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Gender difference in association of cognition with BDNF in chronic schizophrenia

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Summary While numerous studies have reported that brain-derived neurotrophic factor (BDNF) may be involved in the pathophysiology of schizophrenia, very few studies have explored its association with cognitive impairment or gender differences in schizophrenia which we explored. We compared gender differences in 248 chronic schizophrenic patients (male/female = 185/63) to 188 healthy controls (male/female = 98/90) on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and serum BDNF. Schizophrenic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Our results showed that schizophrenic patients performed worse than normals on most of the cognitive tasks, and male patients had significantly lower immediate memory and delayed memory scores than female patients. BDNF levels were significantly lower in patients than controls, and male patients had significantly lower BDNF levels than female patients. For the patients, BDNF was positively associated with immediate memory and the RBANS total score. Furthermore, these associations were only observed in female not male patients. Among healthy controls, no gender difference was observed in cognitive domains and BDNF levels, or in the association between

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BDNF and cognition. Our results suggest gender differences in cognitive impairments, BDNF levels and their association in chronic patients with schizophrenia. However, the findings should be regarded as preliminary due to the cross-sectional design and our chronic patients, which need replication in a first-episode and drug naïve patients using a longitudinal study.

1. Introduction

Schizophrenia (SZ) patients show cognitive deficits across a number of domains, including learning, memory, attention, executive functioning and cognitive processing speed (Sharma and Antonova, 2003; Harvey et al., 2004; Palmer et al., 2009; Condray and Yao, 2011). Several studies have focused on gender differences in the cognitive deficits of SZ, and found gender differences in cognitive performances in both SZ and healthy populations (Goldstein et al., 2002; Halari et al., 2006; Wisner et al., 2011). However, gender differences in these cognitive deficits among SZ patients have produced equivocal findings. For example, some studies indicate men to be more impaired than women (Goldstein et al., 1998; Fiszdon et al., 2003) whereas others report the opposite (Lewine et al., 1996; Brébion et al., 2004) or no difference (Gur et al., 2001; Halari et al., 2006). Moreover, the pathophysiological mechanisms underlying these gender differences in cognitive deficits of SZ are still unclear and have previously received little systematic study.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors and is essential in regulating cell survival, proliferation and synaptic growth in the developing central nervous system (Poo, 2001; Egan et al., 2003). Also, in the mature nervous system, BDNF promotes the elaboration and refinement of neuronal circuit structure, modulates synaptic plasticity, dendritic complexity and spine density, and, consequently, regulates cognitive brain function including learning and memory (Pandya et al., 2013; Lu et al., 2014). In laboratory animals, BDNF can induce long-term potentiation (LTP), which is considered to be the neurophysiological basis for learning and memory (Diógenes et al., 2011). Furthermore, inhibition of BDNF signaling by gene knockout or antisense RNA impairs spatial learning and memory (Guzowski et al., 2000). Preclinical evidence shows that BDNF activity or levels may contribute to alterations in hippocampal function and hippocampal dependent learning and memory (Hariri et al., 2003). Recently, many studies have demonstrated that BDNF serum levels are significantly lowered in patients with cognitive decline-associated diseases, such as Huntington's disease (Ciammola et al., 2007), Alzheimer's disease (AD) (Gunstad et al., 2008), and mild cognitive impairment (Yu et al., 2008). In contrast, up-regulation of BDNF in the hypothalamus has been related to an improvement of cognitive function, including memory (Adlard et al., 2004; Komulainen et al., 2008). Several studies further suggest that peripheral BDNF levels are biomarkers of cognitive function in healthy older adults (Gunstad et al., 2008; Komulainen et al., 2008), as well as in schizophrenia (Vinogradov et al., 2009; Carlino et al., 2011; Niitsu et al., 2011; Nurjono et al., 2012; Zhang et al., 2012; Asevedo et al., 2013; Goff, 2013; Nieto et al., 2013).

Numerous studies have reported that altered peripheral levels of BDNF may be involved in the pathophysiology of SZ (Pillai et al., 2010; Buckley et al., 2011; Favalli et al., 2012; Pillai and Buckley, 2012). The majority of studies report decreased serum BDNF levels in treated and first-episode SZ patients (Toyooka et al., 2002; Shimizu et al., 2003; Pirildar et al., 2004; Tan et al., 2005; Palomino et al., 2006; Grillo et al., 2007; Ikeda et al., 2008; Rizos et al., 2008, 2010; Chen et al., 2009; Xiu et al., 2009; Pillai et al., 2010). However, some authors failed to replicate these findings in both medicated and unmedicated SZ patients (Shimizu et al., 2003; Huang and Lee, 2006), or even found increased serum BDNF levels in treated SZ patients (Reis et al., 2008). The most recent systematic review with meta-analysis of studies has showed that blood levels of BDNF are reduced in both medicated and drug-naïve patients with SZ (Green et al., 2011). Interestingly, in one of our recent studies we found sex differences in BDNF levels in SZ, showing lower BDNF levels in male compared to female patients (Xiu et al., 2009). One recent study also reported a significant reduction in plasma BDNF levels in females as compared to males including both depressed and control subjects (Pillai et al., 2012).

In the view of gender differences in cognitive deficits and the possible gender differences in alterations of BDNF in SZ and the important implication of BDNF in cognition, we explored gender differences in the association of BDNF with cognitive impairments in SZ, which to our knowledge, has not been examined in patients with SZ. We hypothesized that gender differences may exist in cognitive performance, BDNF levels and their association in SZ.

2. Method

2.1. Subjects

Two hundred and forty eight physically healthy patients (male/female = 185/63) who met DSM-IV for SZ were compared with 188 Chinese normal controls (male/female = 98/90). All SZ patients were inpatients of Beijing Hui-Long-Guan Hospital, a Beijing City owned psychiatric hospital. Diagnoses were made for each patient by two independent experienced psychiatrists based on the Structured Clinical Interview for DSM-IV (SCID). All SZ patients were of the chronic type, with a duration of illness for at least 5 years, aged between 25 and 70 years (mean 52.1 ± 8.3 years). Most of patients (93.5%) were considered refractory to treatment according to these criteria: no response to at least three antipsychotics treated 3 months or over at full dose. All patients had been receiving stable doses of oral neuroleptic medications for at least 12 months prior to entry into the study. Their