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Brain-Derived Neurotrophic Factor Expression in Individuals With Schizophrenia and Healthy Aging: Testing the Accelerated Aging Hypothesis of Schizophrenia

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Abstract
Purpose of Review Schizophrenia has been hypothesized to be a syndrome of accelerated aging. Brain plasticity is vulnerable to the normal aging process and affected in schizophrenia: brain-derived neurotrophic factor (BDNF) is an important neuroplasticity molecule. The present review explores the accelerated aging hypothesis of schizophrenia by comparing changes in BDNF expression in schizophrenia with aging-associated changes.
Recent Findings Individuals with schizophrenia show patterns of increased overall mortality, metabolic abnormalities, and cognitive decline normally observed later in life in the healthy population.
Summary An overall decrease is observed in BDNF expression in schizophrenia compared to healthy controls and in older individuals compared to a younger cohort. There is a marked decrease in BDNF levels in the frontal regions and in the periphery among older individuals and those with schizophrenia; however, data for BDNF expression in the occipital, parietal, and temporal cortices and the hippocampus is inconclusive. Accelerated aging hypothesis is supported based on frontal regions and peripheral studies; however, further studies are needed in other brain regions.

Keywords Schizophrenia · Brain-derived neurotrophic factor · BDNF · Aging · Neuroplasticity · Neurodevelopment · Accelerated aging hypothesis

This article is part of the Topical Collection on *Schizophrenia and Other Psychotic Disorders*

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Introduction

Schizophrenia is a chronic, debilitating mental health illness affecting 0.5 to 2% of the worldwide population [1]. Individuals with schizophrenia experience a broad range of psychotic symptoms, including paranoia and hallucinations, often accompanied with a disintegration of thought and cognitive processes and impaired emotional responsiveness. Although the pathogenesis of schizophrenia remains elusive, neuropathological findings of structural alterations in the brains of individuals with schizophrenia suggest aberrancy in brain development [2]. One hypothesis put forth regarding the etiology of schizophrenia is that the observed neurodevelopmental abnormalities in schizophrenia share common features with developmental changes that are observed in normal aging, which suggests that schizophrenia is a syndrome of accelerated aging [3••]. This hypothesis is based on observations that individuals with schizophrenia exhibit decreased life expectancy in comparison to the general population [4] and display medical comorbidities [5, 6], metabolic problems [7–9], and cognitive decline that is often

observed late in life in the healthy population [10–12]. Therefore, developmental processes in the brain and body may occur at an accelerated rate over an abbreviated period of time in individuals with schizophrenia compared with healthy individuals [3••].

In schizophrenia and normal aging, there are marked changes in neuroplasticity processes [13–15]. Neuroplasticity is the capacity of the brain to undergo experience-dependent modifications to the strength of synaptic connections [16]. Synaptic plasticity modifications involve the initiation of specific signaling cascades and mediate structural changes of the brain including synapse formation and elimination, morphological changes in dendritic spines, and changes in axon and dendrite organization [17]. Long-lasting synaptic changes support learning and memory and a variety of cognitive functions on which individuals with schizophrenia display a wide range of impairments [18–21]. Post-mortem studies have found that individuals with schizophrenia demonstrate abnormal levels or express risk alleles of important synaptic plasticity molecules compared with healthy individuals [14]. Therefore, aberrant synaptic plasticity observed in schizophrenia may be due to brain abnormalities acquired early in life [22].

Significant changes in neuroplasticity are observed with normal aging [23]. Learning and memory and a range of cognitive functions mediated by synaptic plasticity processes, including long-term potentiation (LTP) and long-term depression (LTD), show substantial age-related decline [24]. Animal studies have reported impaired LTP and LTD in aged brains that is associated with impairments in memory and spatial learning [25]. Based on these and other findings demonstrating changes in neuroplasticity processes in both schizophrenia and normal aging, it can be postulated that neuroplasticity changes associated with schizophrenia overlap with those observed in aging with respect to the nature, direction, and magnitude of these changes.

Neurotrophins are considered to be molecular mediators of neuronal plasticity [26, 27]. They are essential for neuronal development, differentiation, maturation, and survival [26, 27]. Among these molecules, brain-derived neurotrophic factor (BDNF) plays an important role in neurogenesis, synaptic transmission, and in translating activity patterns into synaptic plasticity changes [28]. Animal studies have shown that BDNF is particularly involved in synaptic consolidation by activating transcription of important genes and stimulating cytoskeletal changes in the neuron [28]. BDNF is a reliable molecular marker of neuroplasticity that has been implicated in both the pathophysiology of schizophrenia and the natural aging process [23, 29]. Thus, the present review explored the hypothesis that schizophrenia is a syndrome of accelerated aging by summarizing findings on BDNF expression levels in schizophrenia and in the older population. Three major questions were addressed: (1) Are there alterations in brain and peripheral BDNF levels in individuals with schizophrenia? (2) Are there changes in brain and peripheral BDNF levels associated with normal aging? (3) Do the changes in BDNF levels observed in normal aging appear to be accelerated in individuals with schizophrenia?

Methods

Literature Search

Articles were identified through an extensive literature search using the following databases: Ovid, PubMed, Google Scholar, and Summon. Literature search was started in January 11, 2013 and the databases were searched up to January 23, 2017. The key terms that were used were BDNF or brain-derived neurotrophic factor and aging or schizophrenia. Most recent review papers on BDNF and aging or schizophrenia were first identified through the electronic search. Subsequently, the cited references in these papers were retrieved and reviewed. Finally, primary papers published after the most recent reviews were retrieved and reviewed.

Selection Criteria

The articles included in this review were restricted to English language, peer-reviewed studies which met the following inclusion criteria: (1) focus on BDNF expression in the central nervous system, (2) focus on aging or schizophrenia. Exclusion criteria were (1) a diagnosis other than schizophrenia and (2) lack of a healthy control group in schizophrenia studies or young control group in aging studies.

Data Extraction

The following variables were extracted from selected papers: (1) study type (animal vs. human), (2) sample type (e.g., cerebrovascular fluid, post-mortem brain slices), (3) measurement type (mRNA vs. protein), (4) measurement methodology type (ELISA, immunoassay, Western blot, etc.), and (5) change in BDNF levels for each group in comparison with the control group (increase, decrease, or no significant difference).

Results

PubMed search for schizophrenia and aging-related articles focusing on BDNF resulted in 721 and 1134 records, respectively. Of these records, the most recent review papers on the topic were selected and cited references were extracted. Primary articles published after the publication date of the most recent review were manually selected based on the

inclusion criteria. Thirty-one papers on the topic of schizophrenia and BDNF (Table 1) and 24 papers on the topic of aging and BDNF (Table 2) were selected to be included in the present review.

Schizophrenia studies of plasma and serum levels of BDNF used moderate- to large-sized samples (ranging from n = 22 to n = 364) [30, 31, 34, 36, 38–40, 43–46, 49–52, 54–56, 59, 60], except for meta-analyses by Cui et al. [32] and Green et al. [35] that included 1663 and 1114 individuals with schizophrenia, respectively. Studies involving post-mortem data had small to moderate sample sizes (ranging from n = 8 to n = 71) [33, 37, 41, 42, 47, 48••, 53, 57, 58]. Five studies included only drug-naïve individuals with schizophrenia [30, 31, 43, 45, 52]. The majority of the studies measuring protein levels of BDNF used enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay (EIA), but four studies used immunohistochemistry [41] or Western blotting [53, 57, 58]. Studies measuring RNA levels of BDNF used in situ hybridization [37, 47, 48••, 57], Northern blotting [57], or RNAse protease assay techniques [57].

There was great variability in the sample type for the aging studies, with 12 studies showing data from animal models of aging [61–64, 67–70, 72, 76, 78, 79] and 12 studies using human samples [65, 66, 71, 73, 74, 75•, 77, 80•, 81–84]. Human aging studies of blood plasma and serum used large sample sizes ranging from n = 48 to n = 4463 and measured protein levels of BDNF using ELISA [65, 66, 71, 73, 74, 80•, 81, 84]. Human post-mortem studies studying BDNF levels in brain structures used moderate to large sample sizes ranging from n = 12 to n = 209, and RNA levels of BDNF were measured using in situ hybridization [77, 82, 83], real-time polymerase chain reaction (RT-PCR) [75•], or RNA protection assay [82]. Majority of animal studies included in this review used rodents to model changes in BDNF levels in aging [61–64, 67, 68, 70, 72, 76, 78, 79], except for one study which used Macaque monkeys [69].

BDNF Levels in the Frontal Cortex and Related Regions

As detailed in Table 3, data from five post-mortem studies reporting protein or mRNA levels of BDNF provided evidence of a reduction in BDNF expression in the frontal cortex and related brain regions in individuals with schizophrenia compared to healthy age-matched controls [37, 42, 48••, 57, 58]. However, Durany et al. found that protein levels of BDNF were higher in the frontal cortex of individuals with schizophrenia than in controls [33]. They also reported a negative correlation of BDNF levels in the frontal cortex with age, with older individuals with schizophrenia displaying lower levels of BDNF [33].

Four studies assessed the effects of aging on BDNF in the frontal cortex and related regions. Three of the four studies found an overall decrease in mRNA levels of BDNF in the frontal regions [64, 69, 75•]. In contrast, Webster et al. observed no significant differences in the mRNA expression of BDNF in the dorsolateral prefrontal cortex (DLFPC) between younger and older subjects [82]. This study also reported a marked decrease in the mRNA levels of tropomyosin receptor kinase B (TrkB), the receptor for BDNF, in the DLPFC of older subjects, which may suggest a decrease in neuronal responsiveness to BDNF in the DLPFC with age [82]. Our literature search did not come up with any studies focusing on the effects of aging on BDNF protein levels in the frontal brain regions.

Taken together, these studies suggest reduced BDNF function in the frontal cortex and related regions of individuals with schizophrenia and healthy older individuals.

BDNF Levels in the Parietal and Occipital Cortices

Durany et al. reported higher protein levels of BDNF in the parietal and occipital cortices of individuals with schizophrenia than in the sex- and age-matched controls (Table 3) [33]. In contrast, two studies reported that there were no significant differences in the protein or mRNA levels of BDNF in the parietal and occipital cortices between individuals with schizophrenia and controls [33, 53]. Two aging studies observed that mRNA levels of BDNF were unaffected by age in the parietal and occipital cortices [63, 82]. However, Calabrese et al. reported a decrease in mRNA levels of BDNF in the parietal cortex [61]. While the former two aging studies are consistent with the results from schizophrenia studies of these brain regions, further research is needed to examine the expression of BDNF in the parietal and occipital cortices in schizophrenia and aging.

BDNF Levels in the Temporal Cortex and Hippocampus

Of the studies assessing BDNF levels in the temporal cortex of individuals with schizophrenia, Durany et al. found increased protein levels of BDNF in this region [33], whereas Ray et al. reported decreased mRNA levels of BDNF compared to healthy controls [48••]. All but one aging study revealed decreased levels of BDNF protein and mRNA in the temporal cortex (Table 3). Croll et al. reported no significant difference in BDNF mRNA expression in the temporal cortex between younger and older subjects [63]. Due to the observed heterogeneity in the findings based on a limited number of studies, further research is needed to make more conclusive observations.

Five studies assessed BDNF expression in the hippocampus of individuals with schizophrenia in comparison to control subjects. These studies revealed considerable variability (Table 3). Iritnai et al. and Takahashi et al. observed increased BDNF proteins in the hippocampus as measured by immunohistochemistry and Western blotting, respectively [41, 53]. On

Table 1 Characteristics of included schizophrenia studies

Study ID	Sample	Mean age ± SD (years)	Matched for	Medication	Structure	Methodology
Chen et al. [30]	88 Scz 90 Ctl	Scz 29.2 ± 9.6 Ctl 29.8 ± 9.8	Age, gender, education, smoking, BMI	Drug Naïve	Serum	ELISA
Chiou and Huang [31]	34 Scz 34 Ctl	Scz 30.6 ± 11.2 Ctl 30.7 ± 8.1	Age, sex	Drug naïve	Serum	ELISA
Cui et al. [32]	1663 Scz 1355 Ctl	Scz 38.8 ± 9.8 Ctl 38.0 ± 9.6	Not indicated	Not provided	Serum	ELISA
Durany et al. [33]	11 Scz 11 Ctl	Scz 77.6 ± 4.0 Ctl 77.2 ± 2.5	Age	400 mg daily chlorpromazine equivalent (n = 6); Not provided (n = 5)	Neocortex (frontal, parietal, temporal, occipital), hippocampus, cingulate gyrus, thalamus	ELISA
Gama et al. [34]	60 Scz 26 Ctl	Scz 35.3 ± 10.4 Ctl 40.7 ± 12.1	Age	Clozapine (n = 27) 583.9 ± 212.6 mg; typicals (n = 14) 561.0 ± 322.9 mg in chlorpromazine equivalents; atypicals (n = 19) 6.0 ± 3.0 mg in risperidone equivalents	Serum	ELISA
Green et al. [35]	1114 Scz 970 Ctl	Scz 35.5 ± 9.7 Ctl matched	Age	Drug naïve (n = 270); medication list not provided (n = 839)	Blood (serum and plasma)	Various (meta-analysis)
Grillo et al. [36]	44 Scz 25 Ctl	Scz 35.5 ± 9.5 Ctl 34.1 ± 13.1	Age, gender	Chlorpromazine (n = 6); clozapine (n = 20); levomepromazine (n = 15); haloperidol (n = 5)	Serum	EIA
Hashimoto et al. [37]	27 Scz 27 Ctl	Scz 47.0 ± 13.1 Ctl 47.5 ± 14.3	Sex, age, PMI	Not provided	Prefrontal cortex	in situ hybridization
Hori et al. [38]	146 Scz 51 Ctl	Scz 33.6 ± 10.2 Ctl 36.7 ± 9.9	Age, sex	413.9 ± 260.7 mg daily chlorpromazine equivalent	Serum	EIA
Huang and Lee [39]	126 Scz 96 Ctl	Scz 34.0 ± 10.3 Ctl 29.1 ± 5.3	None	Drug naïve (n = 10); medication list not provided (n = 116)	Serum	ELISA
Ikeda et al. [40]	74 Scz 87 Ctl	Scz 41.9 ± 11.1 Ctl 39.8 ± 10.7	Age, BMI, smoking habit, sex	Bromperidol (n = 3); chlorpromazine (n = 14); fluphenazine (n = 2); haloperidol(n = 13); levomepromazine (n = 15); nemonapride (n = 1); olanzapine (n = 23); perospirone (n = 7); perphenazine (n = 1); propericyazine (n = 3); quetiapine (n = 16) risperidone (n = 31); sulpiride (n = 6); sultopride (n = 4); timiperone (n = 1); zotepine (n = 10)	Serum	EIA
Iritani et al. [41]	8 Scz 4 Ctl	Scz 59.1 ± 8.5 Ctl 65.0 ± 10.3	None	Bromperidol (n = 1); chlorpromazine (n = 2); haloperidol (n = 5); levomepromazine (n = 4); zotepine (n = 1)	Hippocampus	Immunohistoch-emistry
Issa et al. [42]	15 Scz 15 Ctl	Scz 69.9 ± 12.6 Ctl 70.9 ± 8.5	Age	Not provided	Prefrontal cortex, CSF	ELISA
Jindal et al. [43]	24 Scz 41 Ctl	Scz 22.4 ± 5.5 Ctl 22.3 ± 5.7	Age	Drug naïve	Fasting serum	ELISA
Niitsu et al. [44]	63 Scz	Scz 35.9 ± 8.2	Age, sex		Serum	ELISA

Table 1 (continued)

Study ID	Sample	Mean age ± SD (years)	Matched for	Medication	Structure	Methodology
	52 Ctl	Ctl 34.9 ± 7.3		323.9 ± 184.2 mg daily chlorpromazine equivalent (n = 60); Not provided (n = 3)		
Pillai et al. [45]	34 Scz 36 Ctl	Scz 32.2 ± 8.7 Ctl 38.3 ± 10.3	None	Drug naïve	Plasma and CSF	ELISA
Pirildar et al. [46]	22 Scz 22 Ctl	Scz 27.8 ± 9.5 Ctl 25.7 ± 5.8	Age, sex	Drug naïve (n = 5); 450 mg daily of clozapine (n = 2); 25 mg daily of olanzapine (n = 3); 4 mg daily of risperidone (n = 17)	Serum	ELISA
Ray et al. [47]	15 Scz 15 Ctl	Scz 43 ± 13 Ctl 48.1 ± 10.7	Age, sex race, PMI, brain pH	5×10^4 mg fluphenazine equivalent	Hippocampus (dentate gyrus, cornu ammonis (CA1,3,4), subiculum and entorhinal cortex)	In situ hybridization
Ray et al. [48••]	15 Scz 15 Ctl	Scz 44.5 ± 13.1 Ctl 48.1 ± 10.7	Race, sex, age, brain pH, storage interval, PMI, RNA integrity number	Not provided	Dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, superior and inferior temporal gyrus	In situ hybridization
Reis et al. [49]	40 Scz 20 Ctl	Scz 52.3 ± 9.8 Ctl Not provided	Age, sex	Haloperidol (n = 28); chlorpromazine (n = 3); levomepromazine (n = 3); trifluorperazine (n = 6)	Serum	ELISA
Rizos et al. [50]	47 Scz 44 Ctl	Scz 43.63 ± 10.9 Ctl 46.5 ± 14.9	Age, Sex	1080 ± 179 mg daily of amisulpride (n = 5); 11 ± 3 mg daily of haloperidol (n = 18); 23 ± 3 mg daily of olanzapine (n = 10); 9.78 ± 3.92 mg daily of risperidone (n = 14)	Serum	ELISA
Shimizu et al. [51]	40 Scz 40 Ctl	Scz 34.7 ± 16.0 (drug naïve); 36.0 ± 13.2 (medicated) Ctl 36.5 ± 14.6	Age, sex	727 ± 412 mg daily chlorpromazine equivalent (n = 25); drug naïve (n = 15)	Serum	ELISA
Sotiropoulou et al. [52]	50 Scz 50 Ctl	Scz 29.8 ± 8.2 Ctl 31.4 ± 8.0	Age, sex	Drug naïve	Serum	EIA
Takahashi et al. [53]	18 Scz 36 Ctl	Scz 61.6 ± 15.2 Ctl 59.4 ± 12.9	Age	Chlorpromazine (n = 3); haloperidol (n = 5); levomepromazine (n = 2); oxypertine (n = 1); propericiazine (n = 1); thioridazine (n = 2); thiotixene (n = 1); trimipramine (n = 1); not medicated (n = 6)	Frontal cortex, prefrontal cortex, occipital cortex, hippocampus, anterior cingulate cortex	EIA; Western blotting
Tan et al. [54]	81 Scz 45 Ctl	Scz 48.1 ± 5.8 Ctl 45.6 ± 4.5	Age, sex	Chlorpromazine (n = 5); clozapine (n = 38); haloperidol (n = 12); perphenazine (n = 5); risperidone (n = 19); others (n = 2)	Serum	ELISA
Toyooka et al. [55]	34 Scz 35 Ctl	Scz 48.6 ± 14 Ctl 45.6 ± 11.3	Age	Bromperidol (n = 3); chlorpromazine (n = 5); haloperidol (n = 29); levomepromazine (n = 31); risperidone (n = 1); zotepine (n = 2); others (n = 9)	Blood and serum	EIA

Table 1 (continued)

Study ID	Sample	Mean age ± SD (years)	Matched for	Medication	Structure	Methodology
Vinogradov et al. [56]	56 Scz 16 Ctl	Scz 44.0 ± 9.3 Ctl 44.5 ± 11.7	Age, sex, BMI, smoking history, education	477 ± 482 mg daily chlorpromazine equivalent (n = 56)	Serum	ELISA
Weickert et al. [57]	24 Scz 33 Ctl	Scz 51.0 ± 18.0 Ctl 49.0 ± 15.0	Age, brain hemisphere, PMI, race, sex, tissue pH	376 mg daily chlorpromazine equivalent (n = 21); unknown (n = 3)	Dorsolateral prefrontal cortex	RNase protection assay; Northern blotting; Western blotting; in situ hybridization
Wong et al. [58]	71 Scz 71 Ctl	Scz 48.6 ± 2.5 Ctl 48 ± 2.5	Age, brain pH, PMI	588.9 ± 66.8 mg daily chlorpromazine equivalent	Dorsolateral prefrontal cortex, parietal cortex, hippocampus	Western blotting; RT-PCR
Xiu et al. [59]	364 Scz 323 Ctl	Scz 51.3 ± 9.2 Ctl 50.9 ± 9.1	Age, sex	Chlorpromazine (n = 21); clozapine (n = 157); haloperidol (n = 31); perphenazine (n = 26); risperidone (n = 89); sulpiride (n = 27); others (n = 13)	Serum	ELISA
Zhang et al. [60]	92 Scz 60 Ctl	Scz 47.5 ± 4.4 Ctl 47.7 ± 4.5	None	434.1 ± 369.0 mg daily CPZ equivalent	Serum	ELISA

Scz schizophrenia, *Ctl* control, *BMI* body mass index, *CSF* cerebrospinal fluid, *EIA* enzyme immunoassay, *ELISA* enzyme-linked immunosorbent assay, *RT-PCR* real-time polymerase chain reaction, *PMI* post-mortem interval

the other hand, Durany et al. reported decreased BDNF protein levels using ELISA and a smaller sample size (n = 11) [33]. Levels of BDNF mRNA, as observed by two studies, were decreased in the hippocampus [47, 58].

All aging studies of both human and animal subjects demonstrated lower BDNF protein and mRNA levels in the hippocampus in the aged cohort in comparison to the younger cohort, with the exception of three studies. Two studies revealed that mRNA levels of BDNF did not change significantly with age within the human hippocampus [79, 83]. Likewise, Lapchak et al. reported no difference in BDNF mRNA expression in older Wistar rats in comparison to the younger group [72].

Peripheral BDNF Levels

Data from two schizophrenia studies show that BDNF protein expressions are decreased in the cerebrospinal fluid (CSF) of individuals with schizophrenia compared to healthy controls (Table 3) [42, 45]. Possibly due to the invasive nature of CSF collection from the spinal cord, studies examining change in BDNF expression in the CSF of human subjects with age are currently lacking. Therefore, a comparison could not be made between the two conditions in this domain.

Sixteen of the 22 studies examining BDNF protein levels in the plasma and serum of blood reported that individuals with schizophrenia demonstrate lower peripheral BDNF levels in comparison to healthy controls regardless of whether they were medicated or medication-naïve. Two of the remaining six studies showed an increase in serum BDNF [34, 49], and the rest reported that there was no significant difference in serum BDNF levels between individuals with schizophrenia and healthy controls [38, 39, 44, 51]. Aging studies reported decreased BDNF levels in the serum and plasma with increasing age, with the most reductions observed in the most elderly cohort, with the exception of two studies that showed BDNF levels in plasma and serum are unaffected by age [71, 74].

Findings from schizophrenia and aging studies show a strong overlap with lower serum and plasma BDNF levels observed in both individuals with schizophrenia in comparison to healthy controls and in older subjects in comparison to younger subjects. It is worth noting that all of the schizophrenia studies included in this review that examine serum and plasma BDNF levels use individuals with schizophrenia who are relatively young (mean age 22–51 years), yet a reduction in BDNF expression is observed in comparison to the age-matched controls. Therefore, there is age-related decline in peripheral BDNF levels and individuals with schizophrenia show this decline at an earlier age.

Table 2 Characteristics of included aging studies

Study ID	Sample type	Protein or mRNA	Structure	Methodology
Calabrese et al. [61]	Wistar Han rats	Protein, mRNA	Hippocampus, prefrontal cortex	RT-PCR, Western Blot
Chapman et al. [62]	Fisher/Brown Norway hybrid rats	mRNA	Hippocampus (CA1 and CA3)	In situ hybridization, Northern blot
Croll et al. [63]	Sprague-Dawley rats	Protein, mRNA	Neocortex (frontal, occipital, parietal, temporal), hippocampus, entorhinal cortex, midbrain, brainstem, cerebellum	ELISA, in situ hybridization
Del Arco et al. [64]	Wistar rats	Protein	Prefrontal cortex, amygdala, hippocampus	ELISA
Driscoll et al. [65]	Human	Protein	Plasma	ELISA
Erickson et al. [66]	Human	Protein	Serum	ELISA
Garza et al. [67]	Sprague-Dawley rats	mRNA	Hippocampus	In situ hybridization
Hattiangady et al. [68]	Fisher rats	Protein	Hippocampus (CA1 and CA3), dentate gyrus	ELISA, Immunohistoreactivity
Hayashi et al. [69]	Macaque monkey	mRNA	Frontal cortex, temporal cortex, motor cortex, somatosensory cortex, visual cortex, hippocampus	Northern Blot
Katoh-Semba et al. [70]	Sprague-Dawley rats	Protein	Hippocampus, cerebral cortex, cerebellum, olfactory bulb	Immunohistochemistry
Komulainen et al. [71]	Human	Protein	Plasma	ELISA
Lapchak et al. [72]	Sprague-Dawley and Fischer rats	mRNA	Hippocampus	In situ hybridization, Northern blot
Lommatzsch et al. [73]	Human	Protein	Platelets, plasma, serum	ELISA
Mueller et al. [74]	Human	Protein	Serum	ELISA
Oh et al. [75•]	Human	mRNA	Prefrontal cortex	RT-PCR
Perovic et al. [76]	Wistar rats	Protein, mRNA	Cortex, hippocampus	RT-PCR, Western blot
Quartu et al. [77]	Human	mRNA	Hippocampus	In situ hybridization
Schaaf et al. [78]	Brown Norway rats	mRNA	Hippocampus, dentate gyrus	In situ hybridization
Silhol et al. [79]	Sprague–Dawley rats	Protein, mRNA	Hippocampus, hypothalamus	Ribonuclease protection assay, immunoassay, Western blot
Shimada et al. [80•]	Human	Protein	Serum	ELISA
Soavi et al. [81]	Human	Protein	Plasma	ELISA
Webster et al. [82]	Human	mRNA	Dorsolateral prefrontal cortex	RNAse protection assay, in situ hybridization
Webster et al. [83]	Human	mRNA	Temporal cortex, hippocampus	In situ hybridization
Ziegenhorn et al. [84]	Human	Protein	Serum	ELISA

ELISA enzyme-linked immunosorbent assay, *RT-PCR* real-time polymerase chain reaction

Discussion

The present review summarized and compared protein and mRNA expression levels of BDNF in major brain regions and in the blood and CSF of individuals with schizophrenia and in older subjects in aging studies. The purpose of this review is to determine whether there is overlap in observed BDNF levels between these two conditions, which would indicate contributions of accelerated aging processes to the pathophysiology of schizophrenia. Because synaptic plasticity shows age-related changes, including changes in levels of associated neurotrophins [85], BDNF was selected as the marker of aberrant neuroplasticity. Existing data suggests that there are differences in mRNA and protein levels of BDNF in individuals with schizophrenia compared to healthy controls and in elderly subjects compared to younger subjects. Lower levels of BDNF is observed in the frontal cortices and related regions of the brain and in the periphery, specifically the CSF, plasma, and serum, in individuals with schizophrenia and in older subjects in aging studies. There was heterogeneity in the data for BDNF expression in parietal, occipital, and temporal cortices and the hippocampus due to limited number of existing studies to be conclusive of an overlap in these regions between schizophrenia and late age.

Schizophrenia is associated with impairments in cognitive functions that are known to be supported by the frontal lobes

Table 3 Summary of findings of mRNA and protein levels of BDNF in major brain regions and in serum and plasma in studies of schizophrenia and aging

	Schizophrenia			Aging		
	Protein	RNA	Reference	Protein	RNA	References
Frontal	↑		Durany et al. [33]		↓	Hayashi et al. [69]
		↓	Ray et al. [48••]			
	↓	↓	Weickert et al. [57]			
Prefrontal		↓	Hashimoto et al. [37]		↓	Del Arco et al. [64]
	↓		Issa et al. [42]		↓	Oh et al. [75•]
Dorsolateral prefrontal cortex		↓	Ray et al. [48••]		n.s.d.	Webster et al. [82]
		↓	Weickert et al. [57]			
	↓	↓	Wong et al. [58]			
Parietal	↑		Durany et al. [33]		↓	Calabrese et al. [61]
		n.s.d.	Wong et al. [58]		n.s.d.	Croll et al. [63]
Occipital	↑		Durany et al. [33]		n.s.d.	Croll et al. [63]
	n.s.d.		Takahashi et al. [53]		n.s.d.	Webster et al. [82]
Temporal	↑		Durany et al. [33]	↓		Hayashi et al. [69]
		↓	Ray et al. [47]		↓	*Webster* et al. [83]
					n.s.d.	Croll et al. [63]
	↓		Durany et al. [33]		↓	Calabrese et al. [61]
	↑		Iritani et al. [41]		↓	Chapman et al. [62]
Hippocampus		↓	Ray et al. [48••]	n.s.d.		Croll et al. [63]
	↑		Takahashi et al. [53]		↓	Del Arco et al. [64]
		↓	Wong et al. [58]		↓	Garza et al. [67]
				↓		Hayashi et al. [69]
				↓		Hattiangady et al. [68]
				↓		Katoh-Semba et al. [70]
					n.s.d.	Lapchak et al. [72]
				n.s.d	↓	Perovic et al. [76]
					↓	Quartu et al. [77]
					↓	Schaaf et al. [78]
					n.s.d.	Silhol et al. [79]
					n.s.d.	Webster et al. [83]
Cerebrospinal fluid	↓		Pillai et al. [45]			
	↓		Issa et al. [42]			
Plasma	↓		Green et al. [35]	↓		Driscoll et al. [65]
	↓		Pillai et al. [45]	↓		Katoh-Semba et al. [70]
				↓		Lommatzsch et al. [73]
				↓		Soavi et al. [81]
				↓		Ziegenhorn et al. [84]
				n.s.d.		Komultainen et al. [71]
Serum	↓		Chen et al. [30]	↓		Erickson et al. [66]
	↓		Chiou et al. [31]	n.s.d.		Mueller et al. [74]
	↓		Cui et al. [32]	↓		Shimada et al. [80•]
	↑		Gama et al. [34]			
	↓		Grillo et al. [36]			
	n.s.d.		Hori et al. [38]			
	n.s.d.		Huang and Lee [39]			

Table 3 (continued)

Schizophrenia			Aging		
Protein	RNA	Reference	Protein	RNA	References
↓		Ikeda et al. [40]			
↓		Jindal et al. [43]			
n.s.d.		Niitsu et al. [44]			
↓		Pirildar et al. [46]			
↑		Reis et al. [49]			
↓		Rizos et al. [50]			
n.s.d.		Shimizu et al. [51]			
↓		Sotiropoulou et al. [52]			
↓		Tan et al. [54]			
↓		Toyooka et al. [55]			
↓		Vinogradov et al. [56]			
↓		Xiu et al. [59]			
↓		Zhang et al. [60]			

Levels of BDNF protein or mRNA are in comparison to healthy control for schizophrenia studies or in comparison to younger subjects for aging studies
↑ increase, ↓ decrease, *n.s.d* no significant difference

including planning, organization of responses, processing speed, spatial working memory, and other executive functions, which coincides with the observed reduction in BDNF levels in the frontal regions of the brain [18]. Similar profile of impairments in cognitive functions involving the frontal lobes is observed in late life with normal aging [86, 87]. Older individuals with schizophrenia have also been reported to demonstrate greater levels of cognitive decline compared to the degree of cognitive decline that is observed in normal elderly individuals [10]. Furthermore, it has been shown that the brains of individuals with schizophrenia show deviations from the normal maturational trajectory compared to healthy controls based on estimates of neuroanatomical age made using magnetic resonance imaging (MRI)-based multivariate pattern analysis on structural MRIs [88••]. These results taken together suggest that neurobiological and cognitive changes observed late in life manifest at an earlier age in people with schizophrenia than in the general population.

Most of the data that is presented in this review is based on post-mortem studies. A limitation with post-mortem analysis of gene and protein expression is that they are only able to provide information of processes in the brain specific to a point in time. It is not possible to determine whether the observed protein and mRNA expression levels of BDNF are reflective only of incidents surrounding death or are representative of the dynamic changes in the protein and mRNA expression that may have been present during the lifetime of the individual. Furthermore, changes in BDNF levels observed in post-mortem brain samples may potentially be confounded by other epiphenomena, including antipsychotic type and dosage, co-medications, stress, and other environmental factors, rather than being an isolated reflection of intrinsic pathological changes characteristic to the condition. Finally, animal modeling of human aging and schizophrenia presents an additional limitation. In this review, comparisons are made between studies using different sample types: animal and human. It is possible that the observed heterogeneity in BDNF expression in a specific brain region was due to variability in expression levels between species and not the effects of the conditions under observation. Therefore, it is difficult to make confident comparisons using the current sample of studies.

Conclusions

At the beginning of this review, it was hypothesized that schizophrenia is a disorder of accelerated aging. Although a definitive conclusion cannot be drawn in support of this hypothesis based on the findings, a global reduction BDNF levels is evident in both schizophrenia and normal aging. BDNF levels in the frontal cortex and associated regions, in particular, demonstrate markedly low levels in both individuals with schizophrenia and elderly individuals, which concurs with existing data showing cognitive impairments supported by the frontal regions. Peripheral BDNF levels are also lowered in schizophrenia and with age. However, due to the considerable variability in data for the other brain regions and due to the aforementioned limitations, further research is necessary to test the hypothesis that schizophrenia is a disorder of accelerated aging.

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Compliance with Ethical Standards

Conflict of Interest Farhana Islam, Aristotle N. Voineskos, and Tarek K. Rajji declare that they have no conflict of interest.

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- •• Of major importance

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