Title

Serum BDNF is Positively Associated with Negative Symptoms in Older Adults with Schizophrenia

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Publication Date

2016

Peer reviewed|Thesis/dissertation

Serum BDNF is Positively Associated with Negative Symptoms in Older Adults with Schizophrenia

by

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THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

[redacted]

This manuscript is dedicated to my son, Finnegan, who was a trooper throughout this entire process, and to my family, friends and colleagues who have supported me in one way or another, making this possible.

Thank you.

ABSTRACT

Serum BDNF is Positively Associated with Negative Symptoms in Older Adults with Schizophrenia. Sasha S. Binford

Objectives: Older adults with chronic schizophrenia are at greater risk for functional disability and poorer health outcomes than those without serious mental illness. This population makes up 0.6% to 1% of the elderly population in the US and is projected to number approximately 15 million by 2030. The symptoms of schizophrenia can be disabling for individuals, significantly reducing their quality of life. Often, the negative symptoms are the most resistant to treatment and are considered a marker of illness severity, although challenging to measure objectively. Biomarkers can provide an objective indicator of health status. Brain Derived Neurotrophic Factor (BDNF) is a potential biomarker for schizophrenia and may serve as an indicator of illness severity. **Materials and 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; PANSS). Pearson's bivariate correlations (two-tailed) and linear regression models were used. **Results:** Average serum levels of BDNF were 24.4 ng/mL (SD = 6.0). A significant positive association ($p < .05$) was found between higher serum levels of BDNF and greater severity for the negative symptom items that included passive, apathetic, social withdrawal, and emotional withdrawal. In multivariate analyses, the association remained significant**. Conclusions:** Although the association between BDNF and negative symptoms 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 mechanisms resulting from neurodevelopmental dysfunction.

Keywords: *Schizophrenia, BDNF, Older Adult, Negative Symptoms*

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Introduction

Schizophrenia is a chronic, life-long and debilitating illness that develops through complex, heterogeneous and multifactorial pathways, including genetic, epigenetic, developmental, and environmental (Millan, Fone, Steckler, & Horan, 2014). The prevalence for schizophrenia in older adults (55 years and older) is estimated at 0.6% to 1.0% (Cohen, Meesters, & Zhao, 2015). This population of older adults with schizophrenia encompasses the largest group of older adults with severe mental health disorders (Cohen et al., 2000). These numbers are increasing with the growing aging and aged general population (Harvey, 2012), with projections of those 55 years and older representing about one quarter of all people with schizophrenia by 2025 (Cohen, 2008).

The socioeconomic burdens for those with schizophrenia are huge, both in terms of indirect costs such as loss of employment and social support (Milan, Fone, Steckler, & Horan, 2014) and direct costs associated with their enormous and enduring health-care needs (Cohen et al., 2015). The costs to society are high as well, with total costs for Medicare (particularly for Medicaid) significantly higher for those with schizophrenia compared to those without (Hendri et al., 2014). Although a "survivor effect" theory has been suggested to caution against selection bias for the cohort of older adults with schizophrenia as "only the healthiest persons with schizophrenia continue to live into old age" (Shoos & Cohen, 2003), the current picture of schizophrenia in later life is not that of a stable end state but one that fluctuates both in symptomatology and functioning (Cohen et al., 2015).

Older adults with schizophrenia experience premature aging and decreased life expectancy with significantly greater risk for mortality compared with older adults without schizophrenia (Hendri et al., 2014). Folsom (2002) reported the age adjusted mortality rates for

people with schizophrenia as two times that of the general population, and, according to Parks, Svendsen, Singer, & Foti (2006), people with schizophrenia live on average 20 fewer years than those without a severe, persistent mental illness.

Medical co-morbidities contribute to greater declines in health-related quality of life (Rabinowitz, Berardo, Bugarski-Kirola, & Marder, 2013) and the higher mortality rates seen in this population (Cohen et al., 2015), both leading to and resulting from poor physical health (Leutwyler, Fox, & Wallhagen, 2013). Kilbourne (2005) argued that older persons with schizophrenia are more likely to be diagnosed with multiple medical problems as compared to younger cohorts with schizophrenia. Among people with schizophrenia, it is common to have cardiovascular disease, chronic obstructive pulmonary disorders (COPD), diabetes, gastrointestinal diseases, liver disease, hypothyroidism, and/or skin infections (Berry & Barrowclough, 2008; Hendrie et al., 2014; Chafetz, White, Collins-Bride, Nickens, & Cooper, 2006), along with lower rates of medication adherence for both psychiatric and non-psychiatric medications (Patterson et al., 2002). The capacity to self-manage can be severely challenged in this population due to the susceptibility for difficulties related to managing (often multiple) physical illnesses in addition to the psychiatric symptoms related to their chronic mental illness and to the effects of the normal aging processes (Leutwyler, Wallhagen, & McKibbin, 2010). For example, Friedman (2002) found an association between more severe schizophrenia symptoms and greater number of medical problems.

The population with schizophrenia is also more likely to experience impaired social functioning compared to same-age peers (Berry & Barrowclough, 2009; Bartels, Mueser, & Miles, 1997). In a study by Berry, Barrowclough, Byre, and Purandare (2006), participants with schizophrenia were found to have lower self-efficacy and lower perceptions of their level of

coping skills in relation to everyday stressors than non-clinical controls. Higher levels of need with their activities of daily living (ADLs) are also seen in those with schizophrenia (Ran et al., 2004), as are lower levels of satisfaction (Cohen et al., 2003) contributing to decreased quality of life. The concept of successful aging among patients with schizophrenia remains difficult for most to achieve (Cohen et al., 2015).

Schizophrenia has a wide range of symptoms that generally begin in late adolescence or early adulthood and continue throughout life. Following Hughlings Jackson's approach to neurological symptoms, the symptoms of schizophrenia are divided into positive and negative (Pearlson, 2001). Hallucinations and delusional behaviors primarily constitute the positive symptoms (PS), which have been long treated by first-generation neuroleptics, clozapine, and second-generation antipsychotics (Milan et al., 2014). These medication treatments often have extremely undesirable side effect profiles that for some can be worse than the target symptoms themselves, including secondary symptoms such as depression, extrapyramidal side effects and paranoia that are rarely addressed in the literature (Davis, Horan, & Marder, 2014).

The negative symptoms (NS) of schizophrenia broadly refer to the absence or impairment of normal functions in the areas of emotion, social interaction, productive goal-directed behavior, thought processes, and communication (Kirkpatrick & Galderisi, 2008; Reddy, Horan, & Green, 2015). Unlike with the PS, there are no standard pharmacological treatments for sufficiently improving NS, and they remain a challenge for patients, providers, and caregivers (Niitsu et al., 2011; Chue & Lalonde, 2014), as the NS severely interfere with the functional status of patients more so than with PS (Kring & Elis, 2014). Experiencing predominantly NS is shown to have deleterious effects on financial status, psychological well-being, and social competency (Hunter

& Barry, 2012; Llorca, Blanc, Samalin, Bosia, & Cavallaro, 2012; Straus, Sandt, Catalano, & Allen, 2012).

NS are found in routine practice to have a higher prevalence (up to 58%) than PS (Bobes, Arango, Garcia-Garcia, & Rejas, 2010), and are a predictor of negative treatment response and short- and long-term impaired quality of life (Fujimaki, Morinobu, Yamashita, Takahashi, & Yamawaki, 2012; Fervaha, Foussias, Agid, & Remington, 2014). The poor outcomes correlated with NS are seen throughout the entire course of schizophrenia (Foussias, Agid, Fervaha, & Remington, 2014; Foussias, Siddiqui, Fervaha, Agid, & Remington, 2015; Peralta, Cuesta, Martinez-Larrea, & Serrano, 2000; Tamminga, Buchanan, & Gold, 1998; Kring & Elis, 2014). Although the gold standard for assessing symptom experience is patient self-report (Dodd et al., 2001), the subjective experiences are difficult to evaluate in schizophrenia (Chue & Lalonde, 2014), contributing to the challenges in effectively managing the symptoms. Individuals with schizophrenia are typically not aware of their NS, and, therefore, less able to recognize and report NS to healthcare providers (Altamura & Alliot, 2003; Selton, Wiersma, & van der Bosch, 2000). Impaired insight, a common feature of schizophrenia, is associated with illness severity and negatively influences treatment adherence and clinical outcomes (Gerretsen, Plitman, Rajji, Graff-Guerrero, 2014). Further decline in insight observed late in life is possibly a consequence of the premature aging seen in schizophrenia (Gerretsen et al., 2014). Despite the obvious need for research to improve the health of this vulnerable population, according to Mittal et al. (2006), less than 10% of published research in schizophrenia focuses on older adults.

The UCSF Theory of Symptom Management (TSM) (Dodd et al., 2001) provides a theoretical framework for exploring the associations between the symptoms experienced by individuals with schizophrenia and objective measurements of illness severity that lead to

effective management with the goal of better helping older adults with schizophrenia to achieve optimal health. TSM is grounded in the idea that management of a symptomatology necessitates that the symptom experience, the symptom management strategy, and the outcomes all be considered (Dodd et al., 2001).

The symptom experience dimension includes an evaluation of the severity of symptoms (eg., PS and NS in schizophrenia) as perceived by the individual (Dodd et al., 2001). Personal, health-related, and environmental factors can all influence the perception an individual has of his/her symptom severity (and, therefore, ability to accurately report that to a healthcare provider), what management strategies should be employed, and the outcomes of those (Brant, Beck, & Miaskowski, 2009). An individual with schizophrenia may be influenced to inaccurately report perceptions of experienced PS due to distress over the PS and concerns over how others may react to them, or due to distrust of a provider. Decreased insight, on the other hand, may influence recognition of the NS, interfering with them being reported accurately. Built into the TSM is the concept that an individual does not have to actually be experiencing the symptom (or, perceiving that they do), in order for it to apply to the model (Dodd et al., 2001). In addition, the interpretation of a symptom experienced in an individual unable to communicate that by another person in a caretaking (or, healthcare) role is assumed to be accurate (Dodd et al., 2001).

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 heterogeneous in etiology, expression, and in outcomes, with partially overlapping and interacting pathways (Foussias & Remington, 2010; Millan et al., 2014). From findings in the National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, the prevailing explanation of NS divides them into five core domains

grouped within two major sub-domains (Kirkpatrick, Fenton, Carpenter Jr., & Marder, 2006): decreased expressivity (blunted affect and poverty of speech) and avolition (amotivation, asociality, and anticipatory anhedonia) (Azorin, Belzeaux, & Adida, 2014; Millan et al., 2014; Foussias et al., 2015). A lack in 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 et al., 2015). The hypothesis that schizophrenia may be a neurodevelopmental disorder is gaining support (Pearlson, 2001; Weinberger, 1995). Identification of markers signaling underlying structural and/or functional deviations within the brain is an important area of research for helping 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 during brain development (Numakawa et al., 2010), and in maintaining neuroplasticity and normal brain functioning in adult life (Adachi, Numakawa, Richards, Nakajima, & Kunugi, 2014; Bramham & Messaoudi, 2005; Park & Poo, 2013; Durany & Thome, 2004; Shoval & Weizman, 2005). There is accumulating evidence suggesting BDNF plays a significant role in the pathophysiology of psychiatric diseases, including schizophrenia (Angelucci, Brene, & Mathe, 2005; Nagahara & Tuszynski, 2011; Lu, Nagappan, Gua, Nathan, & Wren, 2013). BDNF is the most widely distributed neurotrophin in the central nervous system (CNS), including brain regions associated with schizophrenia (Durany & Thome, 2004; Shoval & Weizman, 2005), and BDNF is a prime candidate implicated 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 measurements of blood BDNF levels in the peripheral

circulation reflect BDNF levels in the CNS (Pan, Bank, Fasold, Bluth, & Kastin, 1998; 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 et al., 2014). This heterogeneity may be due to factors such as stage of illness, duration of illness, sample sizes, and/or the heterogeneity of the symptomatology itself (Akyo et al., 2015).

With the TSM (Dodd et al., 2001) as the theoretical framework, 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 negative symptoms reported by older adults with chronic schizophrenia.

Methods

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 negative symptoms reported by older adults with schizophrenia. Institutional review board approval was obtained from the University's Committee on Human Research. Anonymity and confidentiality were maintained according to the committee's guidelines.

Participants and settings

Participants in this study were a subsample (N=30) of a larger parent study (Leutwyler et al., 2014) (N = 46). Inclusion criteria from the parent study were that participants be English-speaking adults 55 years or older with a DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) diagnosis of schizophrenia or schizoaffective disorder (based on the Structured Clinical Interview for DSM-IV). A seven-item capacity to consent evaluation was

conducted prior to enrollment to ensure that participants had sufficient understanding of their involvement in the study. Up to three trials were allowed to correctly answer a missed question. If a participant answered more than two questions incorrectly, she/he was deemed ineligible for study participation at that time. If a potential participant who failed the capacity to consent test wanted to repeat the consent process on another day, the principle investigator or her staff re-administered the capacity to consent evaluation.

The participants in the parent study were recruited 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. Participant referrals were also made from the community and other participants. Participants received $90 for their involvement in the study and a bonus payment of $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 et al., 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, poor attention). The original PANSS (Kay, Fiszbein, & Opler, 1987) categorizes the symptoms into only three subscales: positive, 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 of symptoms experienced and their severity. 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 minutes 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.

BDNF. Brain Derived Neurotrophic Factor (BDNF) was measured from 3 mL of blood collected in the early afternoon (approximately 1:00PM ± 1 hour) in a single BD Vacutainer® SST^{TM} 10 mL Transport Tube (BD # 367985). The tube was inverted carefully 5-6 times to mix clot activator and blood before incubation. Whole blood samples incubated for at least 60 minutes at room temperature to clot. The blood tube then incubated at least 60 minutes on ice. After incubations, samples were centrifuged for 10 minutes at 2200RPM (1000g), 4 ^{o}C. Following centrifugation, serum was aliquoted into 2 mL screw-cap cryovials. Serum were stored in an -80 ^{o}C freezer.

Measurements of serum BDNF levels were carried out in the Center for Reproductive Sciences at UCSF by lab personnel. Serum samples were diluted with the diluent included in the R&D Human BDNF Quantikine ELISA kit (Minneapolis, Minnesota) 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% to 14%). Mean serum levels of healthy control subjects using the R&D systems have been reported at 24.81 (SD = 5.87) ng/mL in a sample

with a mean age of 30.7 ± 6.87, range 21-40 (Yoshida, et al., 201), and 31.30 (SD = 8.95) ng/mL in a sample with a mean age of 44.50 (SD = 11.69) (Vinogradov, et al, 2009). The minimum serum BDNF level detected with this assay is typically less than .02 ng/mL. Results are reported in ng/mL.

Data analysis

Statistical analyses were performed using SPSS (Version 20). Pearson's bivariate correlations (two-sided) were conducted on the entire sample (N = 30). Variables that were significant at $p < 0.10$ and had a correlation of greater than 0.30 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 negative symptoms (assessing item 7: passive, apathetic, and social withdrawal, and item 6: emotional withdrawal). Alpha was set to $p < .05$. BDNF level in ng/mL was the dependent variable. The significant schizophrenia negative symptoms and age from the bivariate analyses were the independent variables.

Results

A total of 30 participants were included in the analyses. Sociodemographic and clinical characteristics are presented in Table 1. The majority of the participants were male (70%) and the 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 (SD = 6.02) ng/mL. We did not identify in the literature a standardized "normal" value range for BDNF measured in the serum in adults. Other study

results have reported mean levels of BDNF in the serum for "healthy adult subjects" ranging from 23.71 ± 5.61 ng/mL (Yoshida et al., 2012) to 31.30 ± 8.95 ng/mL (Vinogradov et al., 2009).

There were significant bivariate correlations between BDNF and age and the negative symptoms subscale items 6 (emotional withdrawal – EW) and 7 (passive, apathetic, and social withdrawal – PASW). Older age (p = .06) and higher scores on the negative symptoms subscale items 6 (p = .02) and 7 (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.

Negative symptoms subscale item 6 (emotional withdrawal) was highly correlated with negative symptoms subscale item 7 (passive, apathetic, social withdrawal) and therefore the symptoms were not included in the same models. Results of the first simultaneous multiple regression are given in Table 2. Item 6 (EW) of the negative symptoms subscale and age were included as predictors in the first model. Results of the second simultaneous multiple regression are given in Table 3. Item 7 (PASW) of the negative symptoms subscale and age were included as predictors in the second model.

With two predictors (age and negative symptoms subscale item 6) in the first model, we explained 16% of the variation in BDNF level (p = .04). When controlling for age, negative symptoms subscale item 6 made a significant unique contribution to the model (p = .04). For every 1-point increase in negative symptoms 6 score, there is a 1.95 ng/mL-unit increase in BDNF level. With two predictors (age and negative symptoms subscale item 7) in the second model, we explained 23% of the variation in BDNF level (p = .01). When controlling for age, negative symptoms subscale item 7 made a significant unique contribution to the model (p = .01). For every 1-point increase in negative symptoms 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 negative symptom (NS) subscale items 6 (emotional withdrawal) and 7 (passive, apathetic, social withdrawal). Each of these PANSS subscale items made independent contributions to the model even after controlling for age. Our findings demonstrate similar outcomes to previous studies (Reis et al., 2008; Niitsu et al., 2011; Niitsu et al., 2014), suggesting BDNF measured in the serum may be an objective biomarker of illness severity for specific symptoms in individuals with schizophrenia, though not all previous studies evaluated serum BDNF levels in a sample of older adults with chronic schizophrenia. While our results are consistent with these studies, there continues to be study results that demonstrate negative correlations between BDNF levels measured peripherally and the symptomatology of schizophrenia (Fernades et al., 2014; Akyol 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 (Akyol et al., 2015; Niitsu et al., 2011; Shimada et al., 2014; Fernades et al., 2014; Reddy, Horan, & Green, 2015; Lee et al., 2011).

Much of the past research on the NS of schizophrenia has been criticized for assuming 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). Though evidence is mounting that this is not the case, the arguments about how to differentiate, organize, define and even assess NS have continued (Daniel, 2013; Marder & Kirkpatrick, 2014). 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 (Reddy, Horan & Green, 2015; Marder & Kirkpatrick, 2014; Foussias et al., 2015). 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 PANSS NS subscale items 6 (emotional withdrawal) and 7 (passive, apathetic, social withdrawal) are both encompassed within the amotivation subdomain, and are recognized as some of the most frequently experienced NS among individuals with schizophrenia, and are more strongly associated with serious impacts on long-term functional outcomes (Gruber et al., 2014; Millan et al., 2014). As guided by the TSM (Dodd et al., 2001), 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 to provide opportunities for focusing on the individual experiences, guiding more effective treatment choices. Our study included a thorough analysis of the NS subscale in order

to better tease out these important nuances, and to strengthen any potential relationship between BDNF and the individual symptom experience.

Schizophrenia is a heterogeneous illness with reports of growing favor for a neurodevelopmental model involving numerous distinct and overlapping pathophysiological processes triggered by a perfect storm of genetic, epigenetic and environmental factors (Voineskos et al., 2013; Millan, Fone, Steckler & Horan, 2014; Reis et al., 2008; Foussias et al., 2015). 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., 2014; Millan et al., 2014; Voineskos et al., 2013), with dysregulation in multiple neurotransmitter mechanisms implicated as well (Gruber, Santuccione & Aach, 2014; Galderisi, Merlotti & Mucci, 2015; Chue & Lalonde, 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). 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 (Azorin Belzeaux & Adida, 2014).

BDNF has been cited as the most widely expressed neuroptrophin in the central nervous system (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 (Edelmann, LeBmann & Brigadski, 2014). Impairment in BDNF function has been implicated in multiple psychiatric and neurodegenerative diseases (Adachi et al., 2014; Akyol et al., 2015), and has lead to many investigations into BDNF's potential as a biomarker as well as a potential

treatment target, with a dizzying array of results (Akyol et al., 2015; Fernandes et al., 2014). One of the recognized essential roles of BDNF within the nervous system is in synaptic plasticity (Akyol et al., 2015). Whether underlying aberrations in BDNF expression, such as impaired plasticity, contribute to the development of illnesses such as schizophrenia or if psychiatric illnesses lead to alterations in BDNF is highly debated (Zagrebelsky & Korte, 2014; Akyol et al., 2015;Fernandes et al., 2014; Gruber et al., 2014). 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 established (Millan et al., 2014).

Conclusion

BDNF's role as a neuro-protectant may be illustrated by our results with BDNF representing a compensatory response to the underlying neuropathology in the brain regions implicated in emotional withdrawal, passiveness, apathy, and/or social withdrawal. It has been reported that the fronto-temporal and frontocortico-striatal circuits are the most strongly and consistently implicated in the NS of schizophrenia (Millan et al., 2014; Gruber et al. 2014). The correlation found between BDNF levels and 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. In 2008, Reis et al., reported similar findings of a positive correlation between BDNF and negative symptoms, though the subscales of NS were not individually analyzed and the study sample were not all older adults with chronic schizophrenia (mean age 52.3, SD ± 9.8). A compensatory explanation was offered by Reis et al., (2008), and the authors suggested that the higher levels of BDNF could be indicating a more severe level of neuronal damage at the onset of disease illness (pp.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 towards the TrkB receptor, leading to cellular maintenance (Niitsu et al., 2014; Zagrebelsky & Koste, 2014; Adachi et al., 2014; Benarroch, 2015). 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; Lommatzsch et al., 2005). 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 discriminately measure 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 its correlation with neurological conditions (Niitsu et al., 2014).

To our knowledge, this is the first to study to look specifically at the relationship of BDNF with a comprehensive assessment of symptoms in older adults (≥ 55 years) with chronic schizophrenia. As highlighted in our introduction, older adults with schizophrenia are reported to have an accelerated physiological aging, living on average 20 years shorter than same age peers without mental illness (Jest & Maglione, 2013; Rao et al., 2015), and with greater numbers of medical co-morbidities. Poorer functioning in older adults with schizophrenia may lead to lower levels of recognition and reporting of symptoms to healthcare providers (Berry & Barrowclough, 2009), leading to health conditions going undetected for longer periods of time and/or

inadequately treated or managed (Cohen et al., 2015). For individuals with schizophrenia that do survive into older age (≥ 55 years), higher BDNF levels may be representing 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 regulating synaptic efficacy throughout the CNS, BDNF may be a factor contributing to this phenomenon in a compensatory manner (Adachi et al., 2014).

For older adults with schizophrenia, life in old age is not necessarily a period of stability with symptoms tapering off as has been suggested in past reports, however, and this is especially true with regards to the management of NS and being able to effectively cope within social situations (Cohen et al., 2015; Millan et al., 2014; Rao et al., 2015). Berry & Barrowclough (2009) reported older adults with schizophrenia as being less able than controls to appropriately select coping strategies according to the unique demands of the study situation. With the average age of onset for schizophrenia occurring at a sensitive time in the development of normal social roles (Berry & Barrowclough, 2009), the interruption of the processes of appropriate social learning may, then, potentially be met with decades of maladjusted forms of coping that directly contribute to poor functioning and poorer health outcomes later in life (Cohen et al., 2015). Nonpharmacologic, psychosocial treatments emphasizing social rehabilitation such as Social Skills Training (SST), Cognitive Behavioral Therapy (CBT), Cognitive Remediation Therapy (CRT), and Functional Adaptation Skills Training are showing favorable results for improving social functioning in adults (including older adults) with schizophrenia and improving their quality of life (Carbon & Correll, 2014; Millan et al., 2014; Azorin et al., 2014; Jeste & Maglione, 2013).

A major limitation in 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 evaluating their utility in objectively measuring the effectiveness of interventions such as social rehabilitation as they relate to the individual symptoms of schizophrenia.

Table 1 Sociodemographic and Clinical Characteristics of the Sample

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

Table 2 Effect of Schizophrenia Negative Symptoms Subscale Item 6 (EW) on BDNF Level

Source	R^2	*regression coefficient*	95% CI UB	95% CI LB	R^2 Change (sr^2)	df	*F*	*p*
Overall	.16					2,27	3.81	.04
Intercept			26.73	-49.42				
Age		.53	1.16	-.10	.09	1,27	2.96	.10
Negative Symptoms Item 6		1.95	3.81	.09	.14	1,27	4.63	.04

Table 3 Effect of Schizophrenia Negative Symptoms Subscale Item 7 (PASW) on BDNF Level

Source	R^2	*regression coefficient*	95% CI UB	95% CI LB	R^2 Change (sr^2)	df	*F*	*p*
Overall	.23					2,27	5.32	.01
Intercept			24.84	-48.09				
Age		.52	1.13	-.08	.08	1,27	3.13	.09
Negative Symptoms Item 7		2.15	3.77	.53	.20	1,27	7.41	.01

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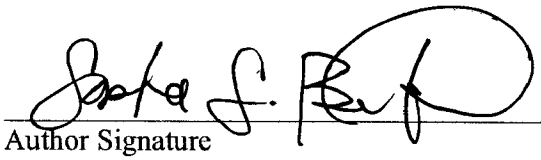

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