Acta Neuropsychiatrica 2014

DOI: 10.1017/neu.2013.59

ACTA NEUROPSYCHIATRICA

BDNF and S100B in psychotic disorders: evidence for an association with treatment responsiveness

van de Kerkhof NWA, Fekkes D, van der Heijden FMMA, Verhoeven WMA. BDNF and S100B in psychotic disorders: evidence for an association with treatment responsiveness.

Objective: Brain-derived neurotrophic factor (BDNF) and S100B are involved in brain plasticity processes and their serum levels have been demonstrated to be altered in patients with psychoses. This study aimed to identify subgroups of patients with psychotic disorders across diagnostic boundaries that show a specific symptom profile or response to treatment with antipsychotics, by measuring serum levels of BDNF and S100B.
Methods: The study sample consisted of 58 patients with DSM-IV psychotic disorders. Comprehensive Assessment of Symptoms and History (CASH), Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression scale for severity and improvement (CGI-S/CGI-I) were applied at baseline and after 6 weeks of antipsychotic treatment. At both time points, serum levels of BDNF and S100B were measured and compared with a matched control sample.
Results: Baseline BDNF and S100B levels were significantly lower in patients as compared with controls and did not change significantly during treatment. Dividing the patient sample according to baseline biochemical parameters (low and high 25% and middle 50%), no differences in symptom profiles or outcome were found with respect to BDNF. However, the subgroups with low and high S100B levels had higher PANSS scores than the middle subgroup. In addition, the high subgroup still showed significantly more negative symptoms after treatment, whereas the low subgroup showed more positive symptoms compared with the other subgroups.
Conclusion: Serum levels of BDNF and S100B are lowered in patients with psychotic disorders across diagnostic boundaries. The differences between high and low S100B subgroups suggest a relationship between S100B, symptom dimensions and treatment response, irrespective of diagnostic categories.

Noortje W.A. van de Kerkhof[1,2], Durk Fekkes[2], Frank M.M.A. van der Heijden[1], Willem M.A. Verhoeven[1,2]

[1]Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Venray, The Netherlands; and [2]Erasmus Medical Centre, Departments of Psychiatry and Clinical Chemistry, Rotterdam, The Netherlands

Keywords: BDNF; psychosis; S100B; symptomatology; treatment response

Dr. N.W.A. van de Kerkhof, MD, Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Stationsweg 46, 5803 AC Venray, The Netherlands.
Tel: +31478527339;
Fax: +31478527111;
E-mail: nvandekerkhof@vvgi.nl/ noortjevandekerkhof@gmail.com

Accepted for publication October 14, 2013

First published online November 22, 2013

Significant outcomes

- Brain-derived neurotrophic factor (BDNF) can be regarded as a marker for reduced neuroplasticity in a variety of psychiatric disorders.
- S100B before treatment may be useful to identify patients in whom either more positive or more negative symptoms persist after 6 weeks of treatment.

Limitations

- Small sample size.
- Relatively short follow-up period.

Introduction

Since the concept of schizophrenia was formulated by Kraepelin and Bleuler, there is an ongoing debate on the aetiological and pathophysiological factors of psychoses. Over the past decades, increasing evidence has emerged that the prototypic psychotic disorder, schizophrenia, has to be considered as a progressive, neurodevelopmental disorder (1,2).

The neurodevelopmental trajectory of the human brain is characterized by an increase in grey matter during early childhood and a subsequent decrease during puberty, which can be attributed to a process called 'synaptic pruning' (3,4). Exaggerated synaptic pruning has been associated with very early onset of first psychotic symptoms (5). Accordingly, adult patients with schizophrenic psychoses show excessive grey matter loss that is paralleled by white matter increase in the first and second decade of their illness (6). It has been postulated, that this excessive synaptic pruning leads to reduced synaptic connectedness ('connectivity'), which enhances the susceptibility to develop schizophrenia and related psychoses (7). Connectivity can be established indirectly by measuring neurotrophic factors involved in the development and maintenance ('plasticity') of the central nervous system (CNS) (8). Some of these neurotrophic factors like brain derived neurotrophic factor (BDNF) and S100B, that both pass the blood brain barrier (9,10) and of which the peripheral levels correlate well with those in the CNS, have been extensively investigated in psychotic disorders [BDNF: (11,12); S100B: (13,14)].

BDNF is the most abundant neurotrophic factor in the brain and plays a crucial role in development, proliferation, regeneration, survival and maintenance of neuronal function of the CNS (15,16). Serum BDNF levels have repeatedly been reported to be decreased in first-episode and chronic schizophrenia (17,18). Consistent associations between BDNF levels and symptom profile of psychotic disorders, however, have not been found as yet (19,20), whereas the results about the effects of class or dosage of antipsychotics on the serum concentration of BDNF are very contradictory (21,22).

S100B is a calcium-binding protein involved in intracellular energy metabolism in the CNS. Depending on the concentration, its extracellular effect is either trophic or toxic. In nanomolar concentrations, S100B stimulates neurite outgrowth and enhances survival of neurons during development and after injury. In micromolar concentrations, however, it induces apoptosis (23,24). With respect to schizophrenia, enhanced levels of S100B and a positive correlation with negative symptoms are repeatedly reported (25–27). Treatment with antipsychotics over a relatively short period of time has been shown to normalize S100B serum levels (28,29). In addition, some evidence is available suggesting a relationship between S100B levels and neurocognitive parameters (30) as well as severity of symptoms (13).

Thus, serum concentrations of these two neurotrophic proteins express to some extent the functional status of the brain, particularly its neuroplasticity. Moreover, circumstantial evidence is available that their concentrations correlate with either severity of symptomatology or symptomatic changes during antipsychotic treatment.

Aims of the study

The present study was designed to investigate whether the neurotrophic proteins BDNF and S100B may be biomarkers for the identification of a specific symptom profile or responsiveness to treatment in patients with psychotic disorders irrespective of their classificatory status.

Materials and methods

Patient recruitment

Patients were recruited over a period of 30 months at the Vincent van Gogh Institute for Psychiatry, a large psychiatric teaching hospital in the South of the Netherlands. The study was performed according to the Dutch medical ethical guidelines (CCMO registration number NL20469.097.07), approved by the Board of Directors of the hospital and in full accordance with the Helsinki Declaration.

All patients provided written informed consent before entering the study. Included were adult patients (male/female, age range 18–65 years) admitted for psychotic symptomatology, for which pharmacological intervention with antipsychotics was warranted. As exclusion criteria served proven genetic syndrome, intellectual disabilities and relevant somatic or neurologic diseases. Patients unable to provide informed consent were also excluded.

During the study period, a total of 194 patients were admitted and subsequently screened for eligibility. Because of severity of psychotic illness, 71 patients had to be excluded for informed consent, whereas 23 did not meet the inclusion criteria. From the remaining 100 patients, 20 refused to participate, yielding a study population of 80 subjects of whom 58 completed the study period of 6 weeks. The latter group ($n = 58$) was included in the analyses.

Treatment process and diagnostic procedures

All patients were treated with first- or second-generation antipsychotic agents during the study period. Pharmacological interventions were performed by

https://doi.org/10.1017/neu.2013.59 Published online by Cambridge University Press

the treating psychiatrist according to hospital standards. At baseline, the Comprehensive Assessment of Symptoms and History (CASH) (31) was applied from which classification according to DSM-IV was done. Severity and distribution of symptomatology were assessed at baseline and after 6 weeks of treatment by means of the Positive and Negative Syndrome Scale (PANSS) (32) and the Clinical Global Impression scale for severity and improvement (CGI-S/CGI-I) (33).

Biochemical assessments

Patients. At both time points of clinical assessment, blood samples were collected to measure serum levels of BDNF and S100B. Sampling was performed between 08:00 and 10:00 a.m. and serum was stored at −80°C until analysis. BDNF was measured by a double antibody sandwich enzyme-linked immunosorbent assay (ELISA; Promega, Madison, Wisconsin, USA) and S100B levels by a two-site one step ELISA (Sangtec, Bromma, Sweden).

Controls. BDNF and S100B levels of control subjects were extracted from a database of the neuropsychiatric laboratory of Erasmus Medical Centre (EMC) comprising data from staff members and students of the EMC and subjects from the general community. None of the control subjects neither their first degree relatives had a history of psychiatric illness. For the S100B assay, control subjects were matched for both age and gender. As we could not find any correlation between BDNF and age in our control group (50 men and 25 women, age 27.5 ± 6.8 years; $p = 0.908$), for the BDNF assay control subjects were matched for gender only. Consequently, separate control groups were created for BDNF ($n = 75$) and S100B ($n = 77$).

Statistics

The Student's *t*-test was used for normally distributed variables (PANSS scores), the Mann–Whitney *U*-test was used for non-normally distributed variables (BDNF/S100B serum levels) and a χ^2-test was used for binary variables. A paired *t*-test (PANSS total and subscales) or Wilcoxon's Signed Rank test (BDNF/S100B serum levels) was used to analyse changes between time points. The Kendall τ-test was used to establish correlations between BDNF/S100B serum levels and clinical variables. Between-group differences were determined by univariate analysis of (co)variance (AN(C)OVA). All analyses were two tailed. Significance was set at $p < 0.05$. Data are presented as mean ±SD, unless stated otherwise.

Results

Patient characteristics

The main characteristics of the 58 patients that completed the study are outlined in Table 1. Mean duration of psychotic illness was 8.1 (±8.4) years. According to DSM-IV, 33 patients were classified as schizophrenia, whereas in the remaining 25 patients various diagnoses from the schizophrenia spectrum were made. Eighteen patients were free from psychotropics at least 2 weeks before study entry. Duration of treatment in the medicated patients varied from 2 weeks to >10 years.

Clinical and biochemical treatment effects

Clinical and biochemical parameters of the patients are outlined in Table 2. As reflected by the score on the CGI-S the study group was 'moderately to markedly ill' (score 4.4). Concerning treatment efficacy, a mean reduction of 20% ($p < 0.001$) on the PANSS total score was noted, corresponding with the generally used definition of 'response'. Reductions on PANSS positive, negative and global scores were 24%, 14% and 18%, respectively (all $p < 0.001$). On the CGI-S, a mean reduction of 23% was noticed.

The mean serum levels of BDNF and S100B were significantly lower as compared with controls (BDNF: 20.3 ± 6.6 versus 24.4 ± 6.7 μg/l, $p \leq 0.001$; S100B: 0.063 ± 0.032 versus 0.069 ± 0.029 μg/l, $p < 0.05$). With respect to BDNF, mean age of the patients was higher compared with control subjects (36.7 ± 11.7 and 27.5 ± 6.8 years, $p < 0.001$). However, this age difference did not result in differences in serum BDNF levels, as there was no correlation between age and BDNF levels in the study sample at both time points (the non-parametric Kendall's τ-test showed *p*-values of 0.143 and 0.323, respectively). Moreover, the laboratory involved found no correlation between age and BDNF levels in healthy subjects ($n = 75$, $p = 0.908$). Serum levels of BDNF and S100B did not change significantly during 6 weeks of treatment with antipsychotics.

Possible confounding factors

Since several factors could possibly influence serum levels of neurotrophic proteins, data were scrutinized for effects of smoking, body mass index, abuse of soft or hard drugs, medication status (naïve, free >2 weeks or medicated), antipsychotic class (first- or second-generation agent), co-medication (antidepressants or mood stabilizers), diagnostic category (schizophrenia or non-schizophrenic psychoses), gender and age.

https://doi.org/10.1017/neu.2013.59 Published online by Cambridge University Press

Table 1. Patient characteristics at baseline ($n = 58$)

Gender (male/female)	38/20 (66%/34%)
Age (mean ± SD)	36.7 ± 11.7 years
Age at first psychosis (years) (mean ± SD)	28.5 ± 11.1
Duration of psychotic illness (years) (mean ± SD)	8.1 ± 8.4
Diagnosis (DSM-IV)	Schizophrenia ($n = 33$)
	Schizoaffective disorder ($n = 2$)
	Brief psychotic disorder ($n = 8$)
	Bipolar disorder ($n = 7$)*
	Psychotic disorder NOS ($n = 6$)
	Delusional disorder ($n = 1$)
	Schizotypal personality disorder ($n = 1$)
Smoking (yes/no)	38/20 (66%/34%)
Hard drugs in month before study entry (yes/no)	2/56 (3%/97%)
Soft drugs in month before study entry (yes/no)	10/48 (17%/83%)
Medication status at study entry	Naïve ($n = 10$)
	Free >2 weeks ($n = 8$)
	Using medication ($n = 40$)
Medication used at study entry	1 AP ($n = 15$)
	1 MS ($n = 5$)
	2 AP ($n = 6$)
	AP + AD ($n = 6$)
	AP + MS + AD ($n = 2$)
	AP + MS ($n = 2$)
	2 AP+AD ($n = 2$)

AD, antidepressant (any); AP, antipsychotic agent (any); MS, mood stabilizer (any).
*Manic episode with psychotic features.

Table 2. Clinical and biochemical parameters of the patients at baseline and after 6 weeks of treatment ($n = 58$)

Assessment method	Baseline	6 weeks
PANSS total score (range)	84.9 (46–138)	68.4 (33–108)*
Positive subscale	22.7 (11–37)	16.6 (7–32)*
Negative subscale	19.8 (7–40)	17.1 (7–29)*
Global subscale	42.3 (22–67)	34.7 (18–57)*
Mean CGI-Severity (range)	4.4 (2–7)	3.4 (1–6)*
Serum BDNF (mean ± SD)	20.3 ± 6.6 μg/l	19.6 ± 6.7 μg/l
Serum S100B (mean ± SD)	0.063 ± 0.032 μg/l	0.062 ± 0.032 μg/l

BDNF, Brain-derived neurotrophic factor; CGI, Clinical Global Impression; PANSS, Positive and Negative Syndrome Scale.
*Difference significant versus baseline (all $p < 0.001$).

Baseline BDNF levels were significantly lower in medication naïve patients as compared with medication-free and medicated patients (15.4 ± 6.6, 20.6 ± 5.6 and 21.5 ± 6.5 μg/l, respectively, $p = 0.022$). In addition, serum levels of S100B were positively correlated with age at both time points (Kendall's τ 0.197 and 0.212, respectively, $p < 0.05$). Moreover, patients who had used soft drugs before study entry ($n = 10$) had significantly lower levels of S100B after 6 weeks of treatment (0.067 ± 0.033 vs. 0.042 ± 0.015). Finally, neither of the other parameters, especially gender, diagnostic category and co-medication, were found to have any influence on serum levels of either neurotrophic protein. For all analyses of BDNF and S100B values, medication status, respectively, age and use of soft drugs, were used as covariates.

Sample division according to baseline biochemical parameters

No correlations were established between BDNF and S100B levels on one hand and PANSS scores on the other hand at both time points in the total patient sample (Kendall's τ, all $p > 0.05$). In order to detect possible differences in symptom profile or symptomatic improvement between patients with high and low levels of neurotrophic proteins, the sample was divided into three subgroups [lowest quarter (L-BDNF/S100B), highest quarter (H-BDNF/S100B), and middle group (M-BDNF/S100B)]. After analysis, all factors that might influence PANSS scores (see: possible confounding factors) appeared to be equally distributed between the BDNF and S100B subgroups demonstrating that they could not have influenced any of the outcome measures. At baseline, mean levels of BDNF and S100B varied significantly from each other. All differences remained significant during the study period [BDNF: 12.9 ± 2.3 (at baseline) and 12.8 ± 4.9 (after treatment) (L: $n = 14$), 19.4 ± 2.5 and 19.9 ± 4.6 (M: $n = 30$), 29.7 ± 4.1 and 25.5 ± 6.3 μg/L (H: $n = 14$); S100B: 0.034 ± 0.005 and 0.044 ± 0.011 (L: $n = 14$), 0.054 ± 0.009 and 0.058 ± 0.025 (M: $n = 29$), 0.107 ± 0.030 and 0.088 ± 0.041 μg/L (H: $n = 15$), all $p \leq 0.001$].

https://doi.org/10.1017/neu.2013.59 Published online by Cambridge University Press

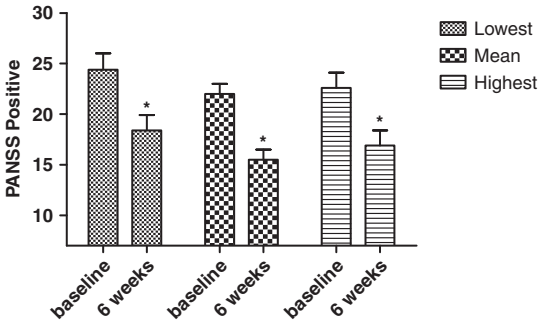

Fig. 1. PANSS positive scores at baseline and after 6 weeks of treatment of the low ($n = 14$), middle ($n = 29$) and high ($n = 15$) subgroups, according to their baseline serum levels of S100B. Between-group differences: univariate analysis of variance, corrected for age and soft drugs, baseline $p = 0.003$, 6 weeks $p = 0.001$. *Within-group differences: paired t-test, all $p \leq 0.001$. PANSS, Positive and Negative Syndrome Scale.

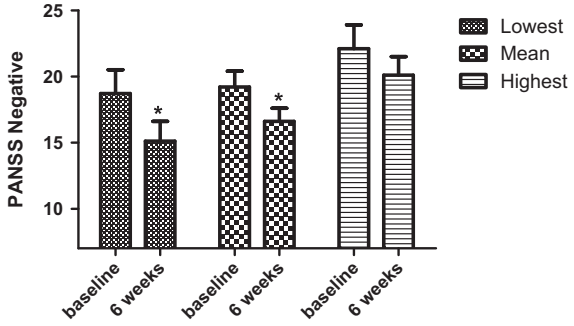

Fig. 2. PANSS negative scores at baseline and after 6 weeks of treatment of the low ($n = 14$), middle ($n = 29$) and high ($n = 15$) subgroups, according to their baseline serum levels of S100B. Between-group differences: univariate analysis of variance, corrected for age and soft drugs, baseline $p = 0.011$, 6 weeks $p = 0.009$. *Within-group differences: paired t-test, $p \leq 0.006$ in L- and M-S100B, H-S100B $p = 0.347$. PANSS, Positive and Negative Syndrome Scale.

As to BDNF levels, no differences concerning psychopathological profile, symptom severity and symptomatic improvement were found between the three subgroups.

As compared with M-S100B, PANSS scores in H-S100B and L-S100B were significantly higher at baseline ($p = 0.003$; data not shown). After 6 weeks of treatment, L-, M- and H-S100B subgroups showed a significant decrease on the various PANSS scores, except for the score on the PANSS negative subscale in H-S100B ($p = 0.347$). Thus, negative symptoms did not improve in the subgroup with high baseline S100B levels. As can be seen in Figs. 1 and 2, in the L-S100B subgroup, the reduction in positive symptoms was less pronounced as compared with the H- and M-subgroups, reflected by a significantly higher mean PANSS positive score in the L-S100B subgroup after 6 weeks (between-group differences $p = 0.001$). In contrast, as could be expected, mean PANSS negative score after 6 weeks was significantly higher in the H-S100B subgroup (between-group differences $p = 0.009$).

Discussion

In the present study, serum levels of the neurotrophic proteins BDNF and S100B were measured in a group of patients with psychotic disorders before and after 6 weeks of treatment with antipsychotics. It was found that levels of BDNF are lowered in patients with an acute psychotic episode irrespective of diagnostic category, psychopathological profile or treatment effectiveness. Furthermore, no effects were found for age or gender.

Interestingly, reduction of positive symptoms was less pronounced in patients with a relatively low S100B level, whereas virtually no effect of treatment on negative symptoms was found in patients with a relatively high S100B level. The observation of lower serum levels of BDNF is in agreement with the findings by several other investigators (15,17,20,21) and supports the hypothesis that psychotic disorders, of which schizophrenia is most widespread, may be considered as neurodevelopmental disorders indeed. Comparable observations have been made in patients with uni- and bipolar affective disorders (18,34,35). These observations indicate that BDNF may have pathophysiological implications across diagnostic boundaries. With respect to the effect of psychotropics on BDNF levels, equivocal results have been reported (15,22,36).

Nearly all literature mentions enhanced serum levels of S100B in schizophrenia (25,27,37). The present observation of subnormal S100B concentrations can therefore not easily be explained. This finding should be considered cautiously, especially as the difference between patients and controls was present at baseline only and the size of the study sample was modest. However, as S100B has neurotoxic as well as neurotrophic effects, it could be that this lower S100B level at baseline reflects deficiencies in neuroprotective mechanisms.

Comparable considerations have to be taken into account for the observation that, in this study, more severe positive psychotic symptoms are associated with lower S100B levels. It could be speculated that subnormal levels of this neurotrophic protein might initially induce positive symptoms while during the course of disease S100B levels might raise, resulting in the development of negative symptoms due to a neurotoxic effect of the higher S100B levels in the brain.

The present observation that severity of negative psychotic symptoms is associated with higher S100B

https://doi.org/10.1017/neu.2013.59 Published online by Cambridge University Press

levels is in agreement with other reports (26,28,29) and is suggestive for either a neurotoxic effect or a compensatory mechanism for damage already done. It should be stressed, however, that the H-S100B subgroup consisted of 15 patients only.

Although all potentially confounding factors have been included in the analyses (14), interpretation of the here presented data has still to be done carefully as the study comprised a relatively small sample size with many differences between individual patients. The sample size, however, can be considered moderate when compared with other studies on BDNF or S100B, with study numbers varying between 18 and 88 patients with respect to BDNF (16,19) and 12 and 98 patients with respect to S100B (14,26).

Given the diagnostic uncertainties in psychiatry in general (38,39), instead of focusing on a particular category of psychoses (e.g. DSM-IV schizophrenia), the here chosen approach of including psychotic disorders irrespective of their classification may disclose a psychopathological phenotype that is associated with the functional status of one of the investigated neurotrophic proteins. This, in turn, may have consequences for either treatment or course of disease. It is therefore suggested that studies on pathophysiological determinants, for example, neurotrophic proteins, of major psychiatric diseases like psychoses and affective disorders, should preferably follow a so-called dimensional approach searching for endophenotypes (40–42).

In conclusion, this study, for the first time, demonstrates that patients with a relatively low serum level of S100B show less reduction in severity of positive psychotic symptoms after treatment with antipsychotics, whereas those with a relatively high S100B level hardly show any improvement of negative symptoms. Further studies are warranted to elucidate the pathophysiological significance and potential clinical implications of these observations.

Acknowledgements

The authors indebted to A.E.S. Sijben, MSc, PhD from ABC/Opes for statistical analyses and to Mrs A. Voskuilen-Kooijman from the Neuropsychiatric Laboratory of the Erasmus Medical Centre for biochemical analyses.

Authors' Contributions

W. Verhoeven designed the study and wrote the protocol. N. van de Kerkhof performed all clinical assessments. D. Fekkes was responsible for biochemical analyses. F. van der Heijden contributed to subsequent versions of the paper. All authors contributed to the clinical study and approved of the final version of the manuscript.

Financial Support

None.

Statement of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

1. Van Haren NEM, Cahn W, Pol HEH, Kahn RS. Schizophrenia as a progressive brain disease. Eur Psychiatry 2008a;**23**:245–254.
2. Owen MJ, O'Donovan MC, Thapar A, Craddock N. Neurodevelopmental hypothesis of schizophrenia. Br J Psychiatry 2011;**198**:173–175.
3. Gogtay N, Giedd JN, Lusk L et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci USA 2004;**101**:8174–8179.
4. Shaw P, Kabani NJ, Lerch JP et al. Neurodevelopmental trajectories of the human cerebral cortex. J Neurosci 2008;**28**:3586–3594.
5. Arango C, Moreno C, Martínez S et al. Longitudinal brain changes in early-onset psychosis. Schizophr Bull 2008;**34**:341–353.
6. Van Haren NEM, Hulshoff Pol HE, Schnack HG et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol Psychiatry 2008b;**63**:106–113.
7. McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry 2000;**57**:637–648.
8. Durany N, Thome J. Neurotrophic factors and the pathophysiology of schizophrenic psychoses. Eur Psychiatry 2004;**19**:326–337.
9. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood–brain barrier. Neuropharmacology 1998;**37**: 1553–1561.
10. Marchi N, Cavaglia M, Fazio V, Bhudia S, Hallene K, Janigro D. Peripheral markers of blood–brain barrier damage. Clin Chim Acta 2004;**342**:1–12.
11. Karege F, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci Lett 2002;**328**:261–264.
12. Pillai A, Kale A, Joshi S et al. Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. Int J Neuropsychopharmacol 2010;**13**:535–539.
13. Rothermundt M, Falkai P, Ponath G et al. Glial cell dysfunction in schizophrenia indicated by increased S100B in the CSF. Mol Psychiatry 2004a;**9**:897–899.

14. Steiner J, Bogerts B, Schroeter ML, Bernstein H. S100B protein in neurodegenerative disorders. Clin Chem LabMed 2011;**49**:409–424.
15. Pirildar Ş, Gönül AS, Taneli F, Akdeniz F. Low serum levels of brain-derived neurotrophic factor in patients with schizophrenia do not elevate after antipsychotic treatment. Prog Neuro-Psychopharmacol Biol Psychiatry 2004;**28**: 709–713.
16. Twiss JL, Chang JH, Schanen NC. Pathophysiological mechanisms for actions of the neurotrophins. Brain Pathol 2006;**16**:320–332.
17. Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry 2011;**16**:960–972.
18. Buckley PF, Pillai A, Howell KR. Brain-derived neurotrophic factor: findings in schizophrenia. Curr Opin Psychiatry 2011;**24**:122–127.
19. Chen DC, Wang J, Wang B et al. Decreased levels of serum brain-derived neurotrophic factor in drug-naïve first-episode schizophrenia: relationship to clinical phenotypes. Psychopharmacology 2009;**207**:375–380.
20. Jindal RD, Pillai AK, Mahadik SP, Eklund K, Montrose DM, Keshavan MS. Decreased BDNF in patients with antipsychotic naïve first episode schizophrenia. Schizophr Res 2010;**119**:47–51.
21. Toyooka K, Asama K, Watanabe Y et al. Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. Psychiatry Res 2002;**110**:249–257.
22. Pedrini M, Chendo I, Grande I et al. Serum brain-derived neurotrophic factor and clozapine daily dose in patients with schizophrenia: a positive correlation. Neurosci Lett 2011;**491**:207–210.
23. Schäfer BW, Heizmann CW. The S100 family of EF-hand calcium-binding proteins: functions and pathology. Trends Biochem Sci 1996;**21**:134–140.
24. Donato R. S100: a multigenic family of calcium-modulated proteins of the EF-hand type with intracellular and extracellular functional roles. Int J Biochem Cell Biol 2001;**33**:637–668.
25. Lara DR, Gama CS, Belmonte-de-Abreu P et al. Increased serum S100B protein in schizophrenia: a study in medication-free patients. J Psychiatr Res 2001;**35**:11–14.
26. Rothermundt M, Ponath G, Glaser T, Hetzel G, Arolt V. S100B serum levels and long-term improvement of negative symptoms in patients with schizophrenia. Neuro-psychopharmacology 2004b;**29**:1004–1011.
27. Rothermundt M, Ahn JN, Jörgens S. S100B in schizophrenia: an update. Gen Physiol Biophys 2009;**28** :F76–F81.
28. Ling S, Tang Y, Jiang F et al. Plasma S-100B protein in Chinese patients with schizophrenia: comparison with healthy controls and effect of antipsychotics treatment. J Psychiatr Res 2007;**41**:36–42.
29. Sarandol A, Kirli S, Akkaya C, Altin A, Demirci M, Sarandol E. Oxidative-antioxidative systems and their relation with serum S100 B levels in patients with schizophrenia: effects of short term antipsychotic treatment. Prog Neuro-Psychopharmacol Biol Psychiatry 2007;**31**:1164–1169.
30. Pedersen A, Diedrich M, Kaestner F et al. Memory impairment correlates with increased S100B serum concentrations in patients with chronic schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry 2008;**32**: 1789–1792.
31. Andreasen NC, Flaum MC, Arndt S. The comprehensive assessment of symptoms and history (CASH): an instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 1992;**49**:615–623.
32. Kay SR, Fiszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;**13**:261–276.
33. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. Bethesda: National Institute of Mental Health, 1976.
34. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. J Psychiatr Res 2007;**41**:979–990.
35. Schroeter ML, Steiner J. Elevated serum levels of the glial marker protein S100B are not specific for schizophrenia or mood disorders. Mol Psychiatry 2009;**14**:235–236.
36. González-Pinto A, Mosquera F, Palomino A et al. Increase in brain-derived neurotrophic factor in first episode psychotic patients after treatment with atypical antipsychotics. Int Clin Psychopharmacol 2010;**25**:241–245.
37. Qi LY, Xiu MH, Chen DC et al. Increased serum S100B levels in chronic schizophrenic patients on long-term clozapine or typical antipsychotics. Neurosci Lett 2009;**462**:113–117.
38. Nasrallah H, Tandon R, Keshavan M. Beyond the facts in schizophrenia: closing the gaps in diagnosis, pathophysiology, and treatment. Epidemiol Psychiatr Sci 2011;**20**:317–327.
39. Bromet EJ, Kotov R, Fochtmann LJ et al. Diagnostic shifts during the decade following first admission for psychosis. Am J Psychiatry 2011;**168**:1186–1194.
40. Verhoeven WMA, Tuinier S, Van der Burgt I. Top-down or bottom-up: contrasting perspectives on psychiatric diagnoses. Biologics 2008;**2**:409–417.
41. Van Os J, Kapur S. Schizophrenia. Lancet 2009;**374**: 635–645.
42. Linscott RJ, Van Os J. Systematic reviews of categorical versus continuum models in psychosis: evidence for discontinuous subpopulations underlying a psychometric continuum. Implications for DSM-V, DSM-VI, and DSM-VII. Annu Rev Clin Psychol 2010;**6**:391–419.

https://doi.org/10.1017/neu.2013.59 Published online by Cambridge University Press