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Serum BDNF Is Positively Associated With Negative Symptoms in Older Adults With Schizophrenia

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Abstract

Objectives: Older adults with chronic schizophrenia are at greater risk for functional disability and poorer health outcomes than those without serious mental illness. These individuals comprise 1–2% of the elderly population in the United States and are projected to number approximately 15 million by 2030. The symptoms of schizophrenia can be disabling for individuals, significantly reducing quality of life. Often, the negative symptoms (NS) are the most resistant to treatment and are considered a marker of illness severity, though they are challenging to measure objectively. Biomarkers can serve as objective indicators of health status. Brain-derived neurotrophic factor (BDNF) is a potential biomarker for schizophrenia and may serve as an important indicator of illness severity. **Methods:** A cross-sectional study with 30 older adults with chronic schizophrenia. Participants were assessed on serum levels of BDNF and psychiatric symptoms (Positive and Negative Syndrome Scale). Pearson's bivariate correlations (two-tailed) and linear regression models were used. **Results:** A significant positive association ($p < .05$) was found between higher serum levels of BDNF and greater severity for the NS items of passive, apathetic, social withdrawal, and emotional withdrawal. In multivariate analyses, the association remained significant. **Conclusions:** Although the association between BDNF and NS was not in the expected direction, the data corroborate findings from previous work in patients with schizophrenia. It is possible that higher serum levels of BDNF reflect compensatory neuronal mechanisms resulting from neurodevelopmental dysfunction.

Keywords

schizophrenia, BDNF, negative symptoms

Schizophrenia is a chronic, lifelong, and debilitating illness that develops through complex, heterogeneous, and multifactorial pathways, including genetic, developmental, and environmental (Millan, Fone, Steckler, & Horan, 2014). The prevalence for schizophrenia in older adults (55 years and older) is estimated at 0.6–1.0% (Cohen, Meesters, & Zhao, 2015). These numbers are increasing with the aging of the population, with projections that those 55 years and older will represent about one quarter of all people with schizophrenia by 2025 (Cohen et al., 2008).

Older adults with schizophrenia experience premature aging and decreased life expectancy with significantly greater risk for mortality compared with older adults without schizophrenia. Folsom et al. (2002) reported the age-adjusted mortality rates for people with schizophrenia as 2 times that of the general population, and, according to Parks, Svendsen, Singer, and Foti (2006), people with schizophrenia live on average 20 fewer years than those without a severe, persistent mental illness.

Individuals with schizophrenia are also more likely to experience impaired social functioning compared to same-age peers (Bartels, Mueser, & Miles, 1997). They have higher levels of need for assistance with their activities of daily living (Ran et al., 2004) and report lower levels of satisfaction, contributing to decreased quality of life. The ideal of successful aging remains difficult for most patients with schizophrenia to achieve (Cohen et al., 2015).

The concept of negative symptoms (NS) of schizophrenia broadly refers to the absence or impairment of normal

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functions in the areas of emotion, social interaction, productive goal-directed behavior, thought processes, and communication (Kirkpatrick & Galderisi, 2008; Reddy, Horan, & Green, 2016). Unlike with positive symptoms, there are no standard pharmacological treatments for sufficiently improving NS (Niitsu et al., 2011). Experiencing predominantly NS has deleterious effects on financial status, psychological well-being, and social competency (Strauss, Sandt, Catalano, & Allen, 2012).

A necessary distinction to make when interpreting assessments of NS for clinical and research purposes is that they are not a homogenous cluster of symptoms but rather are heterogeneous in etiology, expression, and outcomes, with partially overlapping and interacting pathways (Foussias & Remington, 2010). A lack of pharmacological treatment options for NS may in part stem from the absence of any single dysfunction or lesion in the brain identified as responsible for causing the symptoms of schizophrenia (Foussias, Siddiqui, Fervaha, Agid, & Remington, 2015). The hypothesis that schizophrenia may be a neurodevelopmental disorder is gaining support (Pearlson, 2011). Identification of markers signaling underlying structural and/or functional deviations within the brain is an important area of research for helping to manage schizophrenia.

Brain-derived neurotrophic factor (BDNF), a protein in the neurotrophin family, is involved in cellular proliferation, migration, and differentiation in the central nervous system (CNS) during brain development (Numakawa et al., 2010) and in maintaining neuroplasticity and normal brain functioning in adult life (Park & Poo, 2013). There is accumulating evidence suggesting that BDNF plays a significant role in the pathophysiology of psychiatric diseases, including schizophrenia (Lu, Nagappan, Guan, Nathan, & Wren, 2013). It is the most widely distributed neurotrophin in the CNS, including brain regions associated with schizophrenia (Shoval & Weizman, 2005), and is a prime candidate for involvement in the transformation of functional (synaptic) changes into structural changes that result in aberrations (Zagrebelsky & Korte, 2014).

It is well established that BDNF can freely cross the blood–brain barrier (BBB), and animal models provide evidence that the measurement of blood BDNF levels in the peripheral circulation reflects BDNF levels in the CNS (Trajkovska et al., 2007). While synaptic dysfunction is suggested in the pathogenesis of schizophrenia, the relationship between BDNF and schizophrenia is controversial, as there still remains significant heterogeneity across studies (Adachi, Numakawa, Richards, Nakajima, & Kunugi, 2014). This heterogeneity may be due to factors such as stage of illness, sample sizes, and/or the heterogeneity of the symptomatology itself (Akyo et al., 2015). Although research regarding an association between serum BDNF levels and age has been inconclusive, findings tend to point toward a decline in BDNF levels in older age (Diniz et al., 2014; Green, Matheson, Shepherd, Weickert, & Carr, 2011; Nettiksimmons et al., 2014). Data suggest that serum BDNF levels are lower in older adults with schizophrenia when compared to healthy older adults (Green et al., 2011; Valiente-Gomez et al., 2014).

The purpose of this cross-sectional study was to evaluate the association of BDNF as a biomarker of illness severity with the domains of positive and NS reported by older adults with chronic schizophrenia.

Method

Design

We used a cross-sectional study design to evaluate the association of BDNF as a biomarker of illness severity with the individual subscale items of positive and NS reported by older adults with schizophrenia. The university's Committee on Human Research approved the study. We maintained anonymity and confidentiality according to the committee's guidelines.

Participants and Settings

Participants in this study were a subsample ($N = 30$) of a larger parent study ($N = 46$; Leutwyler, Hubbard, Jeste, Miller, & Vinogradov, 2014). The 30 participants in the present study were those who consented to the blood draw in addition to the procedures in the parent study. Inclusion criteria from the parent study were that participants be English-speaking adults 55 years or older with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), diagnosis of schizophrenia or schizoaffective disorder (based on the *Structured Clinical Interview for DSM-IV*). We conducted a 7-item capacity-to-consent evaluation prior to enrollment to ensure that participants had sufficient understanding of their involvement in the study.

We recruited participants in the parent study from three main sites: a transitional residential and day-treatment center for older adults with severe mental illness, a locked residential facility for adults diagnosed with serious mental illness, and an intensive case management program. Participants received US$90 for their involvement in the study and a bonus payment of US$20 if all of the study procedures were completed.

Measures

A trained member of the research staff administered all of the assessments.

Symptom severity. Psychiatric symptoms were measured with the extended Positive and Negative Syndrome Scale (PANSS; Poole, Tobias, & Vinogradov, 2000). The extended PANSS is a 35-item instrument, with each item consisting of one 7-point (1–7) rating scale, categorized under six subscales measuring positive (e.g., delusions), negative (e.g., emotional and social withdrawal), disorganized (conceptual disorganization), excited (e.g., poor impulse control), depressed anxious (e.g., depression), and other symptoms (e.g., preoccupation and poor attention). The original PANSS (Kay, Fiszbein, & Opler, 1987) categorizes the symptoms into only three subscales: Positive,

Table 1. Sociodemographic and Clinical Characteristics of Participants.

Characteristic	Mean (*SD*) or Ratio (%)
Age (years)	59.77 (3.32)
BDNF (ng/ml)	24.36 (6.02)
Male	21/30 (70%)
Current smoker	17/30 (57%)
Past smoker	8/30 (27%)
Never smoker	5/30 (16%)
Psychiatric symptoms, PANSS subscale	
Total	78.87 (24.82)
Positive symptoms	17.00 (8.16)
Negative symptoms	14.10 (5.52)
Depressed/anxious symptoms	10.33 (3.84)
Disorganized symptoms	9.23 (4.17)
Excited symptoms	7.43 (2.75)
Other symptoms	20.77 (7.89)

Note. $N = 30$. BDNF = brain-derived neurotrophic factor; PANSS = Positive and Negative Syndrome Scale.

Negative, and General. The aim of our study was to understand how individual symptom items of schizophrenia are associated with BDNF levels in the peripheral serum. Therefore, we chose the extended PANSS because it provides more details about the variety and severity of symptoms experienced. Lindenmayer, Harvey, Khan, and Kirkpatrick (2007) described the scale to have demonstrated good-to-excellent reliability in assessing symptoms and their change during the course of the treatment in clinical trials with participants diagnosed with schizophrenia. The extended PANSS takes approximately 60 min to administer. The items are summed to determine the scores on the six subscales and the total PANSS score (the sum of all six subscales). Higher scores on the PANSS reflect greater severity in symptom experience as presented and reported by the individual. The PANSS was conducted on either the same day as the blood draw or within a week of the blood draw.

BDNF. BDNF was measured from 3 ml of blood that we collected in the early afternoon (approximately 1:00 p.m. $\pm$ 1 hr) in a single BD Vacutainer® SST™ 10-ml transport tube (BD #367985). We standardized the collection to occur at 1 p.m. because there is limited information on the diurnal variation of BDNF (Piccinni et al., 2008). The tube was inverted carefully 5–6 times to mix clot activator and blood before incubation. Whole blood samples were incubated for at least 60 min at room temperature to clot. The blood tube was then incubated for at least 60 min on ice. After incubations, samples were centrifuged for 10 min at 2,200 rpm (1,000*g*), 4C. Following centrifugation, serum was aliquoted into 2-ml screw-cap cryovials. Serum samples were stored in a -80^{o}C freezer.

Lab personnel carried out the measurements of serum BDNF levels in the Center for Reproductive Sciences at University of California, San Francisco. Serum samples were diluted with the diluent included in the research and development (R&D) Human BDNF Quantikine ELISA kit (Minneapolis, MN) to bring measured levels of BDNF up to the range of the provided standard. A separate control sample was run on each plate to ensure minimal interassay variability (8–14%). Mean serum levels of healthy control subjects using the R&D systems have been reported at 24.81 ng/ml ($SD = 5.87$) in a sample with a mean age of 30.7 $\pm$ 6.87 years, range 21–40 (Yoshida, Ishikawa, Iyo, & Hashimoto, 2013) and 31.30 ng/ml ($SD = 8.95$) in a sample with a mean age of 44.50 years ($SD = 11.69$; Vinogradov et al., 2009). The minimum serum BDNF level detected with this assay is typically less than .02 ng/ml. We report results in nanogram per milliliter.

Data Analysis

We performed statistical analyses using SPSS (Version 20). Pearson's bivariate correlations (two-sided) were conducted on the entire sample ($N = 30$). Variables that were significant at $p < .10$ and had a correlation of greater than .30 in bivariate analysis were included in the simultaneous multiple regression models. Variables that were highly correlated with one another ($r > .8$) were not included in the same model. Two simultaneous regression models were used to examine the relationship between BDNF and NS (assessing Item 7, passive, apathetic, and social withdrawal [PASW], and Item 6, emotional withdrawal [EW]). The α was set to $p < .05$. BDNF level in nanogram per milliliter was the dependent variable. The significant negative schizophrenia symptoms and age from the bivariate analyses were the independent variables. We estimated that with a sample size of 30 and at a significance level of .05, the null hypothesis that the Pearson's correlation coefficient would equal zero will have 80% power to detect a population effect size of .531.

Results

A total of 30 participants were included in the analyses. Table 1 presents the sociodemographic and clinical characteristics of these participants. The majority were male (70%), and their average age was 59.77 years (range = 55–68). More than half of the participants were current smokers (17/30). The mean total PANSS score of 78.87 ($SD = 24.82$) indicated that the sample was moderately ill (Leucht et al., 2005). Higher scores on the PANSS reflect more-severe symptoms. The mean level of BDNF was 24.36 ng/ml ($SD = 6.02$).

There were significant bivariate correlations between BDNF level and age and the NS subscale Items 6 (EW) and 7 (PASW). Older age ($\rho = .30$, $p = .06$) and higher scores on the NS subscale Items 6 ($\rho = .37$, $p = .02$) and 7 ($\rho = .45$, $p = .01$) were associated with higher BDNF levels. We did not find significant bivariate associations with the positive symptom subscale total or any of the subscale's items.

NS subscale Item 6 (EW) was highly correlated with NS subscale Item 7 (PASW); therefore, we did not include the symptoms in the same models. Table 2 provides the results of the first and second simultaneous multiple regressions. We included Item 6 (EW) of the NS subscale and age as predictors

Table 2. Effect of Score on the Schizophrenia Negative Symptoms (NS) Subscale Item 6 (Emotional Withdrawal) and NS Subscale Item 7 (Passive, Apathetic, and Social Withdrawal) on Brain-Derived Neurotrophic Factor Level.

Source	R^2	Regression Coefficient	95% CI [LB, UB]	R^2 Change (sr^2)	*df*	*F*	*p*
Model with Item 6							
Overall	.16				2,27	3.81	.04
Intercept			[−49.42, 26.73]				
Age		0.53	[−0.10, 1.16]	.09	1,27	2.96	.10
Item 6		1.95	[0.09, 3.81]	.14	1,27	4.63	.04
Model with Item 7							
Overall	.23				2,27	5.32	.01
Intercept			[−48.09, 24.84]				
Age		0.2	[−0.08, 1.13]	.08	1,27	3.13	.09
Item 7		2.15	[0.53, 3.77]	.20	1,27	7.41	.01

Note. CI = confidence interval; LB = lower bound; UB = upper bound.

in the first model and Item 7 (PASW) of the NS subscale and age as predictors in the second.

With two predictors (age and NS subscale Item 6) in the first model, we explained 16% of the variation in BDNF level ($p = .04$). When controlling for age, NS subscale Item 6 made a significant unique contribution to the model ($p = .04$). For every 1-point increase in NS Item 6 score, there is a 1.95 ng/ml unit increase in BDNF level. With two predictors (age and NS subscale Item 7) in the second model, we explained 23% of the variation in BDNF level ($p = .01$). When controlling for age, NS subscale Item 7 made a significant unique contribution to the model ($p = .01$). For every 1-point increase in NS 7 score, there is a 2.15 ng/ml unit increase in BDNF level. Age did not make a significant unique contribution to either the first or second model.

Discussion

The major findings in this cross-sectional study of older adults with schizophrenia were positive correlations between serum BDNF levels and the individual PANSS NS subscale Items 6 (EW) and 7 (PASW). Our findings are similar to those of two other studies (Niitsu et al., 2014; Reis et al., 2008), suggesting that BDNF measured in the serum may be an objective biomarker of illness severity for specific symptoms in individuals with schizophrenia. While our results are consistent with these two studies, other studies report negative correlations between BDNF levels measured peripherally and the symptomatology of schizophrenia (Akyo et al., 2015; Fernandes et al., 2015). This persistent heterogeneity in correlating BDNF as a reliable objective biomarker with the symptoms of schizophrenia may represent in part the heterogeneity of the illness itself, but also differences in study designs and the outcomes measured. Some of the confounding factors in studies evaluating serum BDNF levels in patients with schizophrenia could be associated with smoking history, the stage of illness, the duration of illness, antipsychotic medication treatments, sample sizes, genetic risk factors, and not evaluating individual schizophrenia symptoms in the analyses (Akyo et al., 2015; Fernandes et al., 2015; Niitsu et al., 2011; Reddy et al., 2016; Shimada et al., 2014). It is also important to note that not all previous studies evaluated serum BDNF levels in a sample of older adults with chronic schizophrenia.

Much of the past research on the NS of schizophrenia has been criticized for assuming that NS are homogenous in nature—as if the NS boil down to a single syndrome that could be treated as a single target (Marder & Kirkpatrick, 2014). Although evidence is mounting that this approach to NS is not effective, the arguments about how to differentiate, organize, define, and even assess NS have continued. A more current model for conceptualizing NS identifies and divides five core NS features (avolition/amotivation, anhedonia, asociality, alogia, and blunted affect) into two broader subdomains: (1) an experiential or internal dimension (*amotivation*), consisting of the first three features, and (2) an expressive dimension (*diminished expression*), consisting of the latter two features (Foussias et al., 2015; Marder & Kirkpatrick, 2014; Reddy et al., 2016). The consensus in the literature suggests that NS likely reflect anomalies of distributed neural networks rather than the disruption of any discrete brain region (Millan et al., 2014), and though it is unlikely that a single deficit explains the heterogeneity of the subdomains, NS may have some shared neurobiological origins (Foussias et al., 2015). The symptoms described by PANSS NS subscale Items 6 (EW) and 7 (PASW) are both encompassed within the amotivation subdomain, are recognized as some of the most frequently experienced NS among individuals with schizophrenia, and are strongly associated with serious impacts on long-term functional outcomes (Gruber, Santuccione, & Aach, 2014; Millan et al., 2014). Understanding NS in the context of separate but overlapping subdomains and analyzing them as such could provide greater insight into relationships with potential biomarkers and also provide opportunities for focusing on the individual experiences, guiding more effective treatment choices.

The symptomatology of schizophrenia may manifest from disturbances in varying levels of systems, from neuroplasticity and synaptogenesis to altered connectivity of complex neural networks (Fernandes et al., 2015; Millan et al., 2014), with dysregulation in multiple neurotransmitter mechanisms implicated as well (Galderisi, Merlotti, & Mucci, 2015; Gruber et al.,

2014). The different subdomains of NS may stem from distinct as well as partially overlapping perturbations in the neural circuitry (Millan et al., 2014), especially in those areas of the brain critical for sensory, cognitive, and emotional processing (Galderisi et al., 2015). It has been argued that the pathophysiological mechanisms incriminated in the genesis of the NS of schizophrenia are not necessarily the same as those that maintain NS once they are established (Millan et al., 2014). Incorporating a focus on the underlying pathology of each discrete symptom facet in schizophrenia and the associated neurocircuitry could better inform illness assessments and treatment decisions and also what biomarker may be best to consider for use in these assessments and decisions (Azorin, Belzeaux, & Adida, 2014).

Researchers have described BDNF as the most widely expressed neurotrophin in the CNS (Adachi et al., 2014; Reis et al., 2008), including brain regions purported to be involved in schizophrenia, such as the hippocampus, amygdala, nucleus accumbens, and striatum. Impairment in BDNF function has been implicated in multiple psychiatric and neurodegenerative diseases (Adachi et al., 2014; Akyo et al., 2015), which has led to many investigations into BDNF's potential as a biomarker as well as a potential treatment target, with a dizzying array of results (Akyo et al., 2015; Fernandes et al., 2015). One of the essential roles of BDNF within the nervous system is in synaptic plasticity (Akyo et al., 2015). Whether underlying aberrations in BDNF expression, such as with impaired plasticity, contribute to the development of illnesses such as schizophrenia or psychiatric illnesses lead to alterations in BDNF is highly debated (Akyo et al., 2015; Fernandes et al., 2015; Gruber et al., 2014; Zagrebelsky & Korte, 2014).

Our results illustrate BDNF's role as a neuroprotectant, with BDNF representing a compensatory response to the underlying neuropathology in the brain regions implicated in EW, passiveness, apathy, and/or social withdrawal. Researchers have reported that the frontotemporal and frontocortico-striatal circuits are the most strongly and consistently implicated in the NS of schizophrenia (Gruber et al., 2014; Millan et al., 2014). The correlation we found between BDNF levels and scores on the NS subscale Items 6 and 7 in the subjects in our sample may represent a reaction to aberrations in these brain regions from damage that occurred in the early years of disease for these individuals. Reis et al. (2008) reported similar findings of a positive correlation between BDNF and NS, though they did not individually analyze the subscales of NS and the study sample did not comprise all older adults with chronic schizophrenia (mean age = 52.3 years, $SD \pm 9.8$). The authors offered a compensatory explanation, suggesting that the higher levels of BDNF could indicate a more severe level of neuronal damage at the onset of disease illness (p. 159). In these cases, the level of BDNF could be a marker for specific symptom severity due to the underlying pathology and not suggestive of primary impairments in the role of BDNF in the disease progression.

The cellular processes involved in manufacturing and packaging BDNF can ultimately end down two different and opposing pathways depending on the stage of cleavage the BDNF signal peptide remains in—pro-BDNF (the precursor of mature-BDNF) binds to the p75NTR receptor and leads to apoptosis; mature-BDNF has a greater affinity toward the TrkB receptor, leading to cellular maintenance (Adachi et al., 2014; Niitsu et al., 2014; Zagrebelsky & Korte, 2014). Both proteolytic isoforms cross the BBB and would be included in a total peripheral BDNF-level analysis if not separated out (Trajkovska et al., 2007). A limitation of our study, and of many preceding it, is in the assay kit used for BDNF, which, until recently, did not differentiate between these two forms. The newer, commercially available ELISA assay kits can discriminate mature-BDNF from the total BDNF in the sample, and it would be much more informative moving forward to measure the individual levels of pro-BDNF and mature-BDNF when investigating the biomarker's correlation with neurological conditions (Niitsu et al., 2014).

For individuals with schizophrenia who survive into older age, higher BDNF levels may represent a "survivor effect," suggesting that only those with more protective factors live to an older age (Rao et al., 2015). Given BDNF's deep association with neuronal connectivity and regulation of synaptic efficacy throughout the CNS, it may be a factor contributing to this phenomenon in a compensatory manner (Adachi et al., 2014).

A limitation of our study was its small sample size, which limited our analyses and our ability to generalize our results to the larger population of older adults with chronic schizophrenia. We did not include in our analyses participant smoking history, illness duration, medication use, genetic risk factors, or cognitive dimensions associated with schizophrenia. Future work on BDNF and other potential biomarkers in older adults with schizophrenia should include evaluation of the markers' utility in objectively measuring the effectiveness of interventions such as social rehabilitation as they relate to the individual symptoms of schizophrenia.

Authors' Note

Preliminary results were presented at the 2016 annual meeting of the American Association of Geriatric Psychiatry.

Authors' Contribution

Sasha S. Binford contributed to conception, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Erin M. Hubbard contributed to conception, design, acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Elena Flowers contributed to analysis and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Bruce L. Miller contributed to conception, design, analysis, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Heather Leutwyler contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised

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Declaration of Conflicting Interests

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