *TRD* treatment-resistant depression

^aAdapted from Dos Santos RG, Bouso JC, Hallak JEC. Serotonergic hallucinogens/psychedelics could be promising treatments for depressive and anxiety disorders in end-stage cancer. *BMC Psychiatry*. 2019;19:321; Dos Santos RG, Hallak JEC. Therapeutic use of serotonergic hallucinogens: a review of the evidence and of the biological and psychological mechanisms. *Neurosci Biobehav Rev*. 2019; 108:423–434

administration, and the two studies that used the HADS also found significant reductions on this scale at the 6-month follow-up. Moreover, these two studies also reported significant reductions on the scores of these and other scales in the days/ weeks after drug intake (see Table 26.1 for details). Importantly, psilocybin was well tolerated. Adverse reactions included transitory anxiety and distress, sensorial illusions and transitory psychotic-like symptoms, headache, nausea and vomiting and mild increases in blood pressure and heart rate.

Regarding mood disorders unrelated to cancer and other life-threatening diseases, since 2016, four clinical trials were published involving the administration of psychedelics in patients with depressive disorders (see Table 26.1 for details) [13–18]. These studies included one open-label [14, 15] and one controlled study with ayahuasca/DMT [13] and one open-label [16, 17] and one controlled study with psilocybin [18].

The first of these studies was published in 2015 and involved an open-label study assessing the effects of a single oral ayahuasca dose (2.2 mL/kg; 0.8 mg/mL DMT) to six patients with major depressive disorder (MDD) [14]. This study presented the preliminary results of the final study with 17 MDD patients (including the initial 6 patients), published in 2016 [15]. Ayahuasca intake was associated with significant reductions in the scores of the Hamilton Rating Scale for Depression (HAM-D),

Montgomery-Asberg Depression Rating Scale (MADRS) and the Anxiety-Depression subscale of the Brief Psychiatric Rating Scale (BPRS) at 1, 7 and 21 days after its administration. Moreover, ayahuasca intake was also associated with increased blood perfusion in brain areas related to introspection and emotional processing (left nucleus accumbens, right insula and left subgenual area) 8 h after its administration.

The promising results of the open-label trial were confirmed in a randomized, double-blind, parallel-arm, placebo-controlled trial involving the administration of a single oral ayahuasca dose (1 mL/kg; 0.36 mg/mL DMT) to 29 patients with treatment-resistant MDD [13]. Compared to placebo, ayahuasca produced significant reductions in MADRS scores at 1, 2 and 7 days after its administration and significant reductions at HAM-D scores 7 days after its administration. Moreover, ayahuasca administration was also associated with subacute (48 h) normalization of low cortisol levels (hypocortisolemia) and increases in brain-derived neurotrophic factor (BDNF) in these patients [19, 20]. Indeed, increases in BDNF levels were negatively correlated with the antidepressive effects of ayahuasca and were modulated by acute increases in cortisol levels. In the open-label and controlled trials, ayahuasca was well tolerated. No serious adverse effects were observed, and the most common adverse effects included transient nausea and vomiting [13, 15].

Some months after the publication of the open-label trial with ayahuasca in 2016, an open-label trial involving the administration of 2 oral doses of psilocybin (10 mg and 25 mg, 7 days apart) to 12 volunteers with treatment-resistant MDD was published [16]. Eight more patients were included in a 6-month follow-up [17]. This study reported significant reductions in BDI scores 1 week and 3 month after psilocybin intake and at 1 week and 3 and 6 months in QIDS (Quick Inventory of Depressive Symptomatology) and SHAPS (Snaith-Hamilton Pleasure Scale) scores. Psilocybin administration was associated with decreased blood flow in the amygdala and increased functional connectivity within the default-mode network (DMN) and the ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex and decreased functional connectivity in the parahippocampal-prefrontal cortex [21]. These changes were related to antidepressive effects.

Psilocybin administration was also associated with significant improvements in social cognition (processing of emotional faces), which was significantly correlated with a reduction in anhedonia [22]. Psilocybin intake was also related to significant decreases in pessimism 1 week after its administration [23], and with significant decreases in neuroticism and increases in extraversion and openness 3 months after its administration [24]. Psilocybin was well tolerated, with adverse effects including transient anxiety, confusion, nausea and headache [16, 17].

After the open-label study, the most recent psilocybin trial for depression was a randomized, waitlist, controlled trial investigating the effects of two oral psilocybin doses (20 and 30 mg/70 kg) administered in an immediate compared to a delayed condition (the time between conditions was not specified) in 22 MDD patients [18]. Significantly higher reductions in scores of the GRID-Hamilton Depression Rating Scale were observed between immediate vs. delayed treatments at 1- and 4-week follow-ups. Furthermore, while no patients showed clinically significant response

or remission in the delayed condition, in the immediate condition, 62% presented response and 39% presented remission 1 and 4 weeks after psilocybin treatment. Psilocybin was well tolerated, with no serious adverse events reported. The adverse events reported included headache, chest pressure, dizziness, visual distortion, stiffness/soreness and mild repetitive muscle motion [18].

Although the results described above with LSD, psilocybin and ayahuasca/DMT are promising, they should be interpreted with caution. The results of the controlled trials of LSD and especially psilocybin for existential depression are the most robust evidence showing positive results of this treatment, which included administration of these drugs in a safe setting with a non-directive approach (basically the same approach used in all trials reviewed here). This treatment should be better explored by other research groups to further replication, and ayahuasca/DMT was not investigated in this clinical population, yet [25].

The data for MDD and treatment-resistant depression is less compelling, but it is still promising. For instance, the results of the open-label trials with ayahuasca and psilocybin reporting not only symptom reduction but also neural and biological changes simply cannot be causally attributed to the effects of these drugs because of the study design. Thus, together with the small sample sizes of these trials, their results are preliminary and exploratory.

However, both ayahuasca and psilocybin showed antidepressive effects in controlled trials. Indeed, the US Food and Drug Administration (FDA) granted psilocybin therapy a breakthrough therapy designation (i.e. support for clinical development of the treatment) two times in a year. In October 2018, the designation was given to the use of psilocybin in treatment-resistant MDD [26], and in November 2019, it was given for treating MDD [27]. The first designation is related to the work of the for-profit organization COMPASS Pathways, investigating psilocybin as a therapy for treatment-resistant depression in a large, multicentre, phase 2 trial in several sites in the United States, United Kingdom and Europe. The second designation is related to the work of the non-profit organization Usona Institute, investigating psilocybin as a therapy for MDD in a seven-site, phase 2 trial in the United States [26, 27]. Thus, depending on the results of these trials, it is possible that we will see psilocybin being used for the treatment of MDD and treatment-resistant MDD in the following years.

26.3 Neurobiological Mechanisms of Psychedelic Drugs

Psychedelic drugs should not be conceived as a unitary category sharing the same mechanism of action across different substances. Indeed, they can be classified at least in three distinct groups, depending on their primary mode of action: first, serotonergic hallucinogens, which include indolamines such as the semi-synthetic lysergic acid diethylamide (LSD) and the natural compounds psilocybin (present in several mushroom species) and *N,N*-dimethyltryptamine (DMT; main psychedelic present in ayahuasca) and phenylethylamines such as mescaline (present naturally

in some cactuses) and the synthetic 2,5-dimethoxy-4-iodoamphetamine (DOI); second, dissociative anaesthetics like ketamine or phencyclidine; and third, a group of ‘entactogens’ as have been named due to their emotion-enhancement effects. These compounds are less hallucinatory/psychedelic, and the most representative substance would be 3,4-methylenedioxymethamphetamine (MDMA) [28]. Other compounds like salvinorin A (present in *Salvia divinorum*) or tropane alkaloids present in *Solanaceae* plants, which have other mechanisms of action, have also psychedelic properties.

The psychedelic drugs of interest in the case of the treatment of depression are serotonergic psychedelics, particularly the substances classified as indolamines, and some dissociative anaesthetics, such as ketamine. Since Chap. 17 of this book is dedicated to ketamine, we suggest readers to consult that chapter if interested in its mechanism of action. The following sections would be dedicated to describe the mechanisms of action of indolamine psychedelics, such as LSD, psilocybin and DMT.

Psychedelic drugs activate different G-protein-coupled receptors (GPCRs), but the behavioural effects of most of them have been attributed to their agonistic activity on the 5-HT_{2A} receptor [29]. This has been observed in neuroimaging studies, where the administration of 5-HT_{2A} antagonists reduced or blocked both the subjective and neurophysiological effects of serotonergic psychedelics [30–32]. The 5-HT_{2A} receptor is widely distributed in the human brain, but pyramidal neurons and interneurons of the prefrontal cortex (PFC) have a remarkable density [2]. Other regions with notable 5-HT_{2A} receptor density are the parietal, temporal and occipital cortices, the entorhinal area and the mammillary bodies of the hypothalamus, claustrum and the lateral nucleus of the amygdala [33]. All of them are involved in several cognitive processes, emotion regulation, introspection and self-awareness, so the modulatory effects of psychedelic drugs on these regions could partially explain the induced modifications in perception, cognition or interoception, among others [32].

Besides 5-HT_{2A} receptor, the multi-target profile of most of psychedelic drugs should not be overlooked when elucidating their mechanisms of action [34]. For instance, LSD binds to other serotonin receptors (2C+1A+6+7) and dopamine (D₁ and D₂), adrenergic and trace amine-associated (TAAR1) receptors [35]. Notably, TAAR1 agonists have been associated with antidepressant, antipsychotic and anti-addictive effects [36]. In the case of ayahuasca, DMT is also an agonist of sigma-1 (σ1) receptor, which is involved in depression, drug dependence, amnesia, cancer and pain [37]. Regarding depression, other σ1 receptor agonists have shown antidepressant effects [38, 39]. This effect, although not completely understood, has been attributed to the modulating effects of σ1 receptor on serotonergic and dopaminergic transmissions [40]. The β-carbolines that ayahuasca contain (such as harmine, tetrahydroharmine and harmaline) are reversible and specific inhibitors of monoamine oxidase type A (MAO-A) and can also interact with opioid, dopamine, GABA, serotonin, glutamate, acetylcholine and imidazoline receptors [41].

Considering the complexity of the pathophysiology of depression and the failing of the classical monoaminergic hypothesis in providing a potential neurobiological

explanation for depression, we consider that hypotheses regarding the therapeutic effect of psychedelic drugs for this and other mood disorders must include their multi-target profile. We suggest that in the near future, disciplines like systems pharmacology could provide valuable contributions to the field of psychedelic medicine attending to the complex effects of these drugs and vegetal materials [34].

A significant effect of most psychedelic drugs that could be related to their antidepressant effects is the enhancement of both neurogenesis and neural plasticity. In contrast to ketamine, which induces these effects through its antagonism on the *N*-methyl-D-aspartate (NMDA) glutamatergic receptor, serotonergic hallucinogens do it through their agonism on the 5-HT_{2A} receptor [42, 43]. The activation of the 5-HT_{2A} receptor produces an increase in the glutamatergic tone and the activation of alpha-amino-3-hydroxy-methyl-5-4-isoxazolopropionic (AMPA) receptors, which increases cortical electrical activity and information processing [44, 45]. Notably, certain psychedelic drugs like DMT and LSD have been termed ‘psychoplastogens’ due to their promotion of rapid structural and functional neural plasticity [46]. The mechanisms underlying these effects consist in an enhanced *c-fos* expression in the medial prefrontal (mPFC) and anterior cingulate (ACC) cortices. The expression of brain-derived neurotrophic factor (BDNF), which is associated with both neurogenesis and spinogenesis, is also enhanced in PFC [46]. However, the enhancement of BDNF levels and the subsequent therapeutic effects does not necessarily inform about the pathophysiology of depression, since not all the patients show lower BDNF levels [47, 48]. Remarkably, this was also observed in a clinical trial in which the psychedelic drug ayahuasca was administered, where baseline BDNF levels did not predict the depressive state [19]. But there is evidence showing that atrophy in neurons of the PFC plays a key role in mental and neurological disorders, including depression [49, 50], and that this atrophy can be counteracted by compounds capable of increasing neural plasticity in the PFC [51–53]. Other receptors, such as the 5-HT_{1A} receptor, are also involved in neuroplasticity and neurogenesis. Remarkably, when this receptor is blocked with an antagonist (pindolol), the subjective effects of DMT are enhanced, so this receptor could be also acting as a neuromodulator of DMT and other serotonergic psychedelics [54].

The complex effects of psychedelic drugs have been studied through different neuroimaging techniques, showing acute increases and decreases in the activity of several brain regions, depending on the neuroimaging technique and protocol. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have provided consistent results, informing about the excitatory effects of different serotonergic psychedelics (mescaline, psilocybin and ayahuasca) in brain regions like the frontolateral/frontomedial cortex, the medial temporal lobe and the amygdala [32]. In contrast, functional magnetic resonance imaging (fMRI) studies reported less consistent results. A study with psilocybin observed a decreased connectivity between the thalamus and ACC and posterior cingulate (PCC) cortices. A decrease in resting-state connectivity between mPFC and PCC was also observed [55]. A posterior fMRI study with psilocybin reported increases in connectivity of different networks, including the default-mode network (DMN), executive control and dorsal attention networks [56]. In another fMRI study using ayahuasca, a

reduction of activity in key hubs of the DMN, such as mPFC and PCC, was observed [57]. In a later study using LSD, an increase of hemodynamic activity in several brain regions was reported, mostly in those rich in 5-HT_{2A} receptors. The authors concluded that the overall effects of LSD were related to an increased functional connectivity between different brain regions [58]. Finally, a recent fMRI study with LSD showed a decrease in functional connectivity in visual, sensorimotor, auditory and the DMN [59].

It has been suggested that the inconsistencies between PET/SPECT and fMRI studies could be related with the timescales considered in different techniques. For instance, in the first case, radiotracers to measure blood perfusion or glucose metabolism have long half-lives (110 min in the case of [18] F-FDG or 6 h in the case of technetium-99 m). Thus, the detected effects by these techniques can actually consist in compensating or rebound effects [32, 55]. A recent review about neuroimaging studies using psychedelic drugs concluded that the overall effect of serotonergic psychedelics consist in the modulation of brain areas associated with different cognitive functions, such as perception, introspection and emotion processing. Generally, these drugs induce increases in the activity of prefrontal and limbic areas and decreases in key hubs of DMN [32]. The disintegration of DMN could partially explain the therapeutic effect of serotonergic psychedelics, since an increased DMN functional connectivity has been associated with some symptoms of mood disorders, particularly rumination [60]. The effects of these drugs on the amygdala are also relevant, since they reduce its activation to negative emotions and also reduce the recognition of these emotions, therefore improving social cognition [61]. In depressed patients, there is an increased response of the amygdala to negative faces, which is normalized after the administration of selective serotonin reuptake inhibitors [62]. Additionally, modifications in certain brain regions have been observed in long-term users of ayahuasca. Specifically, cortical thinning in mesotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, PCC and superior occipital gyrus was associated with the regular use of ayahuasca [63]. The cortical thickness (CT) alterations in the PCC were inversely correlated with age of onset and intensity of ayahuasca use and with the self-transcendence scale, which is related to spirituality. Remarkably, increased CT was found in the ACC, a region involved in emotional processing [64]. Conversely, decreased CT was observed in patients with mood disorders, including depression [65].

Inflammatory processes are closely related with depression. Patients diagnosed with major depressive disorder (MDD) show an increased expression of pro-inflammatory cytokines and higher levels of acute-phase reactants, chemokines and soluble adhesion molecules in both the peripheral blood and cerebrospinal fluid [66, 67]. Additionally, the administration of IFN α and other inflammatory cytokines to healthy individuals induces symptoms of depression [68, 69]. Due to the association between inflammation and depression, the anti-inflammatory effects of psychedelic drugs could be relevant not only in the case of depression but also in other psychiatric or neurodegenerative disorders in which inflammation processes are involved, such as Parkinson and Alzheimer diseases [70]. Preclinical studies show that psychedelic drugs such as LSD and DOI induce potent anti-inflammatory effects

through the activation of the 5-HT_{2A} receptor [71, 72]. DOI showed a potent anti-inflammatory effect, since it has an EC₅₀ of 15 *picomolar* in preventing tumour necrosis factor alpha (TNF- α)-mediated inflammation in aortic smooth muscle cells [71]. This effect was also found in the case of systemic TNF- α [72]. Notably, the anti-inflammatory effects of DOI have been also observed in human cells *in vitro*, suggesting that these findings could translate to humans, although human studies are lacking in this area. Proteomic analyses in a human cerebral organoid administered with 5-MeO-DMT downregulated proteins associated with inflammation and degeneration [73].

Related to the anti-inflammatory effects of psychedelic drugs, we can mention also their neuroprotective effects as potentially associated with their antidepressant action. This is especially relevant in the case of ayahuasca, where both DMT and β -carbolines induce increases in BDNF levels and neurogenesis [46, 74, 75]. Activation of the σ 1 receptor by DMT can modulate glutamate release and NMDA receptors and dampen the excitotoxic effects of glutamate [40]. Additionally, σ 1 receptor agonists are known to act as indirect antioxidants [76]. Regarding β -carboline compounds, especially harmine, their MAO-inhibiting properties could be involved not only in the antidepressant effects of ayahuasca [77] but also in their neuroprotective effects, since MAO inhibition decreases oxidative stress. Moreover, the antidepressant effects of harmine were associated with increased BDNF levels and antioxidant activities in the rat PFC and hippocampus [78, 79].

The neuroendocrine effects of psychedelic drugs have also been suggested as potentially implicated in their therapeutic effects [80]. The hypothalamus has a high density of 5-HT_{2A} and other receptors associated with the mechanisms of action of psychedelic drugs, so their administration is associated with a release of oxytocin and other neuropeptides [81], an effect blocked by 5-HT_{2A} antagonists [82]. While the administration of oxytocin does not seem to be associated with antidepressant effects [83], some single-nucleotide polymorphisms (SNPs) of the oxytocin receptor have been associated with depression [84], and it has been observed that its administration during the psychotherapeutic process can lead to changes in individual and dynamic factors in patients with depression. This effect can be partially attributed to improvements in social cognition [85]. Similar findings can be observed in the case of cortisol. Deregulations of this hormone are associated with depressive symptoms, mainly consisting in lower levels of cortisol compared to healthy controls [86]. Additionally, hypocortisolemia has been associated with non-specific symptoms of depression, such as malaise, muscle weakness or loss of appetite [87]. Different psychedelic drugs induce increases in cortisol [80, 88, 89]. In this sense, in a placebo-controlled study [20] in which patients with MDD were treated with a single ayahuasca dose, lower levels of cortisol were reported in patients as compared with healthy controls. After administration of ayahuasca, cortisol increases in patients were observed, reaching similar levels to the ones registered in healthy controls. This increase was stable at least until 48 h after ayahuasca administration. Thus, the stimulation of oxytocin or cortisol by different psychedelic drugs could produce or enhance their overall antidepressant effects.

26.4 Future Challenges

There are still so many challenges that have to be addressed in order to show that psychedelic drugs can become an available treatment for some mental disorders. First, as happens in other fields, the published clinical trials until today have been conducted with small (mean of 26 subjects) samples [90]. Additionally, due to the intrinsic risks of psychedelic drugs in terms of exacerbating previous psychotic or bipolar disorders, patients are selected using strict inclusion/exclusion criteria. For instance, one basic strategy in order to avoid both the psychiatric side effects and the appearance of acute anxious effects (commonly known as ‘bad trip’) is the inclusion of people with previous experience with psychedelic drug use without having lived challenging experiences or psychiatric complications. In fact, the prevalence of patients with previous experience with psychedelic drugs included in some clinical trials is much higher than that found in general population: up to 75% of patients in two trials [10, 91] and 50% of patients in two other trials [9, 12]. Thus, the realization of studies with subjects naïve in psychedelic use (as the clinical trials of ayahuasca for depression) and of pragmatic or real-life trials is necessary in order to better assess the efficacy and safety of this treatment in the general population. Similarly, since psychedelic therapy generally involves the combination of psychotherapy with pharmacology, comparative studies in which psychedelic psychotherapy is compared with already commercialized medicines and psychotherapy will be needed as well.

Another challenge that has to be addressed is the specific healthcare structure in which psychedelic therapy will be administered. It has to be noted that these treatments require specialized practitioners, offering support to patients for hours (at least 5–6 h in the case of ayahuasca, 6–8 h in the case of psilocybin and 12–15 h in the case of LSD). The case of esketamine, recently approved by the FDA for treatment-resistant MDD, could be of interest. Patients must take esketamine under the direct supervision of a healthcare provider and must be monitored for at least 2 h post-dose to ensure the resolution of possible transient adverse effects, such as increases in blood pressure, cognitive impairment, sedation and dissociation [92]. Thus, a similar future could be envisioned for psychedelic therapy, where patients would take these drugs under supervised conditions in safe settings.

Despite all of the challenges, the current limitations of psychiatric treatments should be noted [7], so new strategies in mental health are urgently needed. In that sense, psychedelic psychotherapy represents an innovative approach, combining both psychotherapy and pharmacological tools. Furthermore, these tools alone have several mechanisms of action potentially associated with therapeutic outcomes, being some of them unexplored. Lastly, in the particular case of ayahuasca, we should consider its already disseminated ritual and medicinal use thorough South America mainly but also in many other parts of the world in indigenous [93] and non-indigenous [94] communities. Thus, if these promising results are replicated, maybe the traditional medicinal use of ayahuasca will exist and dialogue with a non-traditional use be regulated in a medicinal plant legislation. A similar case is the

decriminalizing process of psychoactive plants that is occurring in several US cities and states and other parts of the world like the Netherlands or Spain, where private practitioners offer psychotherapeutic treatments with *Psilocybe* mushrooms and/or other psychoactive plants. The UN international conventions do not have scheduled plants containing psychedelic principles, so, as happens with the case of ayahuasca, it is not unlikely that biomedical approaches will coexist with cultural uses.

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Chapter 27

Precision Psychiatry: Biomarker-Guided Tailored Therapy for Effective Treatment and Prevention in Major Depression



Candace Jones and Charles B. Nemeroff

Abstract Depression contributes greatly to global disability and is a leading cause of suicide. It has multiple etiologies and therefore response to treatment can vary significantly. By applying the concepts of personalized medicine, precision psychiatry attempts to optimize psychiatric patient care by better predicting which individuals will develop an illness, by giving a more accurate biologically based diagnosis, and by utilizing more effective treatments based on an individual's biological characteristics (biomarkers). In this chapter, we discuss the basic principles underlying the role of biomarkers in psychiatric pathology and then explore multiple biomarkers that are specific to depression. These include endophenotypes, gene variants/polymorphisms, epigenetic factors such as methylation, biochemical measures, circadian rhythm dysregulation, and neuroimaging findings. We also examine the role of early childhood trauma in the development of, and treatment response to, depression. In addition, we review how new developments in technology may play a greater role in the determination of new biomarkers for depression.

Keywords Depression · Biomarkers · Precision psychiatry · Endophenotypes · Genetics · Epigenetics · Neuroimaging

27.1 Introduction

Depression is the leading cause of disability across the globe, affecting over 264 million people worldwide [1–3]. It is a major determining factor of quality of life and survival, with potential to cause significant functional impairment and even

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death in its most severe form [4]. According to the WHO 2020 report on depression, suicide is the second leading cause of death among individuals between ages 15–29 years old [2]. Multiple treatment options exist for patients with symptoms of depression, most commonly being antidepressant medications. However, only about one-third of these patients reach remission with any single antidepressant [5–7]. In a heterogeneous population, response to medical treatment for any given illness can differ significantly. An individual's response to treatment is influenced by multiple factors, including genetic predisposition, heterogeneity of cohorts, ethnicity, metabolic rate, epigenetic variables, and time of illness onset [8]. In addition, a reliable and highly accurate diagnosis optimally requires integrating known biomarkers, symptoms, environmental influences, genetics, epigenetics, and physical exam findings. A biomarker is defined as a biological characteristic that can be measured objectively and used as an indicator of normal biological function, pathology, and treatment response [9, 10].

The goal of precision medicine, also known as personalized medicine, is to predict disease risk, assist in formulating a more accurate and biologically based diagnosis, and help determine the most effective treatment option based on individual biological traits [11]. Precision medicine assumes that the determination of a reliable medical diagnosis and the subsequent treatment plan is unfeasible if based on symptomology alone [8, 12]. This concept is exemplified by Novick and colleagues' 2017 study, in which they followed 1297 subjects over a 6-month period to determine the extent that individual baseline functioning impacts depression recovery. They defined recovery as both clinical and functional remission. The results of this study revealed that depression remission rates are significantly lower when functional status is included in diagnostic criteria, rather than using DSM-V criteria alone. These results imply that a list of symptom-based criteria is an insufficient diagnostic tool for reliably diagnosing depression and predicting outcome. Whether biological, socioeconomic, or psychosocial, there remain missing pieces to our current methods of assessing depression [12]. Current psychiatric research has focused on identifying specific biomarkers of depression with the aim of further developing precision psychiatry and steering away from the practice of empirical medicine [8, 11]. This chapter focuses on how biomarkers can be used as a more reliable and precise measurement of treatment response, as well as aid in predicting vulnerability to the development of depression.

The use of biomarkers has evolved rapidly in some medical specialties such as oncology; however, in psychiatry, biomarkers are only beginning to be researched and incorporated into clinical practice [11]. Their absence contributes to the varying treatment responses that are seen in individuals with major psychiatric illnesses including depression [13]. Depression is not a single illness but rather a syndrome with a heterogeneous presentation comprised of many different etiologies influenced by the many factors noted above. This concept is supported by a study from Takahashi and colleagues in which they assessed antidepressant response in individuals with depression based on their serotonin transporter gene polymorphism. This resulted in identification of a distinct subgroup with significantly less dysphoric-related symptoms than the others, demonstrating a specific example of how

incorporating biomarkers into psychiatric practice can contribute to a more individualized approach of identifying depression subtypes and ultimately improving outcome [14]. In this chapter, we will explore multiple biomarkers, both established and those currently being researched, that are specific to depression. These include gene variants/polymorphisms, endophenotypes, epigenetic factors (methylation), biochemical measures, circadian rhythm dysregulation, neuroimaging findings, and developments in technology [11]. First, however, we will take a broad look at the current tools being used in precision psychiatry as well as the basic principles underlying the role of biomarkers in medical pathology.

27.1.1 The Tools of Precision Psychiatry

The goal of precision psychiatry is to optimize patient care by considering environment, lifestyle, and gene variability at the level of the individual. Biomarkers are an important component of the emerging vision of individualized care in psychiatry [15]. However, in order to identify individual biomarkers, first researchers have to collect and analyze data extracted from a large assortment of cohort studies of psychiatric illness [16]. This is done through tools that are able to evaluate thousands of data entries at once [17]. The most common example of this in psychiatry is genome-wide association studies, or GWASs. These have been helpful in identifying genetic etiology and pleiotropy shared between multiple psychiatric disorders [18].

Genome-wide association studies are observational studies that scrutinize the whole genome in groups of individuals to determine if any particular genetic variant is associated with a specific illness or trait. Advanced computational methods examining large amounts of genetic and biologic data have made these studies possible. As an example, in their review discussing successful GWAS for depression, Ormel et al. [19] note that recent GWASs have found more than 80 genetic loci associated with depression. However, they also caution that these GWASs only identify genomic regions associated with depression without determining the mechanism of underlying biologic function for specific pathophysiology. Genome-wide association studies have been challenging to interpret because gene variants that are directly involved in an upstream biologic process not only affect those upstream processes but indirectly also modulate many processes and traits downstream in biologic and development pathways (which might result in or impact a number of clinical conditions). In the future, researchers hope to determine the biologic mechanisms for depression-related loci and to discover new loci (or groups of loci) associated with affective disorders.

In general, there are currently (and under development) an increasing number of tools to aid the implementation of precision psychiatry. Genetic and epigenetic analyses can help determine disease risk, the course of disease, and perhaps responses to treatment. Neuroimaging can help characterize various syndromes and pathologic mechanisms, identify the neuroanatomical and neurophysiological correlates of illnesses, and be useful in predicting treatment response. Blood plasma

tests (e.g., vitamin D, thyrotropin, testosterone, or C-reactive protein) can serve as indicators of disease risk and can help identify disease subtypes. In addition other tests of blood and body fluids (such as blood or salivary cortisol levels) can assist with the diagnosis of clinical conditions. Electrophysiologic indicators (as examples, EEG patterns or the N1 event-related potential response) can assist the characterization of clinical syndromes and perhaps predict treatment response. In addition, the electronic medical record can serve as a valuable tool when psychiatrically relevant medical history is recorded so that the information is readily available to all healthcare workers (e.g., history of early-life traumatic experiences can impact treatment response in depression). Biotechnology (such as physiologic monitors attached to smart phones) can help to monitor parameters associated with certain conditions (e.g., heart rate in anxiety disorders) and to associate the data collected with symptoms and treatment effects. Overall, the increasing number and diversity of tools becoming available in psychiatry will help implement and shape precision psychiatry through the coming years.

27.2 Biomarkers: The Basics

In biomedical research, a biomarker (occasionally termed “bioindicator”) could be any measurable indicator of a disease [20]. The National Institute of Environmental Health Sciences defines biomarkers as “key molecular or cellular events that link a specific environmental exposure to a health outcome.” Response to treatment varies across heterogeneity of the population due to variables such as genetic predisposition [10]. Biomarkers are already established as risk and diagnostic tools in some medical specialties such as cardiology, for example, high serum cholesterol as a risk factor for cardiovascular disease. In this example, the biomarker is correlated with an aspect of the disease process but does not fall within the genotype to phenotype pathway and, therefore, may not be specifically embedded in the causal chain for the disease. A biomarker can also reflect a biologically detectable effect of an outside agent upon an organism. For example, blood or urine lead levels are biomarkers of environmental lead exposure. A biomarker may be useful in distinguishing between biological factors that occur secondary to an illness but fall outside the realm of endophenotypes (e.g., state markers are not endophenotypes). Biomarkers may be useful when discussing the biological impact of environmental or exogenous factors on the emergence of psychopathology [20]. However, in comparison, an essential component of the endophenotype concept is that it is inheritable. In short, a biomarker may or may not be subject to genetic influences. In a somewhat outdated terminology, biomarkers can be classified as “trait” markers which connote disease risk and “state” markers which are prominent during the course of disease, for example, an elevated white blood cell count during infection.

Biological factors posited to subtype depression into distinct categories include markers of monoamine systems such as norepinephrine and serotonin and their metabolites, variations in hypothalamic-pituitary-adrenal axis activity,

polymorphisms in various candidate genes, and circadian rhythm changes. In addition, neuroimaging techniques including MRI/fMRI and PET are also being investigated as potential biomarkers for depression and other psychiatric disorders.

27.2.1 State-Dependent vs. State-Independent Biomarkers

Researchers had hoped that individual genetic effects on endophenotypes would be large, but thus far this hope has not been realized. The largest GWASs have identified gene variants associated with one or another psychiatric disorder, but the effect size is quite small. Many reports are of candidate genes with small sample sizes that have often not been verified [9].

State-dependent biomarkers that exist only during exacerbation of symptoms are called episode markers [9]. Episode markers can be useful for monitoring course and treatment effectiveness and for disorder identification. Schizophrenia research has illustrated how psychophysiological measures are associated with the presence of psychotic symptoms. Using a vocalization model adapted from primate research, Ford [21] (and Ford and colleagues [22]) identified an N1 event-related potential response in schizophrenic patients that may index the state of psychosis in this disorder as it appears to evaluate the quality of neural processing associated with hallucinations [21]. Hinkley et al. 2011 [23], by using magnetoencephalography (MEG) to examine functional connectivity across cortical regions, also provided evidence of an electrocortical biomarker for schizophrenia. These investigators reported that psychotic symptoms and impaired cognition were associated with diminished alpha-band connectivity and postulated that this observed neurophysiologic effect might be a treatment target.

An independent state biomarker or trait marker (endophenotype) is heritable [8]. An endophenotype is primarily state-independent meaning that it manifests in an individual whether or not the illness is active. However, a provocative challenge may be needed to reveal the indicator [20].

Temporally stable biomarkers are a third category and are markers of environmentally induced susceptibility that identify those who have become susceptible to a disorder as a consequence of environmental exposure [9]. For example, acquired characteristics, such as those arising subsequent to trauma or secondary to perinatal complications or substance abuse, fall into this category. Studies of posttraumatic stress disorder (PTSD) have shown that traumatic exposure may lead to the development of such susceptibility markers. In research comparing monozygotic twins discordant for combat exposure, Orr et al. 2003 [24] determined that elevated heart rate response to startling sounds was present only in the exposed twins, implying that the cardiac response represents an acquired marker of PTSD rather than a sign of preexisting genetic susceptibility. Environmentally mediated responses, such as respiratory rate, have many of the qualities of an endophenotype, but because they are not usually a result of genetic susceptibility, they would have little use in identifying which genetic mechanisms are involved in an associated clinical disorder [20].

27.2.2 *Reverse Nosology as a Model for Diagnosis of Psychiatric Illness*

Current disease classification in psychiatry is founded on symptom-based criteria (traditional nosology). Despite the common use of biomarkers for genetic-, tissue-, organ-, and system-level measures in other fields of medicine, the application of brain biomarkers in psychiatry is currently lacking. Conventional symptom-based psychiatric diagnoses do not track well with the emerging biomarker-driven constructs [25]. The absence of biologically based disease definitions impedes progress in finding mechanistic targets for the development of novel effective treatments. There is a definite need in psychiatry for developing disease entities built on brain biology and supported by objective, quantitative, clinically relevant disease biomarkers –the approach recently emphasized by the Research Domain Criteria [26, 27]. In a proband sample similar to the one that was used in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP), weighted groupings of brain regions or regional brain characteristics are linked to weighted groupings of genetic variables that can then be evaluated for associations [28].

27.3 Endophenotype: A Specific Type of Biomarker

The easiest way to remember the distinction between the two terms “endophenotypes” and “biomarkers” is that all endophenotypes are, by definition, biomarkers, but not all biomarkers are endophenotypes. Whereas an endophenotype must meet all the criteria presented in Table 27.1 [20, 29], a biomarker need only reflect some measurable deviation in the organism, reflective of either internal factors operating in either health/illness or the impact of an external agent. For example, a biomarker that is reflective of an environmental exposure will fail to satisfy those criteria of validity for an endophenotype that concern patterns of familial aggregation (e.g.,

Table 27.1 Criteria for endophenotype

The endophenotype:
[1] Is associated with illness in the population
[2] Is heritable
[3] Is primarily state-independent (manifests in an individual whether or not the illness is active) but may require a challenge to elicit the indicator
[4] Is more prevalent among the ill relatives of ill probands compared with the well relatives of the ill probands (i.e., within families, endophenotype, and illness co-segregate)
[5] Found in affected family members and is found in nonaffected family members at a higher rate than in the general population
[6] Should be a trait that can be measured reliably and ideally is more strongly associated with the disease of interest than with other psychiatric conditions

Adapted from [20, 29]

increased ammonia levels due to some forms of drug abuse do not constitute an endophenotype). Therefore, the term biomarker is not exchangeable with (or equivalent to) endophenotype [20]. Heterogeneity of the cohorts, ethnicity, slow vs. fast metabolizers, epigenetic factors, and early vs. late stage of the disease are all parameters which have an effect on whether a given individual will respond well to a specific treatment. Biomarkers in conjunction with diagnostics can help eliminate the effects of these parameters and enable a shift from empirical medicine (one size fits all) to precision medicine [8].

Historically, the approach to illness/disease has been to classify individuals by their observable characteristics that are often derived from the interactions between genes and the environment. However, this approach to categorization of illness is evolving and leading to research in pathophysiologic mechanisms/processes (molecular/cellular), i.e., endotypes, and their influence on phenotype [30]. Endophenotypes are actually slightly different than a type of biomarker, though some call them biomarkers. They can be distinguished from episode markers and trait markers arising from environmental exposure by their ability to index genetic contributions for a psychiatrically relevant trait. That is, endophenotypes are genetically influenced quantifiable traits that identify those at risk for psychopathology before it manifests and can be used to identify etiologically relevant genetic variants. Assumed to be less genetically complex and closer to the effects of genes, endophenotypes offer a potentially more precise and powerful approach to uncover genetic variants associated with psychopathology [9]. According to Gottesman and Gould, an endophenotype is a measurable component, unseen by the unaided naked eye that lies along the pathway between disease (i.e., observable phenotype) and distal genotype. An endophenotype is not a risk factor; rather it is a manifestation of the underlying disease liability. Thus, an endophenotype is internal and not easily discernable without some technological assistance. An endophenotype may be neurophysiological, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature, and it can include self-report (e.g., inventory) data. The usefulness of an endophenotype is that it represents, in principle, a relatively simpler clue to genetic causes than the disease symptoms [29, 31].

Psychiatric researchers have had a long-term interest in developing reliable biomarkers, i.e., clinically useful biological markers that are associated with mental illness. However, for biomarkers such as neurotransmitter metabolites or measures of inflammatory response in general, there is no consensus regarding which molecules are likely to be the best marker targets. Currently, there is no solid theoretical foundation from which the numerous putative biochemical markers can be reduced to a few plausible ones; therefore, identifying valid biomarkers is an extensive empirical task. The appeal of psychophysiological measures comes from their assessing of the central nervous system function broadly; if the integrity of any element of a brain system is malfunctioning, an electrophysiological measure associated with that system may be altered. As with other types of biomarkers, for psychophysiological measures, the unit of measurement is biological. Like many other types of biomarkers, they depend on a psychological task or circumstance;

understanding the model used to elicit the physiological response is thus essential to the interpretation of the significance of the response [9]. The eyeblink startle electromyographic (EMG) response reveals quite different meanings if it is elicited by an intense unexpected event, or the same event when part of a prepulse inhibition sequence, or the same event presented while viewing pleasant or aversive imagery. In only the first two of these examples is the response heritable, and only prepulse inhibition receives strong support as an endophenotype [32, 33]. The endophenotype concept can be summarized as follows: modern psychopathology research supports the inference that most forms of major mental illness (e.g., bipolar illness, schizophrenia, unipolar depression, anxiety disorders) possess an appreciable heritable component. This component contributes, in interaction with other genetic assets and liabilities as well as environmental and epigenetic factors, to the overall predisposition for an illness. It is likely that the underlying predisposition to an illness will manifest itself before the development of its clinical signs and symptoms. For example, in schizophrenia, this translates to the development of detectable pathology before the appearance of psychotic symptoms, even before the prodromal features. In other words, one should be able to detect some internal manifestation of a genetic liability for an illness within the at-risk population that (a) is not visible to common observation, (b) exists *in situ* (i.e., in place, within (not outside) the person), and (c) predates observable signs or symptoms of illness [20]. One current derivation is from the insect genetics literature, which advocated the term endophenotype to denote a feature *internal* to an organism and visible upon microscopic examination (i.e., *not* an obvious, external feature). Additionally, an endophenotype represents an *unobservable latent entity* (such as a hypothetical latent construct) that cannot be directly observed with the unaided naked eye; rather, an appropriate technology would be needed to “see” the endophenotype. Importantly, the endophenotype is not really “hidden”; rather it can be viewed with the appropriate tools [34].

Advances in psychophysiology, such as improved signal processing and statistical methods, are important. The current level of sophistication used to quantify and process electrophysiological variables is not a significant obstacle to the identification of genetic variants associated with endophenotypes. Electrophysiological variables have psychometric properties that are at least equivalent to, and in many cases are better than, those of phenotypes that have been used successfully in molecular genetic research. However, it is also important to focus on the best practices needed to identify a trait as a suitable endophenotype and to demonstrate its usefulness for uncovering biological pathways to the development of psychiatric disorder [9].

27.3.1 *Endophenotypes in Depression*

It is worth noting that psychosis-related genes participate in brain development, specifically cell differentiation, adhesion, migration, cell signaling, and myelination. A number of these genes have been associated with risk for schizophrenia, bipolar

disorder, and several neurodevelopmental brain disorders, including epilepsy, mental retardation, and autism. Mokhtari et al. 2016 [35] evaluated the overlap in pathway maps, process networks, and gene ontology processes across three different electrophysiological psychosis-related biomarkers (resting electroencephalography [EEG], auditory oddball, auditory paired stimuli). Neuronal developmental and cellular maintenance processes almost completely accounted for this overlap, including neurogenesis, axon guidance, neuronal development, neuronal differentiation, and neuron projection.

In order to be successful in characterizing mental illnesses such as MDD, a far better understanding of the pathophysiology of these disorders will be required and moreover to determine if there are 5, 10, 50, or 200 distinct endophenotypes of a particular syndrome [11]. Depression involves impairments in a range of cognitive and emotional domains. It was unknown at the time of the Etkin et al. 2015 study [36] whether these impaired functions could aid medication choice when considered as a composite predictive biomarker. Etkin and colleagues tested whether behavioral tests, grounded in the neurobiology of cognitive and emotional functions, could predict outcome with some common antidepressants. They tested several cognitive and emotional capacities to examine whether or not they can be used as biomarkers for response to antidepressants including psychomotor, executive, memory, attention, processing speed, inhibitory, and emotional functions. In this report from the International Study to Predict Optimized Treatment for Depression (iSPOT-D) study, 1008 patients diagnosed with MDD (665 of completed patients were matched to 336 controls) were randomly assigned to escitalopram, sertraline, or venlafaxine. Approximately one-quarter of the cases exhibited cognitive impairment across all domains, and those subjects responded very poorly to treatment. However, within this same subgroup only, task performance was associated with remission on escitalopram with a 72% accuracy using the 16-item Quick Inventory of Depressive Symptomatology [11, 36].

Impaired prepulse inhibition (PPI) is one of the endophenotypes (biological markers) of schizophrenia, autism and other neurodevelopmental disorders. The neural circuit for PPI involves the hippocampus, an area of the brain where neurogenesis occurs postnatally. Researchers hypothesize that a disruption of preadolescent neurogenesis is essential for the onset of sensorimotor gating defects. In order to test this hypothesis, a critical period of neurogenesis that can impact PPI was examined. Osumi et al. 2015 [37] introduced an enriched environment to restore neurogenesis, which resulted in recovering PPI deficits in mice. They found impairments in the maturation of newborn neurons in the hippocampal dentate gyrus (DG) and GABAergic neurons in the hippocampus, which can be described as microphenotypes that are associated with PPI defects. Investigations with more exact genetically controlled neurogenesis models (with precise time points or periods) are needed to support this hypothesis [37].

Potential endophenotypes in depression and other mood disorders include baseline activation and neural response patterns in depression [38], cortical thinning in depression [39], and neurotrophic signal transduction pathways in mood disorders [20, 40]. It is easy to see the potential usefulness that a measure of cortical thinning

(a potential endophenotype of major depression) could have in the diagnosis of major depression or evaluation of major depression risk. Such a biological feature could be quite useful as a diagnostic tool [39].

Research on psychiatric disorders has demonstrated the involvement of numerous genes that are associated with neurogenesis and neural development. Neurogenesis is a biological process that is essential in brain development and continues through life in a select few brain regions. Neurogenesis is a process that involves multiple steps starting from the division of neural stem cells/progenitor cells, leading to self-renewal and at the same time to the production of lineage-committed cells, which include neurons and glial cells. Some relatively minor defects in the neurogenesis process, such as production of fewer new neurons and malformation of neural circuits, could plausibly result in phenotypes of psychiatric disorders at molecular and cellular levels in animal models (here termed as “microphenotypes”). However, because they are difficult to evaluate, microphenotypes are not easily used as biomarkers. Because it is readily measurable, some researchers have focused on sensorimotor gating deficits that can be scored in a prepulse inhibition (PPI) test. It is essential for the field of psychiatry to create methods to define the molecular, cellular, and circuit basis of brain diseases. These definitions could be utilized to develop biologically based disease categories. This would enable a better ability to research disease pathophysiology and etiologies. This is critical for serious mental illnesses [28].

27.4 Biomarkers and Disease Vulnerability

27.4.1 Disease Vulnerability

Although it has been three decades since the human genome project was completed, we still know relatively little about how specific genes influence the development of psychiatric disorders. One significant concern has been that identifying genes is constrained by the inadequacy of the American Psychiatric Association’s *Diagnostic and Statistical Manual* (DSM) to categorize biological processes with enough precision to facilitate success. The definition of DSM disorders depends little on biology; instead, disorders remain defined largely by consensus expert opinion, are heterogeneous, and show significant overlap. Therefore, interest in approaches to gene finding that do not depend on the DSM has been high [9].

In addition to genetic influences, researchers have considered other factors as predictors for the development of depression. For example, Wilson et al. 2014 [41] followed 2764 twin children into adulthood and their parents in a prospective study spanning two decades. Risk factors for development of MDD were childhood abuse and having parents with psychiatric disorders. Another risk factor was premorbid dysfunction at age 11 including the following characteristics: lower positive emotionality, higher negative emotionality, higher trait anxiety, substance use/misuse, externalizing symptoms, poorer school functioning, poorer parent-child

relationship quality, and more advanced pubertal development. The risk for a recurrent MDD episode was early onset of MDD [41].

27.4.2 *Genetics*

27.4.2.1 GWAS: Genome-Wide Association Studies

Genome-wide association studies (GWASs) have identified genetic variants of disease that may contribute to disease vulnerability (especially for bipolar disease and schizophrenia, less promising results in major depression) [11]. The experimental design of genome-wide association studies (GWASs) has only been applied relatively recently (primarily, in the past decade). Visscher et al. 2017 [42] reviewed the range of discoveries it has facilitated in population and complex-trait genetics, the biology of diseases, and translation toward new therapeutics. Data generated from genome-wide SNP surveys have been used to address many scientific questions other than SNP-trait associations. GWAS utilizes an experimental design to detect associations between genetic variants and traits in samples from populations. The primary goal of these studies is to better understand the biology of disease. The path from GWAS to biologic traits is not straightforward because the association between a genetic variant at a genomic locus and a trait is not directly informative with respect to the target gene or the mechanism of how the variant is associated with phenotypic differences. However, as reviewed by Visscher et al., new types of data, new molecular technologies, and new analytical methods have provided opportunities to bridge the knowledge gap from sequence to biologic traits. GWASs have also been utilized to better define the relative roles of genes and the environment in disease risk, supporting risk prediction (enabling preventative and personalized medicine), and in investigating natural selection and population differences [42].

Examining data for 807,557 persons, Howard and colleagues performed a GWAS meta-analysis of depression [43]. The meta-analysis revealed 102 independently segregating genetic variants that were associated with depression in 101 loci. This analysis produced evidence for the role of prefrontal brain regions in depression, and the genes identified contributed to the understanding of biological mechanisms and potential drug targets [43]. Chang and colleagues identified and characterized a novel gene with a potential genetic association with risk for mood disorders [44]. Carriers of mood disorder-risk alleles showed shifts in cognitive performance, emotional stability (neuroticism), amygdala structure, and functions during negative emotion processing similar to mood disorder patients. These risk associations seem to be related to the genetic regulation of *PCDH17* expression, which impacts the morphology and structure of dendritic spines. These results may provide new insights into the causes of mood disorders and into novel treatments [44].

Because of the polygenic, multifactorial nature of psychiatric disorders and the limitations of GWAS design, the genetic loci identified are generally small in effect size and individually of questionable clinical significance [45]. GWAS alone will

most likely yield limited translational advances to improve diagnostic accuracy and treatment effectiveness [42]. Our knowledge of expression and functions of genomic factors associated with a disorder is much more likely to be enhanced by a multidisciplinary approach that combines multiple omics data – integrated multidimensional omics to improve diagnosis, prognosis, and treatment development [46]. For example, a recent GWAS meta-analysis revealed a high degree of correlation [average genetic correlation (r_g) = 0.40] among bipolar disorder, major depressive disorder (MDD), and schizophrenia [47]. However, a molecular profiling approach characterizing 181 proteins and small molecules in serum showed excellent potential to distinguish schizophrenia from healthy controls, as well as from subjects with MDD, bipolar disorder, and Asperger's syndrome [48]. Studies utilizing both research methods in the same cohort likely will lead to significant improvement in diagnostic accuracy [15].

One research group (Chang et al. 2018) [44] performed a meta-analysis of very large datasets obtained from two GWASs. The sets included 29,557 subjects with mood disorders and 32,056 control subjects. They found that single-nucleotide polymorphisms (SNPs) along the brain expressed protocadherin gene (PCDH17) region were associated with major mood disorders such as bipolar and depression. Furthermore, in primary neuronal cultures, higher than normal expression of PCDH17 showed changes in dendritic spines. These changes in dendritic spines can affect normal synaptic function and cause abnormalities in synaptic function. Because abnormal synaptic function is thought to be a basic aspect of brain dysfunction in major mood disorders, PCDH17 expression could be implicated in the pathophysiology of major mood disorders and provide a potential novel target for pharmacotherapy.

27.4.2.2 Gene Polymorphisms

Jimenez et al. [49] were also interested in finding a genetic association to mood disorders, specifically depression. The FGF20 gene is part of the fibroblast growth factor (FGF) family which is associated with neural function and development. Therefore, Jimenez et al. examined a functional polymorphism (rs12720208) in the FGF20 gene, which is modulated by miR-433 (a short non-coding RNA) and its association with depressive symptoms in young adults (mean age of 21 years). They did find an association between the functional polymorphism rs12720208 on the FGF20 gene and depressive symptoms.

However, Border et al. [50] obtained differing results when trying to test the validity of candidate genes for depression. They selected 18 candidate genes for depression well examined in at least 10 studies. They analyzed data from large population-based samples and case-control samples examining candidate gene polymorphism main effects and polymorphism-by-environment interaction for association with depression. They found no association between candidate gene polymorphisms and depression nor between polymorphism by environment and

depression. Their results conflict with earlier studies and they suggest that the earlier studies were false positives [50].

Changes in circadian rhythm genes associated with bipolar disorder have also been a focus of research. Mansour and colleagues [51] conducted a small case-control study, in which 234 patients with bipolar I disorder were compared with 180 controls. They focused on 44 SNPs of 8 circadian rhythm genes and found associations with SNPs for aryl hydrocarbon receptor nuclear translocator-like (ARNTL) and timeless circadian clock genes (TIMELESS) [51]. Benedetti and colleagues [52] examined the diurnal activity and nocturnal sleep in 39 patients diagnosed with bipolar disorder and evaluated the role of the rs1801260 SNP within the CLOCK gene. Higher activity levels in the evening, delayed sleep onset, and reduced total amount of sleep per night were associated with this SNP [52].

27.4.2.3 Epigenetics

Using data from the ESPRIT study (a community-based population of individuals > 65 years of age), Lam et al. [53] found that DNA methylation of the serotonin transporter gene (SLC6A4) was associated with depression status, but only in specific genotypes. In individuals homozygous for the short 5-HTTLPR and 5-HTTLPR/r25531 alleles, lower methylation at two CpGs was associated with depression. This study illustrates genotype-dependent associations between SLC6A4 methylation and depression and suggests that genetic variants may also play a role in influencing promoter methylation levels and its association with depression. In another DNA methylation-related study, Thaweethee-Sukjai et al. [54] examined the extent of methylation of the parvalbumin gene (PVALB) promoter in MDD patients with and without suicide attempts compared to healthy controls. PVALB methylation was significantly increased at CpG2 and decreased at CpG4 in the MDD group compared to the control group; however, there was no difference between non-suicidal and suicidal MDD subgroups. Their study demonstrates abnormalities of gene PVALB promoter methylation in MDD and its correlation with MDD severity indicating a role for epigenetics in MDD.

By analyzing monozygotic twin studies, Peng et al. [55] found that altered DNA methylation in stress-related genes was associated with depressive symptoms and postulated that this mediates the association of childhood trauma with depression occurring later in life. They noted that several candidate genes are involved in the stress response system (including glucocorticoid receptor (NR3C1), brain-derived neurotrophic factor (BDNF), serotonin transporter (SLC6A4), and monoamine oxidase (MAOA, MAOB)) and that depression may be a result of altered DNA methylation of these genes. In another study, Tyrka et al. [56] examined the 1F promoter region of NR3C1 in relation to early-life stress and psychiatric disorders and found lower levels of methylation to be associated with stress exposure-related psychiatric conditions. These findings suggest that childhood stress influences NR3C1 methylation and may be a risk factor for the development of psychopathology. In a third study, Humphreys et al. [57] prospectively examined DNA methylation levels at loci within six genes that have been implicated in HPA axis functioning

(i.e., FKBP5, NR3C1, NR3C2, CRH, CRHR1, and CRHR2) in 77 girls at low and high familial risk for MDD who had no past or current MDD diagnosis at baseline. These researchers found that DNA methylation levels within CpG sites in NR3C1, CRH, CRHR1, and CRHR2 were associated with risk for MDD across adolescence and young adulthood. When they reanalyzed their data controlling for genetic variation and for familial risk for MDD, methylation levels continued to be a significant predictor of the onset of MDD. These findings imply that factors which were not inherited such as those from the environment could foretell the onset of MDD through the variation of DNA methylation levels more so than the effects of familial risk and genetic variation. They also noted that genetic and epigenetic factors both probably contribute to depression risk, but because of the modifiability of DNA methylation, epigenetic markers may be more helpful independent predictors of MDD risk.

27.4.3 Serum and CSF Biomarkers of Depression

Possible serum biomarkers have included the concentration of 25-hydroxy-vitamin D, 25(OH)D. In 2014, Milaneschi et al. [58] measured serum levels of 25(OH)D in subjects with depression and controls. They found lower levels of 25(OH)D in the depressed subjects than controls. Furthermore, the 25(OH)D levels were inversely proportional to the depression severity. They suggest that low vitamin D may represent a risk for depression [58].

In contrast to the above 2014 study, 5 years later, Milaneschi et al. [59] applied genomic tools and found no evidence of direct causal effect of 25(OH)D on depression risk. Another study [60] also found that vitamin D concentrations were not associated with the development of depression.

Other potential serum biomarkers for depression are inflammatory markers. This is a vast literature, which space constraints preclude an adequate review. For example, in a case-control study, Mishra et al. [61] found that in late-onset depression (mean age 64.7 years), patients with depression had 40% higher levels of C-reactive protein (CRP) compared to age-matched nondepressed patients. In addition, there was a robust positive correlation between CRP levels and severity of depression [61]. Our group has made similar observations of pro-inflammatory cytokines in depression [62].

27.4.4 Transforming Diagnostic Approach

An example of the transforming diagnostic approach is the the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP). The BSNIP study used statistical methods to sort cases into subgroups, based on multiple neurobiological measures. Biological and behavioral characteristics associated with psychosis were scrutinized in 1872 participants – patients diagnosed with schizophrenia, schizoaffective

disorder, and bipolar disorder with psychosis, their first-degree relatives, and healthy control subjects. Characteristics such as performance on thinking, planning, and memory tasks, eye tracking, inhibition, and brainwave responses to auditory stimuli determined groups of biomarkers that differentiated subgroups of patients. Three distinct psychosis-related biotypes were identified across clinical diagnosis boundaries. In addition, external measures – social functioning, brain structure, and rates of psychosis-related illness and biomarker patterns in patients’ first-degree relatives – validated the neurobiological biotype subgroups more than they did the symptom-based categories, providing evidence of biological overlap between traditional, symptom-based diagnostic categories for disorders in which patients experience psychotic symptoms. “The biotypes outcome provides proof-of-concept that structural and functional brain biomarker measures can sort individuals with psychosis into groups that are neurobiologically distinctive and appear biologically meaningful” [28, 63].

Those with various biotypes differed in their types of psychosis-related impairments. For example, cases classified as biotype 1 showed the most impairment in a set of brain functions that the researchers combined into a concept they term “cognitive control” – the ability to flexibly exert control over attention and information processing to meet one’s goals. The most socially impaired persons were biotype 1. Biotype 2 cases showed intermediate levels of impaired cognitive control but had normal to accentuated brain responses to sensory inputs and fast visual orienting, a set of brain functions called “sensorimotor reactivity” – the ability to detect and process sensory stimuli. Biotype 3 cases showed normal cognitive control and modestly impaired sensorimotor reactivity, were the least socially impaired, and had the lowest positive (e.g., hallucinations and delusions) and negative (e.g., blunted emotion) symptoms.

The BSNIP consortium has developed approaches to perfecting biomarkers and defining subtypes of psychosis using information about brain structure and function instead of clinical symptom characteristics. Brain structure differences also distinguish the three biotypes, further validating the categories. On MRI scans of the brain, biotype 1 cases – and to a lesser degree biotype 2 cases – showed reduced gray matter across several areas of the cortex known to process higher-order information. Alternatively, in biotype 3 cases, the largest of the groups, reduced gray matter was principally localized in emotion-processing areas in deeper brain regions. Biotypes 1 and 2 may successfully be examined with hereditary/genetic studies, while biotype 3 cases may produce more information about environmental contributions to psychosis risk. Treatments for biotype 1 should target cognitive control and enhance brain mechanisms for determining the relevance of environmental stimuli. Patients with biotypes 1 and 2 might be best treated with approaches that correct neuronal activity levels through effects on cellular potassium or calcium channels (Table 27.2) [28, 63].

Psychiatry is in critical need of functional and molecular biomarkers to generate therapeutic targets for drug development. Psychiatry has relied on trial and error for identifying treatments for too long. Moreover, knowledge of the specific neural alterations associated with and causally related to psychotic illness will assist in

Table 27.2 Biotype cluster characteristics (adapted from 28, 63)

Biotype 1	Biotype 2	Biotype 3
Very low cognition	Low cognition	Nearly NL cognition
Very low EEG power	High EEG power	Just low on EEG power
Low gray matter volume	N100, P300 (normal)	Fast visual orienting
Worst negative Sx	Low cortical volume, more focused	Low % affected relatives
Highest affected relatives	High affected relatives	Normal Sz polygene score
High Sz polygene score	Moderate cannabis use	High cannabis use
Lowest cannabis use		

Abbreviations: *EEG* electroencephalography, *NL* normal, *Sx* symptoms, *Sz* schizophrenia

defining actual brain changes, and this may help to diminish the stigma of serious mental illness. Knowledge of molecular, cellular, and biologic systems pathophysiology in psychotic diseases could greatly enhance prospective screening and prophylactic management of psychotic conditions, supporting the importance of early detection [28, 63].

27.5 Biomarkers and Treatment Response

A number of researchers have examined biomarkers in relationship to treatment response. For example, they have considered genetic markers and markers from blood and other peripheral measures.

27.5.1 Genetics

O’Connell et al. [64] examined the relationship between genotype at 16 candidate HPA axis single-nucleotide polymorphisms (SNPs) and treatment outcomes for 3 antidepressants (escitalopram, sertraline, and extended-release venlafaxine) in the 1000 patient iSPOT study. The rs28365143 variant within the corticotropin-releasing hormone binding protein (CRHBP) gene predicted antidepressant outcomes for remission, response, and symptom change. Persons homozygous for the G allele of rs28365143 variant had greater remission rates, response rates, and symptom reduction and responded significantly better to the selective serotonin reuptake inhibitors escitalopram and sertraline than A allele carriers. However, the rs28365143 genotype was not associated with better treatment responses for the serotonin-norepinephrine reuptake inhibitor, venlafaxine. The findings suggest that a specific CRHBP SNP, rs28365143, may have a role in predicting which patients will improve with antidepressants and which type of antidepressant may be most effective [64].

In a separate study, Marsche et al. [65] investigated five functional variants of the norepinephrine (SLC6A2, NET) and serotonin transporter (SLC6A4, SERT) genes

and remission in depressed older adults treated with venlafaxine. They found that NET rs2242446/T-182C may serve as a biomarker to predict the likelihood of remission with venlafaxine in older adults with major depression [65]. Kao et al. [66] evaluated whether the serotonin transporter (5-HTT or SERT or SLC6A4) mRNA expression could be used as a biomarker of treatment response in patients with major depression treated with the antidepressants duloxetine and paroxetine. Patients with 5-HTTPR long-form alleles and STin2.12 alleles had a poor antidepressant treatment response. The 5-HTT mRNA expression was correlated with treatment response [66]. Ising et al. [67] were able to demonstrate that a reduction in *FKBP5* gene and FKBP51 protein expression were associated with successful antidepressant treatment outcome in depressed patients, particularly in those patients who are carrying the risk allele of the *FKBP5* variant rs1360780. Their findings suggest an important role for *FKBP5* and FKBP51 in antidepressant treatment outcome and highlight a promising target for future antidepressant drug development [67].

In their review of convergent neurobiological predictors of mood and anxiety symptoms and treatment response, Jabbi and Nemeroff [68] examined the interaction between environmental-adversity and molecular-genetic mediators of brain correlates of affective symptoms. The molecular focus was on the *GTF2i*, *BDNF*, and *FKBP5* genes that are, respectively, involved in transcriptional, neurodevelopmental, and neuroendocrine pathways of affective functions. Major psychiatric syndromes including mood and anxiety disorders are classic examples of complex medical diseases caused by gene-environment interactions that impact neural development and, as research progresses, can be evaluated with biomarkers. The authors also emphasized the importance of studying gene-dosage effects in understanding the biological risk for affective disorders and how neurogenetic studies could guide identification of novel pharmacotherapeutic targets and help in the prediction of treatment response. They used the term “mental scars” and note that studies identifying these scars in terms of brain structural and functional correlates of affective disorders, along with computational applications to decipher the maladaptive behavioral effects of these mental scars, will result in a better biological understanding of affective disorders [68].

Zeier et al. [69] reviewed the literature for several commercial combinatorial pharmacogenetic decision support tools that have been evaluated in clinical settings. Although some of the preliminary published reports were promising, particularly with regard to the CYP450 gene variants and side effect burden, the authors concluded that there is insufficient evidence to support widespread use of combinatorial pharmacogenetic decision support tools in predicting antidepressant treatment response at this time [69].

27.5.2 Blood and Other Peripheral Measures

Several studies have attempted to identify factors to predict depression outcome over time. Salivary cortisol levels have been just such a candidate. Vreeburg et al. [70] examined salivary cortisol measures in relationship to a 2-year course of depression and anxiety disorders. They found that a lower cortisol awakening response had an increased risk of a poor 2-year chronic course trajectory for depression and anxiety disorders.

Vogelzangs et al. [71] tested several metabolic and inflammatory factors seeking an association with depression outcome at the 2-year point. The subjects were treated with antidepressants. Factors associated with a less favorable outcome were elevated interleukin-6 (IL-6) and metabolic factors including hypertriglyceridemia, low HDL cholesterol, and hyperglycemia. These results suggest that patients with metabolic and inflammatory dysregulation have a poorer response to antidepressants [71]. Rethorst et al. [72] also considered inflammatory factors as an indicator of depression response to antidepressants and whether exercise might be a beneficial addition to treatment. Their result showed that patients with a higher baseline level of tumor necrosis factor- α (TNF- α) responded better to exercise treatment, suggesting that in this particular subgroup, exercise is a viable treatment option for depression [72]. Our group [62] in a study of never-treated depressed patients reported multiple alterations in pro- and anti-inflammatory cytokines as well as in other immune measures. Clearly a sizable subtype of depressed patients exhibits immune system dysregulation including evidence in which inflammation in the CNS was measured in depressed patients with PET imaging [73].

27.6 Trauma as a Predictor of Diagnosis and Treatment

Williams et al. [74] evaluated the role of early-life trauma in predicting acute response outcomes to antidepressants in a large sample of well-characterized patients with major depressive disorder (MDD). The data were derived from the International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial with enrollment in five countries. The study sample was comprised of patients ($n = 1008$) meeting DSM-IV criteria for MDD and 336 matched healthy controls. Randomization was applied to 8 weeks of treatment with escitalopram, sertraline, or venlafaxine with dosage adjusted by the participant's treating clinician per routine clinical practice. The Early-Life Stress Questionnaire was used to evaluate exposure to 18 types of traumatic events before the age of 18. Depressed patients were significantly more likely to report early-life stress than controls. The higher rate of early-life trauma was most evident for experiences of interpersonal violation (emotional, sexual, and physical abuses). Abuse (and abuse occurring at ≤ 7 years of age) predicted poorer outcomes after 8 weeks of antidepressant treatment. Specific types of early-life trauma, particularly physical,

emotional, and sexual abuse, especially when occurring at ≤ 7 years of age, are important moderators of antidepressant response in MDD [74].

Goldstein-Piekarski et al. [75] demonstrated that functional remission with antidepressants may be dependent on the degree of early-life stress (ELS), the degree of amygdala engagement during facial emotion viewing, and their interaction. They were able to predict with a high degree of accuracy (81%) who would and would not remit following pharmacotherapy with commonly prescribed antidepressants. Peng et al. [55] examined the combined association of DNA methylation at multiple CpG probes in five stress-related genes associated with depressive symptoms and tested whether these genes' methylation mediated the association between childhood trauma and depression in two monozygotic (MZ) twin studies. They found that gene-based or gene-set approaches revealed significant joint associations of DNA methylation in all five stress-related genes associated with depressive symptoms in both studies. Two CpG probes in the *BDNF* and *NR3C1* mediated approximately 20% of the association between childhood trauma and depressive symptoms. The authors indicated that their results highlight the importance of testing the combined effects of multiple CpG loci on complex traits and that this approach may unravel a molecular mechanism through which adverse early-life experiences are biologically embedded [55].

27.7 The Role of Neuroimaging

Neuroimaging studies and selected cognitive-emotional domains are being developed as biomarkers for mood disorders to predict disease subtypes and response to treatments. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been frequently found in depressed patients and also is associated with the risk of suicide and the risk of PTSD in those with early-life trauma [11].

Human brain function properties that can be quantified in vivo (e.g., brain structure, cognition, molecular traits, functional behavioral outcomes) are a key to understanding pathophysiology and predicting outcomes in psychiatric conditions and for classifying brain disorders by types of pathophysiology regardless of clinical symptoms. When etiology is unknown, measures of brain function (biomarkers or intermediate phenotypes) are especially important for studying brain diseases. Without biomarkers for these disorders, only clinical signs and symptoms are used to classify and define diseases, an approach that is far from optimal for capturing distinctive neurobiological pathophysiology. Clinical manifestations are not reliable for classifying psychoses, because they are pleomorphic and vary within and across diagnoses. Technical advances have led to innovative tools in clinical neuroscience, which have advanced the biological knowledge in human brain diseases, including tools for brain imaging, cognition, and electrophysiology [37].

27.7.1 *Functional Measures*

EEG measures the brain's electrical activity directly, while other methods record changes in blood flow (e.g., SPECT, fMRI) or metabolic activity (e.g., PET), which are indirect markers of brain electrical activity.

27.7.1.1 **Spatial Neuroimaging: The MRI, fMRI, and PET Scan**

Vulnerability Both functional (fMRI) and structural (sMRI) magnetic resonance imaging have been utilized to determine what markers might be a predictor of depression development. In an fMRI study, low ventral striatum activation was shown to be a predictor of subthreshold or clinical depression 2 years later in adolescents with no previous history of depression [76]. Another study, using sMRI [77], evaluated markers of cortical neurodevelopment in patients with depression and controls. Greater local cortical gyrification (LGI) was found in certain regions in depressed subjects than controls and appeared to be associated with length of disease. These results show that abnormal cortical neurodevelopment may be a potential indicator of future depression [77].

Predictors of Treatment Response Because depression has a relatively low remission rate, it is important to be able to predict which individual will respond favorably to a specific treatment. Much effort has been put forth in this endeavor. Several studies have utilized neuroimaging and found potential indicators of which treatment would be optimal for a particular patient. For example, using PET, one study demonstrated that subjects with insula hypermetabolism responded well to escitalopram, while those with insula hypometabolism responded better to cognitive behavioral therapy [78]. Dunlop et al. evaluated the right anterior insula (rAI) metabolism biomarker as a predictor of outcome in depression. The subjects were depressed patients who had not responded to either CBT or escitalopram and were then given additional treatment. Results showed that when the added treatment matched biomarker-indicated treatment, the patients were more likely to have a favorable outcome than when the treatments were mismatched. Indeed the rAI appears to be a viable biomarker for selecting the best treatment for depression [79].

Schmaal et al. [80] attempted to identify neurobiological factors which could help forecast the outcome of major depression. They tested several neuroimaging metrics using fMRI and sMRI as well as clinical characteristics for predictive value. Neural responses to emotional faces had a better predictive value for depression outcome than clinical data. Finally, Ditcher et al. [81] evaluated the findings of previous fMRI studies and found several factors valid for predicting treatment response in MDD including visual recognition circuits and elevated connectivity between the frontal lobe and limbic system [81].

27.7.1.2 Electrophysiologic Neuroimaging: The EEG

EEG (electroencephalogram) measures have also been considered as a potential predictor of depression. A 2013 study [82] was the first to find an association between a neural measure of reward sensitivity and the initial episode of depression prospectively. The authors followed 68 never-depressed girls over 2 years and found blunted baseline reward sensitivity may be a predictor for the onset of depression. Their findings were substantiated by another study [83] which also found that low baseline reward sensitivity could predict the initial onset of depression. Both studies involved adolescents, which is the age group that the incidence of depression greatly increases, thus an important time to have a viable biomarker for depression risk [82, 83].

In addition, EEG has been considered as a predictor for treatment outcome in depression. Greater right frontal alpha oscillations have been linked to good outcomes with escitalopram and sertraline, though only in females [84]. In addition, baseline gamma oscillations have been associated with response to treatment with paroxetine [85]. However, other studies have found that while baseline EEG measures theta-band rACC-rAI connectivity [86] and rACC theta activity [87] could predict depression outcome, they had no value as predictors for specific treatment outcome. In addition, a meta-analysis study [88] found no predictive value for treatment outcome using QEEG (quantitative EEG).

Rolle et al. [89] studied whether EEG connectivity could reveal neural indicators of antidepressant treatment. In their study, greater alpha-band and lower gamma-band connectivity predicted better placebo outcomes and worse antidepressant outcomes. Their findings established the value of EEG-based connectivity analyses to assist the differentiation of placebo response from antidepressant response in clinical trials, whereas Wu et al. [90] developed a machine learning algorithm for resting-state EEG and applied it to the findings from a large imaging-coupled, placebo-controlled antidepressant study. Symptom improvement was predicted for sertraline. Also, the sertraline resting-state EEG was associated with prefrontal neural responsivity, as measured by concurrent transcranial magnetic stimulation and EEG. Their findings enhanced the neurobiological understanding of antidepressant treatment through an EEG-tailored computational model and help provide a clinical tool for personalized treatment of depression.

27.8 Information Technology in Precision Psychiatry

In the future, developments in technology will have a greater role in the determination of new biomarkers for depression. However, in spite of early enthusiasm, few technological tools have been created that are usable in clinical practice. Tools available now are mostly pharmacogenetic test kits (e.g., the FDA approved AmpliChip CYP450 test from Roche, Switzerland, and GeneSight from Assurex Health, OH, USA), but their utility is doubtful at best [91–94]. In order to have

personalized medicine, it is critical to have practical clinical tools. Extremely large datasets are now easier and more affordable to collect, store, and analyze. Electronic medical records (EMRs) enable clinical information to be stored and potentially available for analysis by researchers. Standardizing EMRs with national and international guidelines would render the data on EMRs more easily studied and comparable between records, such as those from the Department of Health [95].

The miniaturization of physiological sensors, allowing them to be integrated into wearable devices, is another potential advance for precision medicine. Some devices for ambulatory monitoring have existed since the 1960s (e.g., Holter monitors for electrocardiography, arterial pressure, and electroencephalography). However, not till recently have the devices become small enough that they are wearable and useful for studies. These devices include watches, jewelry, smartphones, patches, and more. Some vital signs can now be measured with miniaturized sensors, such as motion/heart rate, body and skin temperature, arterial blood pressure, blood oxygen saturation, electrocardiograms, electroencephalograms (EEGs), and respiration rate [96].

In addition, the connection of devices to the Internet and to each other, the so-called Internet of Things [97], also allows real-time streaming of data and real-time analyses. These wearable devices can be continuously connected to the Internet and permit the collection of data [98] through apps that allow users to insert information, as well as automatically collecting data via the sensors connected to smartphones. With these devices data and warnings can be sent to clinicians, allowing them to monitor their patients' conditions and intervene when necessary. Real-time information can also be sent to patients affording them better awareness of their condition. This approach has been very effective in monitoring pain, and recent studies have investigated the promise of continuous monitoring in subjects with psychiatric disorders (phone, wrist-worn activity monitor, stationary EEG system for periodic measurements, and novel "sock-integrated" electrodermal activity sensor) [99–102].

Electronic medical records and miniaturized sensors embedded in wearable devices, as well as genomics, epigenetics, transcriptomics, and proteomics assessments, enable the collection of a large amount of data for every patient. However, even when useful information is available, making predictions requires models that connect this information with an outcome. Machine learning integrates computer science, engineering, and statistics "that gives computers the ability to learn without being explicitly programmed." The family of machine learning procedures referred to as "supervised" can be used to develop predictive algorithms able to provide the best possible predictions when applied to new cases, for example, making a single-patient prediction of the expected response before a therapy is administered. A number of supervised methods have been developed, e.g., artificial neural network [103], support vector machine [104], random forest [105], and boosting [106], but also traditional statistical methods (i.e., from linear regression to the generalized linear model) can be used to develop predictive models. If predictors are unknown, the best opportunity to reveal them relies on either analysis of datasets already available or determining them from the current scientific evidence, as much as experts' own experience [13].

27.9 Conclusion

Personalized (or precision) medicine as applied to psychiatry is still a relatively new concept but is being actively investigated by numerous researchers and shows promise in helping to improve psychiatric care. In this chapter we have presented current and potential tools that can be used to aid the implementation of precision psychiatry as applied to depression. We have explored and discussed numerous biomarkers, including endophenotypes, gene variants/polymorphisms, epigenetic factors such as methylation, biochemical measures, circadian rhythm dysregulation, and neuroimaging findings. We also examined the role of early childhood trauma in relation to the development of and treatment of depression. Finally, we reviewed how new developments in technology may play an increasing role in the development of biomarkers for depression. In the future precision psychiatry is likely to play a greater role in the diagnosis and treatment of depression and thus help reduce the suffering from this major cause of morbidity and mortality.

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