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Letter to the Editor

Plasma protein levels of brain-derived neurotrophic factor pathways and their association with cognitive performance in patients with clinical high risk for psychosis and first episode psychosis

Dear Editor,

Brain-derived neurotrophic factor (BDNF) was suggested in playing a major role in the pathogenesis of schizophrenia because of their critical importance in neuron development (Tanaka et al., 2008). Evidences for these include the Met mutation of BDNF gene which induce an earlier onset of schizophrenia (Favalli et al., 2012), BDNF modulating expression of D3 receptors which are closely related to the mechanisms of antipsychotic drugs (Guillin et al., 2001), and many others. Studies had been done that examined the relationships between BDNF and executive function or spatial memory of schizophrenia (Beste et al., 2011). However, links between BDNF and schizophrenia remains controversial due to various factors (medication, stage of illness, BDNF isoforms, etc.) (Favalli et al., 2012).

In this study, we measured the plasma levels of BDNF pathway proteins including mature-BDNF (mBDNF), precursor BDNF (proBDNF), tropomyosin receptor kinase B (TrkB), p75 neurotrophin receptor (p75NTR), tissue-type plasminogen activator (tPA) and matrix metallopeptidase 9 (MMP-9) in patients with first episode psychosis (FEP), clinical high risk (CHR) individuals and healthy controls (HCs). In addition, the associations between different BDNF proteins and cognitive performances were also investigated.

Subjects which included 30 CHRs, 30 FEPs, and 29 HCs were recruited from the Second Xiangya Hospital of Central South University. The CHRs were screened by the structured interview for prodromal syndromes (SIPS) and the FEPs were diagnosed with schizophrenia via the Structured Clinical Interview from DSM-IV.

All subjects participated in neurocognitive assessments which contained the Trail Making Test (TMT-A & TMT-B), the Stroop Color-Word Test (SCWT) and the Verbal Learning Test-Revised (HVLT-R). The plasma BDNF levels were measured by a sandwich enzyme-linked immunosorbent assay (Human BDNF/ProBDNF/TrkB/p75NTR/TPA/MMP-9 ELISA Kit, mlbio, Shanghai, CHN).

ANOVA for continuous variables and chi-squared for categorical variables were examined. Protein levels and cognitive scores of groups were compared with one-way ANOVA and Post-hoc comparisons (using LSD and Dunnett T3 correction). The partial correlations were conducted to analyze the associations between cognitive performances and protein levels ($p < 0.05$).

The demographic and clinical data are shown in Table 1 (in Supplementary material). Three groups showed similar gender and age distribution. Regarding cognitive domain, the CHRs had significantly worse performance than the HCs while compared with the FEPs, they had significantly worse performance in the SCWT examination. On the subject of BDNF protein levels (TrkB, tPA, proBDNF, p75NTR, see Fig. 1), the CHRs had the lowest level among the three groups. The mBDNF level of the CHRs was lower than those in FEPs ($p = 0.000$) but there was no difference with those in HCs ($p = 0.668$). The level of MMP-9 was also significantly highest in CHR. After controlling for age and gender, the results showed that the TrkB levels had a weak negative relationship with the SCWT scores ($r2 = -0.299$, $p = 0.01$).

Because all reports and studies of CHRs only measured the total BDNF (mixed mBDNF and proBDNF), the potential influence of different isoforms have been ignored. MMP-9 and tPA converts proBDNF into mBDNF (Lu et al., 2005). mBDNF is able to bind to TrkB while proBDNF can bind to p75NTR (Lee et al., 2001). The present study also measured the main proteins of the BDNF system besides mBDNF such as tPA, MMP-9, TrkB, proBDNF and p75NTR. The results showed an elevated level of plasma BDNF in the FEPs instead of the CHRs which is consistent with Heitz et al.'s CHR study (Heitz et al., 2018). The CHRs had the lowest levels for all proteins except MMP-9. This might be due to MMP-9's other critical functions such as enhancing oxidative stress, etc. (Turner and Sharp, 2016).

In regards to cognitive performance, the executive functions of CHRs (especially the response inhibition represented by SCWT) could be worse than those in FEPs because neurocognitive deficits is already present in the prodromal stage of schizophrenia. We have discovered a weak relationship between SCWT scores and TrkB levels which means that the reduced TrkB in CHRs were corresponding to cognitive impairment. Not surprisingly, the TrkB is the most direct protective agents in our study. Even the neuronal protective function of mBDNF depends on the binding and activating of TrkB (Patapoutian and Reichardt, 2001). Because of these reasons, the decline of TrkB in the early stage of psychosis and its association with executive functions may suggest a potential alert or even a phenotype for psychosis.

In summary, the CHRs showed the lowest levels for almost all proteins regardless of receptor, ligand and enzyme. A possible explanation is that it's an overall overreaction to the abnormal neuropsychiatric progression in the early stages. This is based on the suggestion that the neurodegenerative processes might be more active in prodromal stage than fully developed stage of schizophrenia (Lieberman, 1999). Alternatively, it could also be explained by the compensatory mechanism. In conclusion, these findings in this study support the theory that the BDNF system changes in the early stage of psychosis and it is related to cognitive impairment and resilience.

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Conflict of interest

There is no conflict of interest to declare.

Contributors

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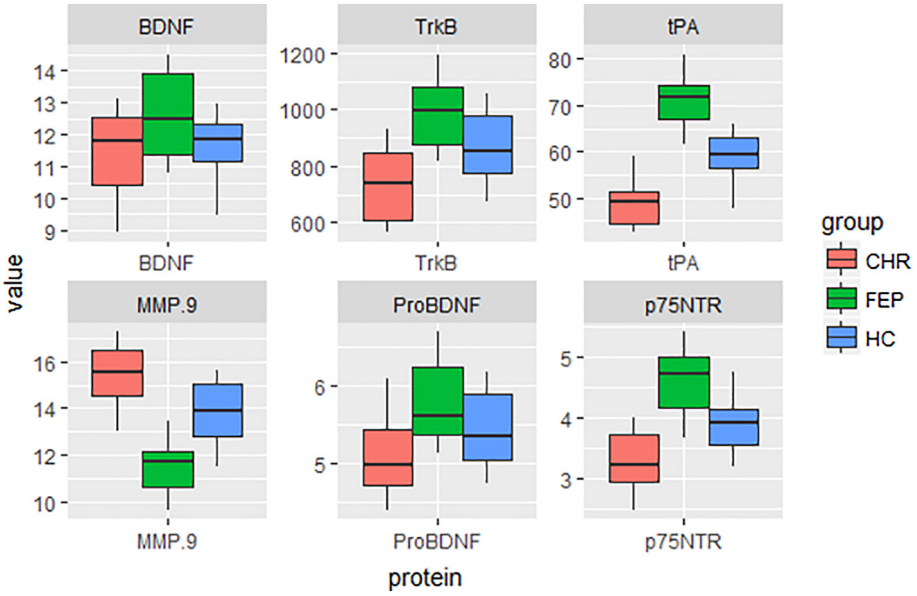

Fig. 1. Plasma protein levels in three groups. There were significantly different levels of all detected proteins (BDNF, TrkB, tPA, MMP-9, ProBDNF, p75NTR) among three groups. The MMP-9 levels in the CHR group were the highest among three groups. In contrast, all other proteins (BDNF, TrkB, tPA, ProBDNF, p75NTR) were significantly lower in the CHR group compared to the FEP group. Regardless, the protein levels of HCs were always between CHRs and FEPs.

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