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Correlates of neurocognitive functions in individuals at ultra-high risk for psychosis - A 6-month follow-up study

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A B S T R A C T

Cognitive deficits are evident at the prodromal phase of psychosis. It has been noted that brain-derived neurotrophic factor (BDNF) is correlated with cognition in both preclinical and clinical studies. However, to our knowledge, no study has evaluated blood BDNF levels and their association with cognitive impairment in individuals at ultra-high risk for psychosis (UHR). We included 13 individuals at UHR and 30 healthy controls (HC) matched by sex, age, and educational level. Plasma BDNF levels were measured at baseline and 6 months. Neurocognitive functions (executive functions, speed of processing, verbal learning and memory, working memory) were examined at 6 months. Regression analyses were conducted to examine the relationship between BDNF levels and cognitive performance. BDNF levels were lower in UHR group than in HC group both at baseline and at 6 months ($P = 0.001$, and $P = 0.007$, respectively). There were no associations between plasma BDNF levels and all of the cognitive domains in both groups. Our findings showed that peripheral BDNF levels were not related to cognitive deficits in UHR and HC groups while the lower BDNF level in the former persisted up to 6 months. Further research is needed in a large sample.

1. Introduction

Cognitive impairments are recognized among core features of schizophrenia and are reported as one of the strongest predictors of functioning in patients with schizophrenia. It is noted that they are already present at early stages of psychosis, such as ultra-high risk for psychosis (UHR) (Bang et al., 2015; Comparelli et al., 2013; Keefe et al., 2006; Liu et al., 2015) and first-episode psychosis (FEP) (Corigliano et al., 2014). A recent meta-analysis reported that UHR individuals show neurocognitive deficits in terms of attention/vigilance, verbal learning, visual learning, social cognition, speed of processing, current Intelligence Quotient (IQ), premorbid IQ (Hauser et al., 2017) compared to HCs and that those with UHR present with better performance in attention/vigilance, verbal learning, working memory, speed of processing, and current IQ compared to those with FEP subjects (Hauser et al., 2017). In addition, a cross-sectional study showed a difference of the characteristics of the cognitive deficits between the UHR and the FEP groups, and suggested a different clinical course between these groups (Ohmuro et al., 2015).

Neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which play crucial roles in the expression of synaptic plasticity underpinning cognitive function, are enhancers of cognitive performance, particularly expression of learning and memory (Hennigan et al., 2007). A number of studies have examined the relationship between BDNF and mental disorders including not only psychotic disorders but also depression, anxiety disorder, post-traumatic stress disorder (PTSD), and Alzheimer's disease (Sanada et al., 2016). Furthermore, with respect to the association between BDNF levels and cognitive performance, it was noted that peripheral levels with BDNF were related to spatial memory in the elderly population (Erickson et al., 2010), and that BDNF polymorphism (Val66Met) was also been associated with executive function in mood

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disorders (Rybakowski, 2008). A recent meta-analysis concluded that peripheral levels of serum and plasma BDNF were moderately decreased in patients with schizophrenia, including those with FEP, compared with healthy controls (HCs) (Fernandes et al., 2015). At preclinical level, some studies indicated the correlation between BDNF levels and cognition, e.g., spatial learning and memory (Minichiello et al., 1999; Mizuno et al., 2000). As for schizophrenia, we previously reported a positive association between plasma BDNF levels and cognitive function in several neurocognitive domains: abstract reasoning, processing speed, learning capacity and delayed memory in patients with FEP (Ruiz de Azúa et al., 2013). Likewise, several studies revealed that peripheral BDNF levels were positively correlated with neurocognitive function in patients with chronic schizophrenia (Carlino et al., 2011; Wu et al., 2015; Zhang et al., 2012, 2014). To support these findings, a recent meta-analysis demonstrated positive correlations between peripheral BDNF levels and cognitive function in reasoning and problem-solving domains in patients with schizophrenia, including FEP (Ahmed et al., 2015).

To our knowledge, however, no study evaluated the levels of blood BDNF and their association with cognitive performance in UHR individuals. We initially hypothesized: (1) plasma BDNF levels would be different between the UHR group and HC group, (2) cognitive functions would be lower in UHR individuals than those in HCs, and (3) plasma BDNF concentrations could be correlated with cognitive performance in the UHR group. The current study therefore examined neurocognitive functioning and plasma BDNF levels in UHR populations and HCs during 6 months follow-up to seek the differences between them and to examine the relationship between neurocognitive functioning and plasma BDNF levels between these two groups. In addition, we also explored relationships between neurocognitive functioning, and clinical symptoms, and drug and alcohol use in this population.

2. Methods

2.1. Participants

The eligibility criteria are shown in Table 1. In total, 13 patients (age range, 14 to 40 years; 6 ≦ 18 years) in UHR group were recruited from the health care program and research of FEP of the Araba University Hospital in the Alava catchment area in three years from 2012 to 2014. We included only participants with the total scores of Intelligence Quotient (IQ) above 70 using Wechsler Adult Intelligence Scale (WAIS). The UHR group was assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS): APS group (attenuated psychotic symptoms), BLIPS group (brief limited intermittent psychotic symptoms), and Trait group (trait and state risk factor) (Yung et al., 2005).

Thirty healthy control (HC) participants were recruited from the same catchment area and matched to the UHR group regarding sex, age, and educational level. HCs were clinically assessed using the Structured Clinical Interview for the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I (SCID) (First et al., 1999) in order to exclude those who had history of psychiatric disorders, had substance use disorders, or had a family history of schizophrenia and bipolar disorder in the first-degree relatives.

Table 1
Summary of the eligibility criteria.

	Inclusion criteria	Exclusion criteria
UHR	Diagnosed as UHR using CAARMS Age, between 14 and 40 years No history of previous antipsychotic treatments	Intellectual disability (IQ below 70 using WAIS) Previous alcohol or substance abuse Previous organic brain disorders with loss of consciousness Neurological diseases Autistic disorders

UHR: Ultra-High Risk for psychosis; CAARMS: Comprehensive Assessment of At-Risk Mental States; IQ: Intelligence Quotient; WAIS: Wechsler Adult Intelligence Scale.

2.2. Procedure

The study was approved by the Ethical Committee of the Basque Country. All participants were informed about purposes and procedures of the study with a thorough careful explanation and provided written consent. In the case of participants under 18, their parents gave written informed consent and patients assented to participate in the study. Subjects were assessed for clinical variables and socioeconomic status at baseline. All the patients were followed up for 6 months and were assessed with the same clinical battery at 6 months from baseline. Neurocognitive assessments were conducted at 6 months after the inclusion in the study due to avoid the interference of psychopathology with cognitive performance such that the patients were stable enough to undergo the neurocognitive battery. We also collected peripheral blood from all the patients at baseline and 6 months after the inclusion in the study while blood was collected from HCs only at baseline.

2.3. Measures

2.3.1. Measurement of BDNF

Plasma BDNF levels were analyzed using a BDNF Sandwich ELISA Kit, according to the manufacturer's instructions (Millipore, USA, Cat. No. CYT306). Blood samples were collected from all participants at approximately 8:30 am following overnight fasting. The details of procedures were described previously (Ruiz de Azúa et al., 2013). Briefly, diluted plasma samples (diluted 1:100) and serial dilutions of the BDNF standards (ranging from 7.8 to 500 pg/ml BDNF) were incubated for 24 h in 96-well immunoassay plates pre-coated with mouse anti-human BDNF monoclonal antibody. The plates were then washed and a biotinylated mouse anti-human BDNF monoclonal antibody (diluted 1:1000 with diluent) was added to each well and incubated for 3 h at room temperature. After washing, a streptavidin-enzyme conjugate (diluted 1:1000) was added and incubated at room temperature for 1 h. After further washing, a substrate solution was added to the plates to initiate a reaction, which was stopped after 15 min by adding the stop solution (HCl). The amount of BDNF was determined immediately by measuring absorbance at 450 nm using a microplate reader. The standard curve demonstrated a direct relationship between optical density and BDNF concentration.

2.3.2. Clinical and functional assessments

We assessed psychotic symptoms, mood, anxiety, psychosocial functioning, and global severity with the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale (HDRS-21) (Hamilton et al., 1960), State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), Functioning Assessment Short Test (FAST) (González-Ortega et al., 2010; Rosa et al., 2007), and Clinical Global Impression-Schizophrenia scale (CGI-SCH) (Haro et al., 2003)-Severity of illness, respectively.

Drug and alcohol use was evaluated using the Addiction Severity Index (ASI) (McLellan et al., 1992) and assigned into one of four categories (no use, use, abuse, or dependence) following the criteria based on a previous study (González-Pinto et al., 2011). They were regrouped into either use or no use in order to describe the demographic characteristics.

2.3.3. Neurocognitive assessments

A neurocognitive battery was administered to all the participants. It consisted of four domains: executive functions using the Wisconsin Card Sorting Test (WCST) (Heaton, 1981), the Stroop Color and Word Test (SCWT) (Golden, 1978) and the Trail Making Test (TMT) B (Reitan and