Plasma and serum brain derived neurotrophic factor (BDNF) levels and their association with neurocognition in at-risk mental state, first episode psychosis and chronic schizophrenia patients

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Abstract

Background: Brain derived neurotrophic factor (BDNF) is involved in numerous cognitive processes. Since cognitive deficits are a core feature of psychotic disorders, the investigation of BDNF levels in psychosis and their correlation with cognition has received increased attention. However, there are no studies investigating BDNF levels in individuals with an at-risk mental state (ARMS) for psychosis. Hence, the aims of the present study were: (1) assessing peripheral BDNF levels across different (potential) stages of psychosis; (2) investigating their association with cognition.

Method: Plasma and serum BDNF levels and neuropsychological performance were assessed in 16 ARMS, 6 first-episode psychosis (FEP), and 11 chronic-schizophrenia (CS) patients. Neuropsychological assessment covered intelligence, verbal memory, working memory, attention and executive functioning.

Results: Both plasma and serum BDNF levels were highest in CS, intermediate in FEP and lowest in ARMS. Multiple regression analysis revealed a significant positive association of plasma BDNF levels with planning ability across all groups.

Conclusion: The lower peripheral BDNF levels in ARMS compared to FEP and CS might point towards an important drop of this neurotrophin prior to the onset of frank psychosis. The associations of peripheral BDNF with planning-abilities match previous findings.

Key words:

BDNF – psychosis – blood – prodromal – neuropsychology

1. Introduction

The presence of cognitive deficits is a consistent finding in patients with psychotic disorders. These apply to most cognitive domains including working memory, verbal memory, executive function, attention, speed of information processing and visuo-spatial abilities (Fusar-Poli et al. 2012; Bora and Murray 2014; Hauser et al. 2017), and are considered to be a core feature of these disorders (Szoke et al. 2008).

Long-term (Agnew-Blais et al. 2015) and cross-sectional studies (Bora et al. 2014) have shown that cognitive impairments are present long before the onset of overt psychotic symptoms (Riecher-Rössler et al. 2009; Mollon and Reichenberg 2017). However, they do not appear to progress after the transition to full-blown psychosis or during the further course of the illness (Szoke et al. 2008; Bozikas and Andreou 2011; Irani et al. 2011; Bora and Murray 2014; Bora et al. 2017). Moreover, among subjects identified as having an at-risk mental state for psychosis (ARMS), those with a later transition exhibit more pronounced neurocognitive deficits than those who will not go on to develop a psychotic disorder (Studerus et al. 2016; Riecher-Rössler and Studerus 2017). However, despite their obvious significance for psychosis prediction as well as their importance for functional outcome, the neurobiological underpinnings behind the observed impairments remain largely unknown (Ruiz de Azua et al. 2013).

Over the last years, the role of brain-derived neurotrophic factor (BDNF) in cognitive impairments in patients with psychosis has become a focus of interest. BDNF is the most common neurotrophin in the human brain and is involved in the synthesis, differentiation, maintenance, and survival of neurons, both in the central and in the peripheral nervous system (Kuipers and Bramham 2006). Its role in learning and memory has previously been supported by animal (Yamada and Nabeshima 2003; Bekinschtein et al. 2008) as well as human studies (for a review see Carlino et al. 2013). In line with these observations, BDNF is highly

expressed in hippocampal and prefrontal cortical areas which are crucial for these cognitive processes (Conner et al. 1997; Bekinschtein et al. 2008).

BDNF is also found in the peripheral nervous system and can be assessed in blood serum and plasma. Although the exact source of the peripheral BDNF is not yet completely understood, animal studies have shown that BDNF can cross the blood-brain barrier (Pan et al. 1998). Furthermore, several animal studies have reported positive correlations between serum BDNF and BDNF in both the prefrontal cortex and hippocampus (Karege et al. 2002; Sartorius et al. 2009; Elfving et al. 2010), suggesting there might be a link between peripheral and central BDNF. Moreover, Klein and coworkers (2011) reported that blood BDNF concentration reflects brain-tissue BDNF level even across species.

Also, in patients suffering from psychotic disorders altered BDNF levels were found. Post-mortem studies in patients with schizophrenia point towards decreased cortical BDNF levels, especially in memory related brain areas such as the hippocampus (Durany et al. 2001; Weickert et al. 2003).

Peripheral BDNF levels have also been investigated in patients with psychosis. In drug-naïve FEP patients, serum BDNF levels have also been reported to positively correlate with BDNF levels measured in the cerebrospinal fluid (Pillai et al. 2010). Based on these findings, BDNF blood levels are widely used in research as correlates of cortical BDNF. However, so far there is no consensus whether plasma or serum BDNF levels are more suitable correlates of cortical BDNF levels. While some authors have suggested to use serum as it might provide a more reliable measurement (Tsuchimine et al. 2014), others have argued in favour of plasma as it might better reflect processes in the central nervous system (Fernandes et al. 2014).

In patients with psychotic disorders, recent reviews and meta-analyses point towards reduced peripheral BDNF levels with peripheral levels being already decreased in FEP patients and further declining in chronic and accordingly older patients (Buckley et al. 2011; Green et al. 2011; Martinotti et al. 2012; Fernandes et al. 2014; Toll and Mane 2015).

Until now, several studies have investigated the association between cognitive impairments and BDNF in patients with psychosis. The findings of these studies (summarized in Supplementary Table 1S) are inconsistent regarding the link of peripheral BDNF levels to cognition. The majority of these studies point towards a positive association of certain cognitive functions with peripheral BDNF levels (Carlino et al. 2011; Niitsu et al. 2011; Zhang XY, Chen da, et al. 2012; Zhang XY, Liang, et al. 2012; Asevedo et al. 2013; Ruiz de Azua et al. 2013; Hori et al. 2016; Sun et al. 2016; Hori et al. 2017; Zhang Y et al. 2018). However, other studies found mixed results, i.e., positive and negative associations depending on the cognitive domain (Niitsu et al. 2014; Xiao et al. 2017). Lastly, other research groups did not find any association between these two parameters. A recent meta-analysis concluded that there is a small but significant positive association of peripheral BDNF with reasoning and problem-solving, and with overall cognitive capacity in patients with schizophrenia (Ahmed et al. 2015).

Despite the strong interest in the prodromal phase of psychosis and the above described observed onset of cognitive deficits prior to transition to frank psychosis, no study has investigated peripheral BDNF levels in an ARMS sample yet. Therefore, we aimed (1) to investigate plasma and serum BDNF levels across different (potential) stages of psychosis, including for the first-time ARMS as well as FEP and CS patients, and (2) to examine the association of BDNF with neurocognitive performance in these patient groups.

Based on the above described literature, the following hypotheses were formulated: (1) Both plasma and serum BDNF are highest in ARMS, intermediate in FEP, and lowest in CS; (2) higher BDNF levels are associated with better cognitive performance in all patient groups.

2. Methods

2.1. Recruitment and setting

FEP and ARMS patients were recruited via the Früherkennung von Psychosen project (**FePsy**; English: early detection of psychosis) within the University of Basel Psychiatric Hospital (UPK), Switzerland. ARMS and FEP criteria were assessed using the Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al. 2008) which is based on the PACE criteria (Yung et al. 1998) and includes parts of the Brief Psychiatric Rating Scale (BPRS, expanded version by Lukoff et al., (1986); Ventura et al., (1993)). A detailed description of the FePsy study design can be found elsewhere (Riecher-Rössler et al. 2007; Riecher-Rössler et al. 2009). Individuals were classified as being in an ARMS if they met one of the following inclusion criteria: (1) attenuated or brief limited psychotic symptoms according to the criteria by Yung et al. (1998); (2) familial aggregation of psychotic disorders in combination with at least 2 further risk factors according to screening instrument in line with the criteria by Yung et al. (1998); (3) a minimal amount and combination of certain risk factors according to screening instrument by Riecher-Rössler et al. (2007). FEP patients had to fulfil the transition criteria of Yung et al. (1998), namely one of the following symptoms: Suspiciousness (BPRS $\geq$5); Unusual thought content (BPRS $\geq$5); Hallucinations (BPRS $\geq$4); or Conceptual disorganisation (BPRS $\geq$5), with the symptom occurring at least several times a week and being present for more than one week. Exclusion criteria were age < 18 years, insufficient knowledge of German, IQ < 70, previous psychotic episode, antipsychotic medication exceeding a cumulative chlorpromazine equivalent (CPE) dose of 2500 mg (according to Gardner et al. (2010) and (Leucht et al. 2014)), psychosis clearly due to organic brain diseases or substance use, or psychotic symptomatology within a clearly diagnosed affective psychosis or borderline personality disorder.

CS patients were recruited in the forensic department of the UPK and had a diagnosis of schizophrenia, paranoid type according to ICD-10 criteria (International Statistical Classification of Diseases and Related Health Problems; World Health Organization et al. 1994). There were no restrictions regarding comorbidities or medication in this group.

Only male participants were included in the present study, as BDNF levels can vary between the sexes and fluctuate along the menstrual cycle (Begliuomini et al. 2007). Additionally, nicotine use was measured in cigarettes per day, as nicotine has previously been found to be associated with higher BDNF levels in clinical and non-clinical populations (Bhang et al. 2010; Zhang XY et al. 2010). All participants gave their written informed consent. The study was approved by the committee of North-West and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz (EKNZ)) and was carried out in accordance with the declaration of Helsinki.

2.2. BDNF measures

Peripheral BDNF is mainly stored in blood platelets, while a small part circulates freely. Therefore, we assessed total soluble BDNF in serum, which includes BDNF released from platelets through clotting, in addition to plasma BDNF levels. For the assessment of BDNF levels, a blood sample was drawn between 7 and 9 am after overnight fasting according to a standardized protocol, using serum vacutainer tubes (Becton Dickinson) or citrate vacutainer tubes (Becton Dickinson). For serum sampling, the tube was inverted 5-6 times gently and allowed to stand for 60 min at room temperature. Subsequently, it was centrifuged at 1300xg for 10 minutes. Regarding plasma BDNF, poor-platelet-plasma was carefully prepared from blood centrifuged at 2000xg for 10 min. All samples were stored in aliquots at −80°C before assaying BDNF content. Serum and plasma BDNF levels were assessed with an enzyme-linked immunosorbent assay (ELISA) kit (Promega BDNF Emax®, Madison, WI, United States). Serum samples were appropriately diluted (between 1:100-1:150), while plasma samples were used undiluted, and detection of BDNF was carried out in an antibody sandwich format as described in the manufacturer's protocol. The absorbance was measured within 30 min in a microplate reader set at 450 nm and a correction wavelength set to 690 nm, to

determine BDNF concentrations according to the standard curve. All assays were carried out in duplicate and means were calculated.

2.3. Neuropsychological assessment

The following measures were used to cover the cognitive domains of interest:

- Verbal and non-verbal intelligence: Mehrfachwahl-Wortschatz Test (MWT-A; Lehrl 1977) and Leistungsprüfsystem, scale 3 (LPS-3; Horn 1983), respectively

- Verbal learning and memory: California Verbal Learning Test (CVLT; Delis et al. 1987)

- Working memory: 2-back test of the Test of Attentional Performance (TAP; Zimmermann and Fimm 1993).

- Executive functioning: computerized version of the Tower of Hanoi (ToH; Gedika and Schöttke 2001) and Go/No-Go task of the TAP (Zimmermann and Fimm 1993)

- Sustained attention: computerized version of the Continuous Performance Test (CPT-OX; Rosvold et al. 1956).

2.4. Statistical analyses

BDNF values were tested for normality and plasma levels were log-transformed to achieve a normal distribution. In all subsequently described analyses, the log-transformed plasma values were used. BDNF levels were compared between the patient groups (i.e., ARMS, FEP, and CS) using a one-way ANOVA, with Bonferroni-corrected post-hoc pairwise comparisons. Due to the small sample size, bootstrapping was performed to provide more robust estimates. Subsequently, an ANCOVA was carried out including age, CPE and cigarettes per day as possible confounding factors. In case of no antipsychotic or nicotine use, a value of 0 was used to include these participants in the analysis.

A global neuropsychology score comprising all tested domains was created. Furthermore, composite scores for each test of the neuropsychological battery were created. Variables for which high values indicated worse performance (e.g., reaction times) were inverted prior to the z-transformation, so that high values always indicated good performance. The test specific composite scores were the averages of the z-transformed performance scores of each test. The global cognitive performance score was the average over all z-transformed performance scores. This procedure was used to reduce the number of tests and hence to reduce the risk of false positive results due to multiple testing. A description of this procedure can also be found in a previous publication of our research group (Rapp et al. 2013). An overview of the test variables used to create the composite scores can be found in the appendix (Supplementary Table 2S).

The composite scores were compared between patient groups using a one-way ANOVA, with Bonferroni-corrected post-hoc comparisons. Again, bootstrapping was performed due to the small sample size. A second group comparison was carried out using an ANCOVA including age and CPE as possible confounding factors.

A Bonferroni-corrected multiple linear regression analysis was performed to assess the associations of group, age, years of education, CPE, and the two BDNF measures with each neuropsychological composite score.

Statistical significance was set at alpha $\leq$ .05. All analyses were carried out using IBM SPSS Statistics Version 24 running on Windows 7 Enterprise.

3. Results

3.1.   Sample characteristics

A total of 33 participants were included in this study: 16 ARMS, 6 FEP and 11 CS patients. The CS sample was significantly older than the two other groups and received higher antipsychotic dosages (see Table 1). Nicotine use, measured in cigarettes per day, differed

significantly between groups, being highest in CS, intermediate in FEP and lowest in ARMS individuals. There were no significant group differences regarding years of education.

-Insert Table 1 about here-

3.2. BDNF

A significant main effect of group was found for both plasma and serum BDNF levels (Table 2 and Figure 1). Post-hoc pairwise comparisons revealed that serum BDNF was significantly lower in ARMS as compared to both other groups (FEP $p=.033$; CS $p<.001$), while plasma BDNF differed at a significant level only between the ARMS and CS group ($p<.001$), again with lower values in the ARMS group. Plasma BDNF levels differed at a trend level between CS and FEP patients ($p=.089$), being lower in FEP.

After controlling for age, CPE and cigarettes per day use, serum BDNF values still differed significantly between the groups, while the main effect for plasma levels was only significant at a trend level (see Table 2). None of the included covariates had a significant effect on BDNF parameters.

-Insert Table 2 about here-
-Insert Figure 1 about here-

3.3. Neuropsychology

The unadjusted group comparison of the neuropsychological composite scores revealed significant differences for the following tests: TAP Go/No-Go and the CVLT (see Table 3). Post-hoc pairwise comparisons indicated that the differences in Go/No-Go performance were due to poorer performance of the FEP group as compared to the other groups (ARMS $p=.004$;

CS p=.003). The CS group performed worse in the CVLT than the other groups (ARMS p=.007; FEP p=.058).

After including age as covariate, only the main effect for the TAP Go/No-Go remained significant (p=.003).

-Insert Table 3 about here-

3.4. Multiple Regression

The results of the multiple regressions can be found in Table 4. There was a significant positive association between plasma BDNF and ToH performance (p=.015) and trend-wise significant positive association between plasma BDNF and global cognitive performance (p=.071).

-Insert Table 4 about here-

4. Discussion

In this cross-sectional study we found that plasma and serum BDNF levels differed between ARMS, FEP and CS patients, with the highest levels being evident in CS and the lowest in ARMS patients. Moreover, higher plasma BDNF levels were significantly associated with better ToH performance and at a trend-level with a better global cognitive performance score. The observed pattern regarding peripheral BDNF levels contradicts the existing literature (Green et al. 2011; Martinotti et al. 2012) as well as our hypothesis of higher BDNF levels in ARMS and a decrease over the course of illness. In the present study, serum BDNF levels were significantly lower in ARMS patients compared to both other groups, but did not differ between FEP and CS patients. Plasma levels were only significantly lower in ARMS compared to CS patients. Unfortunately, we were not able to differentiate further between

those ARMS patients who transitioned to psychosis and those who did not; therefore, it is not possible to interpret the observed pattern regarding transition to psychosis and hence the presence of a true prodromal state. Based on the present findings it might be speculated that the low peripheral BDNF levels in ARMS patients are associated with the clinical observation of a drop in functioning prior to the onset of frank psychosis, including poorer cognitive performance which occurs already in the pre-psychotic phase (Riecher-Rössler et al. 2009; Bora and Murray 2014). This might imply that the low BDNF levels in ARMS point towards pathological processes preceding the actual transition to psychosis. It might be possible that during the course of the illness and possibly due to the (pharmacological) treatment of psychotic disorders, BDNF levels normalize while cognitive deficits persist, as the latter have been suggested by meta-analyses of longitudinal studies (Irani et al. 2011; Bora and Murray 2014). However, as this is the first study to investigate peripheral BDNF levels in ARMS individuals, more research is needed before any firm conclusions can be drawn.

The factors leading to altered BDNF levels in patients with psychotic disorders are still under debate. A recent review by Martinotti et al. (2012) revealed higher peripheral BDNF levels in patients suffering from paranoid psychosis compared to other psychotic subtypes. As the CS sample in the present study consisted only of patients with such a diagnosis, the higher plasma and serum BDNF levels in the CS group might partly be related to this factor. The restriction to the paranoid type in our study was made to reduce the variability in this patient group and to avoid a potential symptomatic overlap between depressive symptoms and negative symptoms, the latter being more present in other types of schizophrenia, since peripheral BDNF levels are also altered in patients with depression (Molendijk et al. 2014).

Contrary to previous studies (Zhang XY et al. 2010; Green et al. 2011) that reported an influence of age and nicotine on BDNF levels, these factors were not found to influence BDNF in the present study. Regarding medication, the observed lack of effect on BDNF levels in our study is in line with the meta-analysis of Green et al. (2011). However, in the

more recent meta-analysis of Fernandes et al. (2014) the authors found an increase of BDNF in plasma but not in serum after antipsychotic medication, independent of the patient's response to the treatment. In our study, the inclusion of CPE reduced the significance to a trend level in plasma but not in serum. It might be speculated that plasma levels react more sensitively to antipsychotic treatment, but clearly more research is needed before any firm conclusions can be drawn. It should however be mentioned that it is still possible that these factors do influence BDNF levels and the present sample was too small to detect this association. We can therefore not completely rule out the possibility that the unexpectedly higher BDNF levels in the CS group compared to ARMS and FEP patients was influenced by the higher medication dosage and longer medication intake with a larger cumulative medication dose in the chronic patients.

Plasma BDNF levels were significantly and positively associated with ToH performance and at a trend-level with global cognitive performance, which is in line with our hypothesis and with most previous reports investigating the association of peripheral BDNF levels with neurocognitive performances. A recent meta-analysis (Ahmed et al. 2015) also indicated a positive association of peripheral BDNF levels with neurocognition in patients with schizophrenia. In the meta-analysis, higher BDNF levels were associated with better performance in reasoning/problem solving and with overall performance across all neurocognitive measures. However, the authors suggested that the association with combined neurocognitive measures was driven by the positive association of BDNF levels with reasoning/problem solving. A similar pattern could also underlie the present results.

Due to its exploratory character, the present study suffers from certain limitations. First, the small sample size limits statistical power, which might have impeded the detection of group differences, and prevented further subgroup analyses. Second, no healthy control or clinical control groups were included. Therefore, the specificity of the results for psychosis cannot be clarified, especially as altered BDNF levels have also been found in other psychiatric

disorders such as depression, bipolar disorder and anorexia (for a review see Cattaneo et al. 2016). Furthermore, BDNF levels in healthy control groups vary considerably across studies due to methodological differences (Green et al. 2011), so that the present BDNF levels cannot be compared to previous reports. Third, many factors that are known to affect BDNF levels, such as antidepressant medication (Polyakova et al. 2015), sleep deprivation (Guzman-Marin et al. 2006), stress (Giese et al. 2013), body weight (Pillai et al. 2012), drug consumption (D'Souza et al. 2009), or physical exercise (Dinoff et al. 2017) were not assessed in the present study. However, we tried to account for the most important confounding factors, namely age, years of education, nicotine use and antipsychotics. Fourth, the cross-sectional design limits the interpretability of the findings. Longitudinal studies are warranted to investigate the time course of BDNF levels across different stages of psychosis.

Strengths of the present study should also be mentioned, especially the inclusion of innovative elements that led to new insights. First, this is the first study to investigate BDNF levels in an ARMS sample. The pattern of results indicates that it is vital to further study peripheral BDNF levels in this patient population, to promote understanding of the biological underpinnings of clinical and cognitive processes preceding the onset of frank psychosis. A second strength of this study is the simultaneous analysis of plasma and serum BDNF, considering that there is no consensus so far as to which one of the two parameters is a more suitable peripheral biomarker. Our results indicate that the free circulating plasma BDNF may be more closely associated with cognitive performance and should therefore be considered in future investigations.

In summary, the present study observed lower serum and plasma BDNF levels in ARMS patients compared to FEP and CS. This finding, although unexpected at first glance, might point towards an important pathological process prior to the onset of full-blown psychosis. The observed positive correlation between plasma BDNF and executive functions might

provide a link to the well-established cognitive deficits of psychotic disorders, which are already present in the at-risk mental state.

Regarding the potential implications of our study for the field of early detection, the surprisingly low peripheral BDNF levels in ARMS patients might be a valuable further marker to detect individuals at-risk for psychosis which might, in combination with other markers, improve the accuracy of early detection.

5. Acknowledgments

6. Conflict of Interest

All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

7. Funding

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Table 1: Sample characteristics

Variable	ARMS (n=16)	FEP (n=6)	CS (n=11)	Significance
Age (years)	24.56 (±5.27)	29.40 (±6.27)	38.38 (±6.63)	>.001
Years of education	12.69 (±2.80)	11.25 (±1.37)	10.91 (±1.26)	.211[a]
Current use of antipsychotics (yes/no)	1/15	4/2	11/0	
CPE	20 (±0)	85.00 (±88.49)	1216.78 (±987.92)	.049[b]
Current use of nicotine (yes/no) [c]	11/5	4/2	11/0	
Cigarettes per day[c]	11.82 (±11.68)	15.00 (±16.58)	31.88 (±14.62)	.044[a]

Note. Mean (± standard deviation); [a]Kruskal-Wallis test, otherwise one-way ANOVA; [b] independent sample t-test; [c] mean calculated based on those participant with current use only; antipsychotic dosage in chlorpromazine equivalents (CPE); at-risk mental state (ARMS), first-episode psychosis (FEP), chronic schizophrenia (CS); not applicable (n.a.).

Table 2: BDNF level comparison between ARMS, FEP and CS patients

BDNF (ng ml^{-1})	ARMS (n=16)	FEP (n=6)	CS (n=11)	Significance (ANOVA)	Significance (ANCOVA) [c]
Serum	19.11 (±4.67)	24.48 (±2.40)	28.08 (±3.99)	$F_{(2, 30)}=$ 15.688; p <.001	$F_{(2, 5)}=$ 5.322; p=.015
Plasma	0.30(±0.29)[a]	0.54(±0.54)[a]	1.31(±1.06)[a]	$F_{(2, 30)}=$ 9.835; p=.001[b]	$F_{(2, 5)}=$ 2.761; p=.090[b]

Note. Mean (± standard deviation); [a] non-log transformed values reported; [b] analysis carried out using the plasma log value; [c] significance after inclusion of age, nicotine use and chlorpromazine equivalent (CPE) as covariates; brain-derived neurotrophic factor (BDNF), at-risk mental state (ARMS), first-episode psychosis (FEP), chronic schizophrenia (CS).

Table 3: Neuropsychological composite score comparison between ARMS, FEP and CS

Variable	ARMS (n=13)	FEP (n=5)	CS (n=9)	Significance (ANOVA)	Significance (ANCOVA)[a]
IQ	0.12 (±0.78)	-0.37 (±0.61)	-0.25 (±0.87)	$F_{(2, 24)}=$ 1.027; $p=.373$	$F_{(4, 25)}=$ 1.041; $p=.409$
ToH	-0.04 (±0.56)	-0.66 (±1.11)	0.25 (±0.85)	$F_{(2, 24)}=$ 2.176; $p=.135$	$F_{(4, 25)}=$ 1.226; $p=.330$
TAP Go/No-Go	0.18 (±0.55)	-0.93 (±0.95)	0.29 (±0.33)	$F_{(2, 24)}=$ 8.171; $p=.002$*	$F_{(4, 25)}=$ 3.529; $p=.024$*
TAP WM	0.02 (±0.77)	0.07 (±0.82)	-0.05 (±0.43)	$F_{(2, 24)}=$ 0.019; $p=.981$	$F_{(4, 25)}=$ 0.134; $p=.968$
CPT	0.12 (±0.47)	0.17 (±0.39)	-0.23 (±0.84)	$F_{(2, 24)}=$ 1.027; $p=.373$	$F_{(4, 25)}=$ 0.807; $p=.535$
CVLT	0.42 (±0.63)	0.36 (±0.94)	-0.71 (±0.84)	$F_{(2, 24)}=$ 6.402; $p=.006$*	$F_{(4, 25)}=$ 2.744; $p=.056$
Global	0.13 (±0.3)	-0.24 (±0.43)	-0.08 (±0.38)	$F_{(2, 24)}=$ 1.881; $p=.174$	$F_{(4, 25)}=$ 0.952; $p=.454$

Note. Mean (± standard deviation); * significant at p<.05; [a] including age and chlorpromazine equivalent as covariate; at-risk mental state (ARMS), first-episode psychosis (FEP), chronic schizophrenia (CS).

Table 4: Multiple Regression

Predictor	Global	IQ	ToH	TAP Go/No-Go	TAP WM	CPT	CVLT
Group	-.241 (192)	-.137 (.375)	-.028 (.392)	.039 (.340)	.422 (.362)	-.875 (.302)°	-.505 (.375)
Age	-.289 (.015)	.303 (.030)	-.328 (.029)	.153 (.027)	-.434 (.029)	.055 (.024)	-.343 (.030)
Years of education	.073 (.038)	.219 (.074)	-.153 (.072)	.408 (.066)°	-.063 (.071)	-.124 (.059)	.060 (.072)
CPE	-.116 (.000)	-.095 (.000)	.023 (.000)	.241 (.000)	-.381 (.000)	.100 (.000)	-.116 (.000)
Serum BDNF	-.230 (.022)	-.148 (.043)	-.435 (.042)	-.312 (.040)	-.376 (.041)	.252 (.036)	.404 (.044)
Plasma BDNF	.560 (.150)°	-.042 (.205)	.804 (.201)*	.132 (.183)	.298 (.198)	.406 (.163)	.026 (.202)

Note. Standardized coefficient (standard error); * significant at p<.05; ° trend at p<.1

Legend to Figure 1: Plasma and Serum BDNF levels in ARMS, FEP and CS

Note. BDNF = brain-derived neurotrophic factor; ARMS = at-risk mental state for psychosis; FEP = first-episode psychosis; CS = chronic schizophrenia. Plasma and serum BDNF values are presented as non-log transformed values (ng/ml) with mean and 95% confidence intervals of the mean.