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*Review article*

# Relevance of Brain-derived Neurotrophic Factor Levels in Schizophrenia: A Systematic Review and Meta-Analysis

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**Abstract:** Background: Brain Derived Neurotrophic Factor (BDNF) is one of the neuromodulators crucial for the survival, development and function of neurones in the brain and nervous system. Several authors linked its changes in production and concentration to Schizophrenia syndromes. Aim: This systematic review examined the available evidence to clarify the association between plasma BDNF levels and Schizophrenia. Method: Initial searches revealed 266 records. After screening of abstracts, 20 studies were selected. Following a preliminary review, 14 studies were included in this systematic review and meta-analysis. Results: Of the 14 studies (910 patients, 717 controls) 8 reported decreased BDNF levels in patients with schizophrenia as compared to controls; 3 studies (274/128) found increased BDNF levels; while 3 (62/62) reported no group differences. Meta-analysis of all pooled studies confirmed reduced BDNF levels in schizophrenia versus controls (medium effect size); however, the group difference was not significant when studies using unmedicated cases were considered. Conclusion: The cumulative evidence indicates reduced BDNF levels existing in schizophrenia. However, findings are less clear in unmedicated cases, suggesting that reduced BDNF

levels in schizophrenia may be associated with symptom chronicity and/or chronic effects of antipsychotic medication.

**Keywords:** BDNF; neurones; neuromodulator; development; function; schizophrenia; serum; plasma; levels; brain derived neurotrophic factor

## 1. Introduction

Brain Derived Neurotrophic Factor (BDNF) is a protein that is heavily involved in development of the nervous system across species, and in the regulation of synaptic transmission.

During development, BDNF has been implicated in survival of stem cells, neurogenesis and neuronal differentiation along with the polarization and guidance of neurones. In addition, once neurones become differentiated, it plays a key part in their branching and survival. BDNF also regulates aspects of plasticity in the developed brain and thereby is implicated in cognitive functioning [1].

The Brain-Derived Neurotrophic Factor (BDNF) was characterized for the first time more than a decade ago. It belongs to the neurotrophin family, which also includes nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). Neurotrophins are a family of proteins that induce the survival, development, and function of neurones. They belong to a class of growth factors, secreted proteins, which are capable of signalling to particular cells to survive, differentiate or grow. BDNF modulates neurotransmitter synthesis, metabolism and neuronal activity [2]. It is involved in the development of dopaminergic related systems [3], and the mesolimbic dopamine systems [4,5]. Abnormal BDNF signalling can influence neuronal differentiation and synaptic function, leading to altered brain development and functioning. Neurodevelopmental abnormalities [5–8] and a dysregulated dopamine system [9] have been implicated in the pathophysiology of schizophrenia. Therefore, BDNF may be a marker of abnormal neurodevelopment and neurotransmission in schizophrenia. Decreased serum BDNF levels have been reported in neuroleptic free patients with schizophrenia relative to healthy controls [10,11], and in chronic schizophrenia patients taking antipsychotics [12]. Increased BDNF levels, however, have been reported in chronically medicated patients [13]. BDNF levels have also been associated with the severity of psychotic symptoms [10,11]. Against the above background, we aimed to review existing literature in order to clarify: a) whether serum BDNF levels in patients with Schizophrenia would be reduced or increased, compared to healthy controls; b) correlation of serum BDNF levels with positive and negative, acute and chronic, psychotic symptoms. It should also be noted that other studies have been performed which have explored BDNF in other psychiatric disorders.

## 2. Method

### *2.1. Inclusion criteria*

We included only studies recruiting patients with Schizophrenia and healthy controls. All studies were using blood sampling and established laboratory bio-tests and methods to determine plasma BDNF levels. An attempt was made to establish differences in serum BDNF levels between patients with schizophrenia and controls.

### *2.2. Literature search*

A database search (EMBASE 658, MEDLINE 424, PsycINFO 2 , combined 1353, title only 266) and manual search was conducted to identify individual studies that measured BDNF blood levels (serum or plasma) in schizophrenia (first episode, chronic schizophrenia and schizoaffective disorder) for both chronically medicated and drug naïve patients. The initial search yielded 266 records; of these 76 were removed due to duplication leaving a total of 190. 170 studies did not meet the required criteria, following a screening of abstracts. Out of 20 papers reviewed in full, we included 14 case control studies that met the inclusion criteria (Figure 1). The studies used in this review were case control studies which used live subjects and matched controls. Two of the studies, which considered post mortem brain samples, were excluded from the final list.

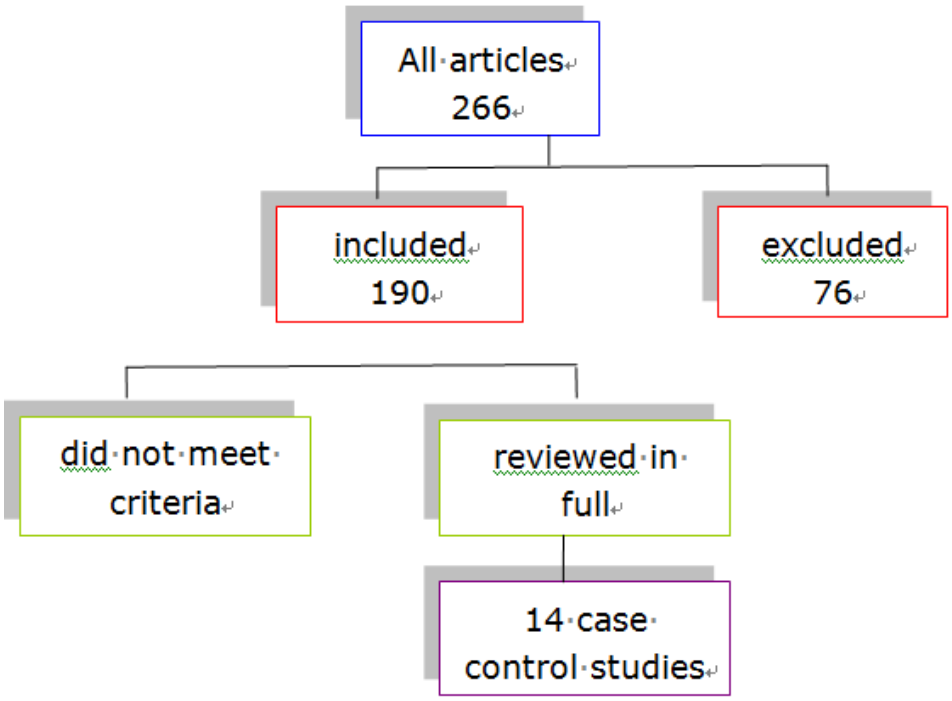


**Figure 1. Flow chart diagram of selection process.**

### *2.3. Data extraction and synthesis*

Two of the authors assessed each paper from the final list, and four reviewers who were each allocated a set of papers performed data extraction. Two of the authors carried out a final review of all the papers. An assessment criteria grid was used for each paper (table 1) according to whether BDNF levels were significant or not significant, and whether they were increased, unchanged or decreased. The category of symptoms experienced by the sample type, e.g. positive or negative, early or chronic, was recorded. Control groups, when data were available, were also described. The biomarker test employed was stated, and the blood sample component noted. The diagnostic tests used for selection were incorporated, and where stated medication details were included in the grid. Finally, study type and the sample sizes were recorded.

The data were collated into a single table (table 2), and were arranged according to year of publication.

Meta-analysis was then undertaken by using 'Comprehensive Meta-Analysis v2.0' (www.meta-analysis.com) entering means, standard deviations, and sample sizes for the schizophrenia and control groups (weighted fixed effects model). We explored all studies pooled, and then considered studies with medicated and unmedicated patients separately. Results were reported in terms of standard difference in means and 95% confidence intervals.

**Table 1. Assessment criteria**

| **BDNF change** | significant | not significant | | |
|---|---|---|---|---|
| **BDNF** | increased | decreased | no variation | |
| **Sample type** | positive | negative | chronic | early |
| **Control type** | matched | extra data | | |
| **Bio test** | ELISA | other (specify) | | |
| **Blood** | serum | platelets | | |
| **Psychometrics** | PANSS | +/−other | | |
| **Medication** | antipsychotic | no antipsychotic | | |
| **Type** | longitudinal | cross | | |
| **Sample size** | Case (n)/control (n) | | | |

**Table 2. Collated data**

| ***Criterion*** → ***Author*** ↓ | ***BDNF Significant*** | ***BDNF increased/ decreased*** | ***Sample type: eg positive/negative symptoms/chronic etc*** | ***Control type*** | ***Bio test*** | ***Blood*** | ***Psychometrics*** | ***Medication*** | ***Type of study*** | ***Sample size: patients/controls*** |
|---|---|---|---|---|---|---|---|---|---|---|
| Toyooka 2002 | Significant | Decreased | Chronic | Healthy volunteers (randomly selected hospital employees) | Enzyme Immuno assay | Serum (2 sites), platelets | DSM-IV | Haloperidol, Levopromazine | Cross sectional | 34/35, 34/27 |
| Shimizu 2003 | Not significant | No variation | Chronic, early | Age and sex | ELISA | Serum, platelets | PANNS, DSM-IV, BPRS | Cases taking antipsychotic | Case/control | 40/40 |
| Jockers-Scherubl 2004 | Significant | Increased | Positive, negative, chronic | Age plus cannabis | ELISA | Serum | DSM-IV, Structured clinical interview | Drug naive | Case/control | 151/72 |
| Pirildar 2004 | Not significant | No variation | Chronic/early | Age and sex | ELISA | Platelets | PANSS | Anti-psychotics | Case/control | 22/22 |
| Tan et al 2005 | Significant | Decreased | Chronic | Age and sex | ELISA | Serum | PANSS, DSM-III | Anti-psychotics | Case/control | 81/45 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Huang 2006 | †Not significant * Significant only between types of schizophrenia | † no variation between cases and controls * Decreased | Chronic (5 years) | Medical staff at same hospital screened by same psychiatrist | ELISA | Serum | PANSS, DSM-IV (cases),Chinese HealthQuestionnaire-12 and semi-structured interviews to rule out psychiatric cases ij controls | Stopped 1/52 before (if taking any), otherwise drug naive | Case/control | 126/96 |
| Buckley 2007 | Significant | Decreased | Positive, negative | Matched for age and sex | ELISA | Serum(=plasma) | PANSS, BPRS | Medication naïve | Case/control | 15/14 |
| Gama 2007 | Significant | Increased | Positive, ( > 5 years) | Matched for age; no ΨH, no FH | ELISA | Serum, platelets | DSM-IV | Long term | Case/control | 60(schizophrenia),30(euthymic BPAD)/26 |
| Grillo 2007 | Significant | Decreased | Chronic: (mean = 13.45 years) | Matched for social back-ground, age and sex *(NB no data on recruitment method for controls)* | Streptav-idin | Serum. platelets | SCID-1 | 1st generation anti-psychotics, Clozapine | Case/control | 44/25 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Zhang 2007 | Significant | Decreased | Chronic | Local, healthy, similar ethnicity, s/e status and dietary patterns | ELISA | Serum | PANSS | Clozapine, Risperidone | Case/control | 124/50 |
| Ikeda 2008 | Significant | Decreased | Positive, negative, chronic | Local, no ΨH, similar demographic, matched for s/e status, BMI, smoking | ELISA | Serum (2 sites), platelets | DSM-IV, BPRS, clinical interview, notes | All cases taking *high dose anti-psychotic medication (1st and 2nd generation) *936.6 +/−588.8 mg od chlorpro-mazine equivalents | Case/control | 74/87 |
| Rizos 2008 | Significant | Decreased | Early | Matched | ELISA | Serum | PANSS, SCID , DSM IV | Nil | Case/control | 14/15 |
| Mei 2009 | Significant | Decreased | Positive , negative, chronic (> 5 years) | Normal | ELISA | Serum, platelets | PANSS | 12 months (oral) anti-psychotics | Case/control | 364/323 |
| Kuo 2012 | Significant | Increased | Chronic | Healthy | ELISA | Serum | DSM-IV, BPRS | Stable antipsychotic medication > 3/12 | Case/control | 33/30 |

* Between cases/controls (meaningful only between different types of schizophrenia)

**Table 3.**

| **Study** | schizophrenia mean | schizophrenia SD | schizophrenia N | controls mean | controls SD | Controls N | Medication status (1 = medicated) |
|---|---|---|---|---|---|---|---|
| Toyoka 02 | 6.3 | 3.4 | 34 | 11.4 | 7.7 | 35 | 1 |
| Shimizu 03 | 26.4 | 11 | 40 | 28.5 | 9.1 | 40 | 1 |
| Jockers 04 | 13.1 | 5.9 | 157 | 13.2 | 5.5 | 72 | 0 |
| Pirildar 04 | 14.19 | 8.12 | 22 | 26.8 | 9.3 | 22 | 1 |
| Tan 05 | 7.3 | 2.6 | 81 | 9.9 | 4.3 | 45 | 1 |
| Haung 06 | 14.2 | 6.92 | 126 | 14.17 | 6.86 | 96 | 0 |
| Buckley 07 | 17 | 3 | 15 | 49.1 | 6.7 | 14 | 0 |
| Gama 07 | 12.1 | 9.8 | 60 | 1.9 | 0.8 | 26 | 1 |
| Grillo 07 | 12.4 | 44.5 | 44 | 168 | 26.3 | 25 | 1 |
| Zhang 07 | 8.4 | 4.2 | 124 | 9.3 | 4.4 | 50 | 1 |
| Ikeda 08 | 37.1 | 20.4 | 74 | 52.2 | 25.3 | 87 | 1 |
| Rizos 08 | 23.9 | 5.99 | 15 | 30 | 8.43 | 14 | 0 |
| Mei 09 | 9.9 | 2 | 364 | 11.9 | 2.3 | 323 | 1 |
| Kuo 12 | 4.45 | 0.63 | 33 | 21.47 | 1.05 | 30 | 1 |

## 3. Results

Studies meeting inclusion criteria, and their findings, are summarised in the table 2. From a total of 14 studies used in the final list, 8 showed a decrease in BDNF levels in patients with schizophrenia [11,12,14–19] [and 3 studies reported no significant difference in BDNF between cases and controls [20–22], of which 1 [20] found differences only between types of schizophrenia. 3 studies showed an increase in relation to controls [13,23,24]. Case groups were also defined according to types of symptom and disease chronicity. 8 studies were based on patients with chronic illness only, 1 on those with early illness, 2 included both types and 3 did not state stage or duration of illness.

Results from the meta-analysis are indicated in Table 3 and Figure 2. It can be seen that when data from all studies were pooled, BDNF levels were significantly lower in patients with Schizophrenia as compared to controls ($Z = -12.057$, $p < 0.001$). This was also the case when only studies including medicated patients were considered ($Z = -13.224$, $p < 0.001$). When studies with unmedicated patients were considered, BDNF levels in patients did not differ significantly from controls ($Z = -1.315$, $p = 0.189$).

| Group by medicated? | Study name | Statistics for each study | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
| 0.00 | Buckley 07 | -6.262 | 0.902 | 0.814 | -8.030 | -4.493 | -6.940 | 0.000 |
| 0.00 | Rizos 08 | -0.839 | 0.388 | 0.150 | -1.599 | -0.080 | -2.165 | 0.030 |
| 0.00 | Haung 06 | 0.004 | 0.135 | 0.018 | -0.261 | 0.270 | 0.032 | 0.974 |
| 0.00 | Jockers 04 | -0.017 | 0.142 | 0.020 | -0.296 | 0.262 | -0.122 | 0.903 |
| 0.00 | | -0.124 | 0.095 | 0.009 | -0.310 | 0.061 | -1.315 | 0.189 |
| 1.00 | Mei 09 | -0.932 | 0.080 | 0.006 | -1.090 | -0.774 | -11.580 | 0.000 |
| 1.00 | Zhang 07 | -0.211 | 0.168 | 0.028 | -0.540 | 0.118 | -1.259 | 0.208 |
| 1.00 | Tan 05 | -0.787 | 0.192 | 0.037 | -1.164 | -0.410 | -4.089 | 0.000 |
| 1.00 | Ikeda 08 | -0.651 | 0.162 | 0.026 | -0.969 | -0.333 | -4.015 | 0.000 |
| 1.00 | Toyoka 02 | -0.853 | 0.251 | 0.063 | -1.346 | -0.360 | -3.390 | 0.001 |
| 1.00 | Grillo 07 | -3.993 | 0.422 | 0.178 | -4.820 | -3.165 | -9.457 | 0.000 |
| 1.00 | Shimizu 03 | -0.208 | 0.224 | 0.050 | -0.647 | 0.231 | -0.928 | 0.353 |
| 1.00 | Pirldar 04 | -1.444 | 0.339 | 0.115 | -2.108 | -0.781 | -4.267 | 0.000 |
| 1.00 | Gama 07 | 1.240 | 0.253 | 0.064 | 0.744 | 1.736 | 4.899 | 0.000 |
| 1.00 | Kuo 12 | -19.888 | 1.790 | 3.203 | -23.396 | -16.381 | -11.113 | 0.000 |
| 1.00 | | -0.738 | 0.056 | 0.003 | -0.848 | -0.629 | -13.224 | 0.000 |
| Overall | | -0.580 | 0.048 | 0.002 | -0.674 | -0.485 | -12.057 | 0.000 |

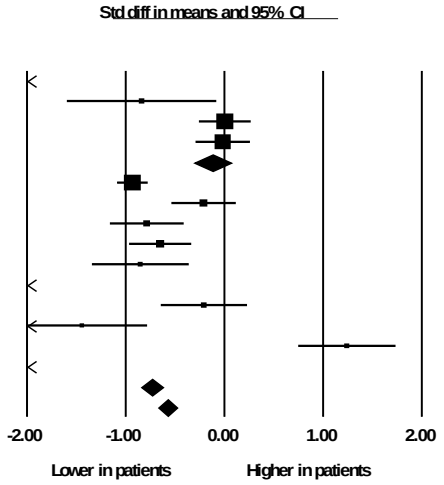


**Figure 2. Results from the meta-analysis**

### *3.1. Selection of controls*

The controls varied in the method of selection. Examples of likely weaknesses in the control selection (or in its reporting) include 'medical staff at same hospital screened by the same psychiatrist' [20] and undefined 'healthy volunteers' [18]. Some controls methods were more thorough: for example where controls were selected on the basis of not having any family psychiatric history [13], whilst another excluded controls who smoked cannabis [23]. The majority of studies screened controls for age, sex, demographics and psychiatric history.

### *3.2. Biological tests*

The biological tests to determine BDNF levels showed a much smaller degree of heterogeneity. 13 out of the 14 studies used Enzyme Linked Immunosorbent Assay or close equivalent (ELISA) and 1 used Streptavidin [12]. Similar procedures occurred with samples: 7 used serum only, 6 used serum and platelets and 1 used platelets only.

### *3.3. Case selection*

In order to determine case validity, subjects were screened for schizophrenia using PANSS, DSM-IV, DSM-III, SCID-1, and structured clinical interview other than SCID-1. 3 papers used PANSS only, 5 used PANSS in combination with 1 or more diagnostic tests, such as DSM-IV, BPRS, SCID-I and/or DSM-III, 2 used DSM-IV only, 3 used DSM-IV with a test or tests other than PANSS and 1 used SCID-I only.

### *3.4. Medication*

Antipsychotic medication use was reported in 10 of the studies, and 4 studies reported that patients were not taking any antipsychotics, of which 2 looked at medication naïve patients [11]. In 1 of these 4 studies [20] participants were either drug naïve or antipsychotics were stopped a week prior to entering the study. However, no rationale was offered as to why this latter step had been taken. Out of the 10 studies where antipsychotics were reported as being used, chronicity was mentioned in 3, dosage in 1, and actual drug names in 3. One high dose study, in which patients were taking either or both first and second generation antipsychotics [17], quoted chlorpromazine equivalents.

### *3.5. Types of study*

All of the papers selected were case/control studies.

### *3.6. Study sizes*

4 of the studies had case numbers of in excess of 100, the largest being 364 cases with 323 controls [14], with the smallest having 14 cases and 15 controls [19].

## 4. Discussion

This systematic review found that the majority (72.7%) of the available case-control studies identified significantly reduced BDNF levels in patients with schizophrenia as compared to controls.

This group difference was significant in a confirmatory meta-analysis of the available trials, with medium effect size. Interestingly, when meta-analysis was conducted as a function of patient medication status, BDNF was significantly reduced in patients with schizophrenia versus controls when studies in medicated cases were considered; but not when studies in unmedicated cases were considered.

Several of the studies had medium to large sizes of cases and controls. 1 study used stable doses of antipsychotics as well as ensuring that assessing psychiatrists and technicians were blinded to the clinical status of the person they were examining [14]. In addition this study screened the controls for psychoactive drug use and used ANOVA for both patients *vs.* controls as well as male *vs.* female participants. These straightforward measures might be considered in any future study of a similar nature. In 3 of the studies, cases were re-sampled in respect of sex, smoking and/or BMI [17,15,24,12]. In 1 study, different antipsychotics were measured in chlorpromazine equivalents, facilitating comparison [17].

If we consider Schizophrenia as a neurodevelopmental disorder [25] and because BDNF is implicated in the modulation of neurotransmitter synthesis, metabolism and neuronal activity, the fact that 11 out of 14 studies showed BDNF dysregulation, as did pooled meta-analysis, strongly suggests an association between Schizophrenia and reduced serum BDNF levels. Nearly half the studies used fewer than 50 cases, therefore results from these should be interpreted accordingly.

Several studies have looked for an association between BDNF levels and response to treatment. The authors looked at 3 papers which showed variously: no change in BDNF with treatment [26], increases in BDNF associated with hippocampal volume changes [27] and one study that showed normalized levels of BDNF following olanzapine use [28]. In addition this last paper showed that increases in BDNF were associated with a reduction in the positive symptoms of Schizophrenia and an increased level of functioning.

## 5. Limitations of some Studies

While the available case-control studies measured BDNF levels using similar testing methods (ELISA or EIA), and used (similar) validated diagnostic criteria (e.g., DSM-IV), several potential limitations should be considered. Amongst the cases, we found variation in sampling. One example was the selection of chronic cannabis (and other substance) users in the patient group, and in another those who were medication naïve (1st episode and relatively younger, with mean age 31)—significantly different from other selected patient groups [23]. In addition illness duration varied, and some studies included chronically ill patients who were treated with psychotropic medication, or could be treatment resistant. Inclusion criteria were markedly different between studies; some included Schizophrenia only, and others included other psychotic diagnoses (Schizoaffective disorder, Delusional disorder) or mood disorder (Bipolar Affective disorder), further possible factors in the variability of BDNF levels between studies.

The fact that no information on the recruitment process was found in four of the studies [13,21–23]

might be considered a limitation. In other studies, narrow demographic/selection bias was demonstrated. For example, the cases were all inpatients from the same hospital [20], and age discrepancies were noted between the case and control groups [11]. Grillo 2007 [12] did not give information about controls. Another study [20] did not screen patients for family psychiatric history and, as stated above, mentioned a one week drug washout the validity of which might have been questionable. There was an absence of power calculations in some of the papers which include Jockers-Scherubl 2004 [23], Pirildar 2004 [22], Rizos 2008 [19] and Shimizu 2003 [21]. Jockers-Scherubl [23] gave no details of randomization, and Rizos [19] did not mention blinding. Other studies were small in size [11,19] and there was multiple hypothesis testing in 2 of the papers [16,19].

The studying of BDNF in live subjects is problematic. However, a study by Durany et al [29], which studied brains post mortem, showed an increase in schizophrenia patients in the frontal cortex, temporal lobes and occipital region with a reduction in the hippocampal area. How these plasma changes relate to BDNF in the living brain could not be addressed within the confines of this study. This could, in theory, be addressed by the use of radio ligands.

## 6. Conclusions

This review shows that a majority of the studies examined demonstrated an association between Schizophrenia and reduced BDNF levels, as compared to controls. This was confirmed by meta-analysis, with medium effect size overall for pooled data. It is noted that an earlier meta-analysis found overall reductions in BDNF levels in patients with schizophrenia, who were both medicated and drug-naïve. The authors concluded that the evidence was of moderate quality with unexplained heterogeneity across results [30]. Caution is warranted in attributing this finding to schizophrenia *per se*, as opposed to effects of symptom chronicity and conceivably medication status. If reduced BDNF is a consequence of schizophrenia, synthetic BDNF neurotrophin supplementation could possibly represent a future novel treatment direction [31].

## Conflict of Interest

All authors declare no conflicts of interest in this paper.

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