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Increased plasma Brain-Derived Neurotrophic Factor (BDNF) levels in females with schizophrenia

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ABSTRACT

Brain-Derived Neurotrophic Factor (BDNF) acts as a critical regulator of synaptogenesis and synaptic plasticity. Sex differences have been demonstrated in many aspects of schizophrenia. This study tested for sex-specific differences in peripheral BDNF levels in people with schizophrenia and healthy controls. We measured circulating plasma BDNF levels in 95 people with schizophrenia and 80 healthy controls. Plasma BDNF levels were significantly elevated in females with schizophrenia compared to males with schizophrenia and to female healthy controls. These results suggest that sex differences in peripheral BDNF levels may contribute to other sex related differences in schizophrenia.

1. Introduction

Brain-Derived Neurotrophic Factor (BDNF) is a widely distributed neurotrophin involved in learning and memory-associated neuroplasticity and synaptic strength (Lu, 2003). BDNF is highly expressed in the cerebral cortex and hippocampus and most studies show decreased BDNF levels in brains of people with schizophrenia (Hashimoto et al., 2005; Reinhart et al., 2015; Thompson Ray et al., 2011; Weickert et al., 2003). In contrast, two early studies found increased BDNF in the frontal, parietal, and cingulate cortices and hippocampus of people with schizophrenia compared to controls (Durany et al., 2001; Takahashi et al., 2000). Similar inconsistent findings have also been reported regarding peripheral BDNF levels in schizophrenia relative to healthy controls. Some studies reported increased peripheral BDNF levels in patients with schizophrenia (Reis et al., 2008) or no change in blood BDNF levels between schizophrenia and control groups (Shimizu et al., 2003). However, the predominant finding from our meta-analysis was significantly reduced peripheral BDNF levels in schizophrenia compared to healthy controls (Green et al., 2011). Thus, heterogeneity in both brain and blood BDNF levels has been reported in schizophrenia, suggesting that BDNF levels may vary based on undetermined factors. Given the unexplained heterogeneity for BDNF levels in schizophrenia, we aimed to assess some potential factors that may affect peripheral BDNF levels in schizophrenia compared to healthy controls.

Of the multiple environmental and biological factors that may impact peripheral BDNF levels in schizophrenia, sex appears to be particularly relevant. Sex differences have been reported for many characteristics of schizophrenia with men having an earlier age of onset, more severe course of the illness and being less responsive to treatment (Gonzalez-Rodriguez et al., 2014). Peripheral BDNF levels can also differ according to sex in healthy adults and in mental illness (Pillai et al., 2012). Furthermore, BDNF mRNA and protein levels are regulated by sex steroids in the brain of adult rats; for example, ovariectomy reduces, while estrogen replacement restores, brain BDNF levels (Gibbs, 1998, 1999; Jezierski and Sohrabji, 2000; Singh et al., 1995). In chronically ill people with schizophrenia, sex differences in serum BDNF levels have also been reported such that men with schizophrenia have lower serum BDNF levels compared to females with schizophrenia (Xiu et al., 2009; Zhang et al., 2014). Taken together, this suggests that sex specific alterations in BDNF levels could exist in people with schizophrenia. Thus, we hypothesized that there may be sex differences in

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peripheral BDNF levels in men and women with schizophrenia compared to controls.

BDNF levels are also modified by environmental factors and BDNF levels are especially responsive psychiatric medications. Two classes of medication often prescribed to people with schizophrenia can influence BDNF levels. Antipsychotics may reduce brain BDNF levels (Chlan-Fourney et al., 2002; Lipska et al., 2001) whereas antidepressants may increase BDNF levels (Bjorkholm and Monteggia, 2016; Thompson Ray et al., 2011). Thus, we also hypothesized that antipsychotic dose would negatively correlate with blood BDNF levels, whereas antidepressant dose would positively correlate with blood BDNF levels in schizophrenia.

2. Materials and methods

2.1. Participants

Participants consisted of 97 chronically ill adults with a diagnosis of schizophrenia or schizoaffective disorder (mean age: 35.7, SD: ± 8.4; mean education level: 12.5, SD: ± 2.4) and 87 healthy adults (mean age: 31.9, SD: ± 8.3; mean education level: 14.6, SD: ± 2.3). Patients were recruited following interest generated from a national television documentary on schizophrenia research and through the South Eastern Sydney and Illawarra Area Health Service. All patients were between the ages of 18 and 51 years old and met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for schizophrenia or schizoaffective disorder on the basis of the Structured Clinical Interview for DSM-IV Axis 1 disorders (SCID) (First et al., 2007). All patients had been receiving antipsychotic medication for at least 1 year prior to participation (89% received second generation antipsychotic medication only, 5% received first generation antipsychotic medication only and 6% received a combination of first generation and second generation antipsychotic medication). Exclusion criteria consisted of patients who had an additional Axis 1 psychiatric diagnosis other than schizophrenia or schizoaffective disorder, a history of substance abuse/dependence within the past five years, head injuries with a loss of consciousness, seizures, central nervous system infection, uncontrolled diabetes or hypertension, mental retardation and for women, those who were pregnant.

Using standard guidelines, the mean daily dose of antipsychotic medication for all patients were converted to approximate mean daily chlorpromazine (CPZ) equivalent dose (Andreasen et al., 2010) and the mean daily dose of antidepressant medication for each patient receiving antidepressants (10 females and 28 males) was converted to approximate mean daily imipramine equivalent dose (Hayasaka et al., 2015) in 18 of the 38 patients receiving antidepressants for whom such conversions could be calculated. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Healthy controls, between the ages of 20 and 50, were recruited through advertisements placed in the community. Healthy people who had a personal history of or a first- degree relative with a DSM-IV Axis I psychiatric diagnosis, history of substance (including alcohol or cannabis) abuse or dependence within the past five years, head injuries with a loss of consciousness, seizures, central nervous system infection, uncontrolled diabetes or hypertension, learning disabilities or mental retardation were excluded. All participants were initially screened for inclusion/exclusion criteria by telephone and followed up with in-person questionnaires/interviews. Depression, anxiety and stress scores were measured in all participants (patients and healthy controls) using the Depression, Anxiety and Stress Scale (DASS) self-report questionnaire (Lovibond and Lovibond, 1995). Level of daily function was assessed using the Short Form 36, version 2 Health Survey Questionnaire (SF36-v2) (Ware et al., 2000) in both patients and healthy controls. All participants and data in this study were taken from the baseline data that was part of our previous publication (Weickert et al., 2015).

All procedures were approved by the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service Human Research Ethic Committees and the Queen Elizabeth Hospital Ethics and Human Research Committee, Adelaide. The procedure was explained and written informed consent was obtained from each participant before entry into the study.

2.2. Blood collection and peripheral BDNF measurement

Plasma BDNF levels were available from 95 people with schizophrenia and 80 controls. Fasting venous whole blood samples were collected from all participants in 9 ml EDTA tubes on the morning of clinical assessment between 9 and 11 am. Immediately after collection, samples were placed on ice, then centrifuged, and the plasma was separated and stored at −80 °C until assayed. BDNF protein was measured in each plasma sample by an enzyme-linked immunosorbent assay (ELISA) kit (#G7611, Promega Corporation) per standard protocol (Skilleter et al., 2015), see Supplementary Data for details. All samples, assayed blind to diagnostic group, were performed in duplicate across 2–3 days. The average inter-assay coefficient of variability (COV) was 16% and the average intra-assay COV was 11%.

2.3. Statistical analyses

Patients were compared to healthy controls on the basis of demographic variables using independent *t*-tests or χ^2 analyses as appropriate. Age, education, DASS depression, DASS anxiety, DASS stress and SF36-v2 total score were compared among all four groups (based on sex and diagnosis) using ANOVAs. A series of t-tests were used to compare male and female patients based on clinical factors.

Given the significant age differences between diagnostic groups and that age influences BDNF levels (Lommatzsch et al., 2005; Yatham et al., 2009), differences in plasma BDNF levels by diagnosis and sex were determined using ANCOVA, with age as a covariate. Given that antidepressants may influence peripheral BDNF levels, a separate ANCOVA assessing the effects of diagnosis and sex on plasma BDNF levels, with age as a covariate, was also performed after excluding individuals receiving antidepressants. Any significant interactions were followed up using Least Significant Difference (LSD) post hoc tests. Relationships of PANSS scores, age of illness onset duration of illness, physical functioning, mean daily CPZ equivalent dose and mean daily imipramine equivalent dose to plasma BDNF levels in people with schizophrenia were determined using Pearson product moment correlations.

3. Results

3.1. Cohort characterisation

3.1.1. Demographic results

The demographic and clinical characteristics between healthy controls and people with schizophrenia are summarized in Table 1. There was no significant difference in the frequency of males and females or ethnicity classifications between healthy controls and people with schizophrenia (see Table 1). The people with schizophrenia were mildly to moderately ill based on their PANSS symptom severity scores.

3.1.1.1. Age. Results of a 2 × 2 ANOVA with sex and diagnosis as grouping factors and age as a dependent factor showed a significant main effect of diagnosis, $F(1,180) = 10.32$, $p = 0.002$ (on average, controls were 3–4 years younger than patients, see Table 1), a significant main effect of sex, $F(1,180) = 4.34$, $p = 0.04$, with males (mean: 33.0, SD: ± 8.7) being significantly younger than females (mean: 35.2, SD: ± 8.2), and no significant diagnosis by sex interaction, $F(1,180) = 0.01$, $p = 0.94$, see Table 2.

Table 1
Demographic and clinical characteristics of the schizophrenia and healthy control samples.

	Controls ($n = 87$)	Schizophrenia ($n = 97$)	df	t-Value/F-value/$\chi 2$	p value
Age	31.9 ± 8.4	35.7 ± 8.4	182	−3.08	0.002
Years of education	14.6 ± 2.3	12.5 ± 2.4	182	5.98	<0.001
Sex (males/females)	46/41	59/38	1	1.18	0.28
Ethnicity (Caucasian/Asian/other)	69/14/4	84/10/3	2	1.74	0.42
DASS depression	3.6 ± 5.5	12.3 ± 9.6	176	−7.3	<0.001
DASS anxiety	2.9 ± 4.1	10.1 ± 7.8	176	−7.5	<0.001
DASS stress	6.7 ± 7.8	14.6 ± 9.4	176	−6.1	<0.001
SF36-v2 total score	140.9 ± 10.7	114.3 ± 19.7	172	10.9	<0.001
Body Mass Index (BMI)	–	31.0 ± 6.4	–	–	–
Age of illness onset	–	22.9 ± 5.6	–	–	–
Duration of illness (yrs)	–	12.9 ± 7.4	–	–	–
CPZ equivalent dose (mg/day)	–	551.5 ± 465.7	–	–	–
Imipramine equivalent dose (mg/day)	–	184.9 ± 137.8	–	–	–
PANSS positive score	–	15.0 ± 4.7	–	–	–
PANSS negative score	–	14.4 ± 6.2	–	–	–
PANSS general score	–	30.6 ± 8.7	–	–	–
PANSS total score	–	60.0 ± 16.6	–	–	–

Means ± SD are provided where applicable. – = not applicable. DASS = Depression, Anxiety and Stress Scale. SF36-v2 = Short Form 36, version 2 Health Survey Questionnaire. CPZ = daily Chlorpromazine equivalent dose. PANSS = Positive and Negative Syndrome Scale.

3.1.1.2. Education. Results of a 2 × 2 ANOVA with sex and diagnosis as grouping factors and education as the dependent variable showed a significant main effect of diagnosis, $F(1,180) = 37.6$, $p < 0.001$, (such that controls had significantly greater years of education compared to patients, see Table 1), no significant main effect of sex, $F(1,180) = 0.77$, $p = 0.38$, and a trend towards a significant diagnosis x sex interaction, $F(1,180) = 3.48$, $p = 0.06$, see Table 2.

3.1.2. Comparison of male and female patients on clinical factors

A series of *t*-tests between male and female patients in relation to clinical factors revealed that PANSS negative symptom severity score ($df = 95$, $t = -2.86$, $p = 0.01$) and age of illness onset ($df = 95$, $t = -2.59$, $p = 0.01$) were significantly different between male and female patients (see Table 2), with male patients having significantly worse PANSS negative symptom severity scores and having a significantly earlier age of illness onset than female patients. There were no other significant differences between male and female patients on the basis of clinical or demographic variables.

Given the significant differences between male and female patients on the basis of PANSS negative symptom scores and age of illness onset, we performed correlations between those factors and BDNF levels. There was no strong, significant correlation between plasma BDNF levels and PANSS negative symptom scores in either male ($r = -0.09$, $p = 0.52$) or female ($r = 0.06$, $p = 0.71$) patients. Additionally, there were no strong, significant correlations between plasma BDNF levels and PANSS positive (males, $r = -0.24$, $p = 0.08$; females, $r = -0.05$, $p = 0.75$), general (males, $r = -0.09$, $p = 0.50$; females, $r = 0.04$, $p = 0.80$), or total (males, $r = -0.14$, $p = 0.30$; females, $r = 0.02$, $p = 0.89$) scores. There were no strong, significant correlations between plasma BDNF levels and age of illness onset in male ($r = 0.20$, $p = 0.14$) or female ($r = 0.06$, $p = 0.74$) patients. There were also no strong, significant correlations between plasma BDNF levels and duration of illness in male ($r = 0.16$, $p = 0.25$) or female ($r = 0.04$, $p = 0.82$) patients. Additionally, there were no strong, significant correlations between plasma BDNF levels and physical functioning subscale scores of the SF36-v2 in male ($r = -0.22$, $p = 0.10$) or female ($r = -0.29$, $p = 0.09$) patients, or male ($r = -0.24$, $p = 0.15$) and female

Table 2
Comparison of demographic and clinical factors in male and female patients and healthy controls.

	Controls (n = 87)		Schizophrenia (n = 97)		Statistical results		
	Males	Females	Males	Females	df	t-Value/F-value/$\chi 2$	p value
Age	30.7 ± 8.6	33.3 ± 7.9	34.8 ± 8.4	37.2 ± 8.2	1, 180	0.01	0.94
Years of education	14.1 ± 2.3	15.1 ± 2.3	12.6 ± 2.3	12.3 ± 2.5	1, 180	3.48	0.06
Sex frequency	46	41	59	38	1	1.18	0.28
Ethnicity (Caucasian/Asian/other)	34/11/1	35/3/3	52/5/2	32/5/1	6	8.60	0.20
DASS depression	3.5 ± 6.2	3.6 ± 4.5	12.1 ± 9.7	12.5 ± 9.5	1, 174	0.01	0.92
DASS anxiety	2.6 ± 3.5	3.2 ± 4.8	9.9 ± 7.4	10.4 ± 8.5	1, 174	<0.01	0.95
DASS stress	5.3 ± 5.1	8.2 ± 9.8	14.1 ± 8.8	15.4 ± 10.4	1, 174	0.36	0.55
SF36-v2 total score	142.1 ± 11.0	139.6 ± 10.3	114.7 ± 19.8	113.6 ± 19.7	1, 170	0.08	0.78
Body Mass Index (BMI)	–	–	30.5 ± 6.5	32.0 ± 6.2	83	−1.03	0.31
Age of illness onset	–	–	21.7 ± 4.4	24.6 ± 6.7	95	2.59	0.01
Duration of illness (yrs)	–	–	12.8 ± 7.8	13.1 ± 6.7	95	0.25	0.80
CPZ equivalent dose (mg/day)	–	–	574.8 ± 435.0	515.3 ± 513.7	95	−0.61	0.54
Imipramine equivalent dose (mg/day)	–	–	172.1 ± 148.7	204.1 ± 126.9	16	0.50	0.62
PANSS positive score	–	–	15.6 ± 4.3	14.1 ± 5.2	95	−1.54	0.13
PANSS negative score	–	–	15.8 ± 6.7	12.3 ± 4.5	95	−2.86	0.01
PANSS general score	–	–	31.0 ± 9.5	30.0 ± 7.6	95	−0.52	0.60
PANSS total score	–	–	62.4 ± 17.4	56.4 ± 14.8	95	−1.75	0.08

Means ± SD are provided where applicable. – = not applicable. DASS = Depression, Anxiety and Stress Scale. SF36-v2 = Short Form 36, version 2 Health Survey Questionnaire. CPZ = daily Chlorpromazine equivalent dose. PANSS = Positive and Negative Syndrome Scale. Age, education, DASS depression, DASS anxiety, DASS stress and SF36-v2 total score were compared among all sex X diagnosis groups using ANOVAs. *P* values represent the interaction effect. Sex and ethnicity were compared using χ^2 tests. A series of independent samples t-tests were used to compare male and female patients based on clinical factors.

($r = 0.17$, $p = 0.32$) healthy controls. More male patients (47%) were receiving antidepressants than female patients (26%).

3.2. Plasma BDNF levels

Results of a 2 × 2 ANCOVA with sex and diagnosis as grouping factors, age as a covariate, and plasma BDNF levels as the dependent variable revealed trends towards significant main effects of diagnosis, $F(1, 165) = 3.59$, $p = 0.06$, and sex, $F(1, 165) = 2.84$, $p = 0.09$, and a significant diagnosis by sex interaction, $F(1, 165) = 11.00$, $p = 0.001$. LSD post-hoc analyses revealed that females with schizophrenia displayed significantly higher plasma BDNF levels compared to males with schizophrenia ($p = 0.004$), and relative to female healthy controls ($p = 0.003$) (see Fig. 1).

Results of the ANCOVA with those patients receiving antidepressants removed from the analysis were similar to the results with all participants included (see Supplemental results). In addition, results of separate ANCOVAs were similar in both people with schizophrenia only and schizoaffective disorder alone (see Supplemental Results). Regarding the relationship of plasma BDNF to medication dosages, plasma BDNF levels did not show any strong, significant correlations with mean daily CPZ equivalent dose (males: $r = 0.03$, $p = 0.81$, females: $r = 0.27$, $p = 0.10$) or imipramine equivalent dose (males: $r = 0.28$, $p = 0.40$, females: $r = -0.04$, $p = 0.94$) in patients.

4. Discussion

We identified sex differences in peripheral BDNF levels, such that females with schizophrenia had significantly increased plasma BDNF levels relative to males with schizophrenia and relative to healthy female controls. Our results do not support the findings of our meta-analysis, which suggested that peripheral BDNF levels are reduced in schizophrenia (Green et al., 2011).

Men and women with schizophrenia may differ in terms of many clinical features of schizophrenia and we show that this may extend to sex differences in blood biomarkers, specifically plasma BDNF levels. Clinically, our male and female patients differed significantly on PANSS negative symptom severity score and age of illness onset, such that females had less severe negative symptoms and a later age of illness onset (mean of 3 years later) than males, which is consistent with previous research (Zhang et al., 2012). However, we did not find a significant correlation of blood BDNF levels with negative symptom severity scores or with age of illness onset in male or female patients in our study.

There are inconsistencies regarding sex differences in peripheral BDNF levels of people with schizophrenia. Many studies examining sex differences in peripheral BDNF levels often do not find sex differences in schizophrenia (Jindal et al., 2010; Koeva et al., 2014; Rizos et al., 2008; Tan et al., 2005). However, while some studies show increased plasma BDNF levels in females with schizophrenia relative to males with schizophrenia, the same studies also show that peripheral BDNF levels are decreased in females with schizophrenia relative to healthy females (Xiu et al., 2009; Zhang et al., 2014). In these two studies finding higher levels of BDNF in female patients compared to male patients, the average patient age was 51–53 years old and thus, many older postmenopausal women were included. In contrast, our study had younger female patients (mean age = 37.2, SD = 8.2). Since plasma BDNF levels have been reported to decrease with age (Lommatzsch et al., 2005), younger females with schizophrenia may have increased plasma BDNF levels. Given that females in our study were younger and not as chronically ill compared to those patients in most previous studies of peripheral BDNF levels in schizophrenia (Tan et al., 2005; Vinogradov et al., 2009; Xiu et al., 2009; Zhang et al., 2014) we would expect higher BDNF levels in females from our sample.

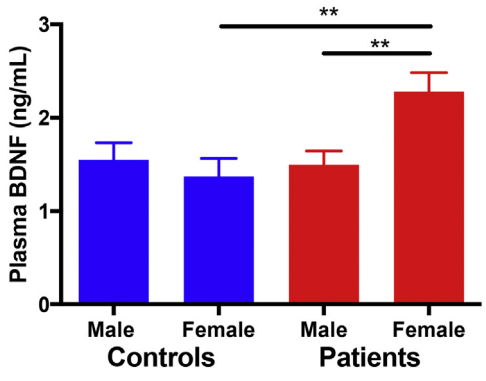

Fig. 1. Means ± SD of plasma BDNF levels (ng/ml) in male and female patients with schizophrenia and healthy controls. $^{**}p \leq 0.01$.

Further, the number of female patients in our study was higher than that in many of the other studies that tested for sex differences in BDNF in schizophrenia. Those studies that failed to find sex differences in blood BDNF levels included low numbers of females with schizophrenia (varying from $n = 4$ to $n = 10$), (Jindal et al., 2010; Koeva et al., 2014; Rizos et al., 2008; Tan et al., 2005). Therefore, many previous studies were likely to be underpowered to detect sex differences in females with schizophrenia. The lack of significant difference in plasma BDNF levels in men with schizophrenia was also surprising, but again this finding may reflect our younger mean patient age (approximately 35 years old) than in other studies.

Another potential reason why females with schizophrenia may have elevated BDNF levels is that they may be more likely to be prescribed BDNF-inducing antidepressants (Watanabe et al., 2010). However, in our study only 10 (26%) of the females with schizophrenia were receiving antidepressants compared to 28 (47%) of the male patients, suggesting that antidepressant medication alone is not a major contributor to the increased BDNF levels in female patients in our study. In support of this, antidepressant dose (mean daily imipramine equivalent) was not correlated with plasma BDNF levels and when individuals who were receiving antidepressant medication were removed from the analysis, we found that the females with schizophrenia still had significantly higher plasma BDNF levels compared to their male counterparts.

A strong, significant relationship between mean daily CPZ equivalent dose and plasma BDNF levels may not have been shown in our study since patients were receiving many different antipsychotics that have different binding properties with potentially different downstream effects on BDNF levels. While converting doses of various antipsychotics to mean daily CPZ equivalent dose is the accepted standard in the field, it has limitations. In this case, using a similar scale for antipsychotics with opposite effects on BDNF levels may be problematic. For example, haloperidol decreases BDNF mRNA expression; conversely, clozapine and olanzapine upregulates BDNF mRNA in the hippocampus of rats (Bai et al., 2003). Future studies should assess the effects of specific antipsychotic medications when considering the effect of medication on blood BDNF levels.

Given that we demonstrated increased plasma BDNF levels in female patients only, we suggest that the increase in plasma BDNF levels may be related to a differential influence of sex hormones. Estrogen has been shown to regulate BDNF mRNA and protein in the brain of rodents (Gibbs, 1999; Jezierski and Sohrabji, 2000; Liu et al., 2001; Singh et al., 1995). BDNF levels vary across the estrous cycle in both rodent brain and human plasma (Begliuomini et al., 2007; Cavus and Duman, 2003; Cubeddu et al., 2011; Scharfman et al., 2003). Conversely, testosterone treatment significantly decreased BDNF gene expression in the hippocampus of gonadectomized, diabetic rats (Ebrahimzadeh et al., 2015). The potential of sex hormones to regulate peripheral BDNF levels should be further explored in future studies of humans.

It is also important to consider that the standard BDNF ELISA assay protocol that we used to detect BDNF levels in peripheral blood provides total BDNF, which is comprised of mature BDNF (mBDNF) and its

precursor, proBDNF (Yamamori et al., 2013). ProBDNF and mBDNF have been shown to bind to p75 and TrkB receptors and to mediate different and opposing effects on the synaptic plasticity in the hippocampus with mBDNF supporting dendritic spines and proBDNF (acting through p75) inducing spine loss (Bachis et al., 2016; Holm et al., 2009). Due to the opposing roles of proBDNF and mBDNF in spine plasticity and their differing interactions with their receptors, it would be important to determine the relative amounts of these two types of BDNF in the blood and brain of people with schizophrenia. For example, one possibility may be that in females, where BDNF is elevated, the deleterious proBDNF form may be increased.

In conclusion, this study reveals sex-specific differences in the plasma BDNF levels of people with schizophrenia. Our results demonstrate that when sufficient numbers of younger females are included in the sample then diagnosis by sex differences in plasma BDNF levels become apparent. Future work should determine whether increased BDNF levels in females with schizophrenia are beneficial or detrimental to cognitive abilities and symptom expression.

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Conflicts of interest

All authors declare that they have no competing financial interests in relation to the work described in this report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.04.015.

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