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Gray matter volume alterations in first-episode drug-naïve patients with deficit and nondeficit schizophrenia

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ABSTRACT

Different patterns of gray matter volume (GMV) abnormalities have been reported between chronic patients with deficit schizophrenia (DS), relative to nondeficit schizophrenia (NDS) patients. However, it is not clear whether these differences are characteristic to the pathophysiology of DS or due to the effects of medications or illness durations. To address this issue, GMV in 88 first-episode, drug-naive patients with schizophrenia (44 DS and 44 NDS), 67 of their first-degree relatives and 84 healthy controls were assessed using voxel- based morphometry (VBM) and compared between groups. Correlations between GMV and clinical symptoms in patients were also assessed. Compared to controls, DS patients displayed more severe GMV reduction in the cerebellar culmen than NDS patients. GMV reduction in culmen was also observed in the first-degree relatives of DS (but not NDS) patients, suggesting possible different genetic risk in DS and NDS. The left insula was significantly smaller in DS patients than both NDS patients and controls, and smaller GMV of this region was associated with more severe negative symptoms in patients. Our results collectively indicate that DS might represent a distinct subtype of schizophrenia from NDS and the GMV change in left insula may be a morphological signature of DS.

1. Introduction

Deficit schizophrenia (DS) is a syndrome with enduring, primary negative symptoms in patients with schizophrenia (Kirkpatrick and Galderisi, 2008). Patients with DS comprises 15–20% of schizophrenia cases in epidemiological samples (Messias et al., 2004). Relative to non-deficit schizophrenia (NDS) patients, DS patients have more severe negative symptoms, worse long-term prognosis, poorer premorbid adjustment, greater cognitive impairment, and a high frequency of family history with schizophrenia (Kirkpatrick et al., 2000; Kirkpatrick et al., 2001; Tek et al., 2001; Galderisi et al., 2002; Cohen et al., 2007; Réthelyi et al., 2011). Consequently, it has been suggested that DS could be a distinct disease entity from nondeficit forms of schizophrenia (Galderisi and Maj, 2009). It was also hypothesized that DS and NDS might involve different pathophysiological changes in the brain (Kirkpatrick et al., 2001; Kirkpatrick and Galderisi, 2008). Indeed, several previous studies reported different patterns of grey matter volume (GMV) abnormalities in DS and NDS patients, although the results remain inconclusive (Sigmundsson et al., 2001; Galderisi et al., 2008; Cascella et al., 2010; Fischer et al., 2012; Volpe et al., 2012). For instance, using the voxel-based morphometry (VBM), Cascella et al. reported that GMV abnormalities in the left insula, bilateral superior temporal gyrus, and left precuneus were characteristic of DS (Cascella et al., 2010). In addition, Fischer et al. found that the reduction in GMV of bilateral superior prefrontal and superior and middle temporal gyrus was only

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associated with DS (Fischer et al., 2012). However, some other studies suggested that the difference in GMV abnormality between DS and NDS was largely a matter of severity rather than a characteristic feature. Using the volumetric approach, Galderisi et al. showed no selective regional change in GMV that was specific to patients with DS, with only a greater GMV reduction in the right temporal lobe in patients with DS than patients with NDS (Galderisi et al., 2008). Meanwhile, another volumetric study performed by Volpe et al. found that both DS and NDS patients showed reduction in GMV in the dorsolateral prefrontal cortex as compared with healthy controls (HCs), though with a greater reduction in GMV found in patients with NDS (Volpe et al., 2012). Similarly, ÖZDEMİR et al. reported less GMV in several brain regions in NDS patients than DS patients (Özdemir et al., 2012). Nevertheless, Voineskos et al. found that DS and NDS did not differ significantly on either cortical thickness reduction or surface areas and subcortical volumes (Voineskos et al., 2013).

A number of confounding factors, such as small sample sizes, heterogeneous treatment conditions, durations of illness and/or different imaging techniques may count for inconsistent results of previous studies (Galderisi and Maj, 2009). The majority of previous imaging studies on DS had relatively small sample sizes (from 8 to 34). In addition, previous brain structural analysis used the data from chronic patients with DS or NDS, with the duration of illness usually longer than 10 years (Galderisi et al., 2008; Cascella et al., 2010; Fischer et al., 2012; Volpe et al., 2012). Particularly, since antipsychotics was likely to be less effective with negative symptoms (Leucht et al., 2003), possible different treatment effects of antipsychotics on patients with DS or NDS may also compound the comparison between the two subpopulations (Kirkpatrick and Galderisi, 2008). Considering the progressive loss of cortical GMV in brain regions involving frontal and temporal lobes in patients with schizophrenia (Nakamura et al., 2007; Yoshida et al., 2009; Vita et al., 2012), chronicity and longer duration of the illness might also significantly affect the results of aforementioned studies.

It has also been shown that family members of DS patients have more severe subclinical negative symptoms such as social withdrawal, and an increased risk of schizophrenia (Kirkpatrick et al., 2001) compared with relatives of NDS probands (Hong et al., 2003). However, the manifestation of potentially different genetic risk in GMV alterations between the DS and NDS remains unknown.

For the purpose of investigating the characteristic pattern of gray matter abnormalities occurring at the onset of DS and NDS and the potential genetic risk, the present study has gathered a relatively large sample of structural magnetic resonance imaging (MRI) dataset in first-episode, DS and NDS patients (most of them were treatment-naïve), their first-degree relatives and matched healthy controls. GMV in these subjects has been analyzed by utilizing the VBM method. The relationship between regional GMV and the symptomology has also been examined.

2. Materials and methods

2.1. Participants

A total of 239 subjects including 88 patients with first-episode schizophrenia (FES), 67 of their first-degree relatives and 84 HCs participated in this study. All patients were recruited from in-patient and out-patient psychiatric units at the Mental Health Centre of the West China Hospital, during 2006–2012. The first-episode schizophrenia sample comprised individuals presenting to the Mental Health Center who had been diagnosed as schizophrenia. To be included, an individual was required to fulfill the inclusion criteria of the present study: age between 16 and 45 years; Han Chinese; right-handed; Intelligence Quotient (IQ) $\geq$ 70; at the first episode of schizophrenia; treatment-naïve or had no more than 3 days of antipsychotic treatment before MRI scan.

The medical history of each patient was reviewed using the Structured Clinical Interview for the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) Patient Edition (SCID-P) (First and Gibbon, 1997). Patients with a history of any major psychiatric disorders (such as affective and schizo-affective disorders), mental retardation, head trauma, substance abuse (including cocaine and heroin), alcoholism, any major nervous system diseases, serious endocrine or metabolic diseases were excluded. Information about previous treatment and duration of untreated psychosis (DUP) was collected at diagnosis. Diagnoses were assigned based on the diagnostic criteria for schizophrenia and schizophreniform psychosis as specified in DSM-IV. Patients initially diagnosed with schizophreniform psychosis (n=24, 10 DS and 14 NDS) were included as they were confirmed for the diagnosis of schizophrenia after being followed up for at least 6 months. The diagnoses of DS and NDS were reached using the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989), 12 months after admission. Eight patients (9%; 5 DS and 3 NDS) were taking low dose antipsychotics (risperidone or olanzapine; 25–75 mg of chlorpromazine daily dose equivalent) for less than 3 days prior to MRI. All others (91%, 39 DS and 41 NDS) were treatment-naïve before scanning. Patients also underwent further evaluation on clinical symptoms using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

The data of HCs were selected from our database of 158 adult HCs. These HCs were recruited between 2006 and 2012 via posting advertisements. Where available, the first-degree relatives were recruited along with patients. The inclusion criteria for HCs and relatives are as follows: Han Chinese; right-handed; IQ $\geq$ 70. All controls and relatives were screened for a lifetime absence of Axis I illness of DSM-IV psychiatric illnesses with the SCID non-patient version (SCID-NP) (First and Gibbon, 1997). In addition, HCs were interviewed to ascertain that there was no psychiatric illness in their first-degree relatives. Relatives or controls with any major psychiatric disorder, serious physical illness, substance abuse (including cocaine and heroin), alcoholism, pregnancy, head trauma, or mental retardation were excluded from the study.

Relatives were assigned into 2 subgroups, relatives of DS (DS_R) or with NDS (NDS_R). Two groups of 'healthy controls' were age- and sex-matched with patients (HC1) and relatives (HC2) respectively. For the patient group, HCs with the same gender and similar ages were selected in a case-match manner (HC1). For the relative group, the health controls in the same age range as the relative group (16–60 years) were selected which were no significant difference in mean age and sex distribution between groups. We arranged two HC groups because the relatives were markedly older than patients (Please see Section 3.1. Demographic and clinical characteristics), and this could compound the brain structural difference (Nenadić et al., 2012).

Current IQ was estimated for all subjects using the seven-subtest version (including Information, Similarities, Arithmetic, Digit Span, Picture Completion, Block Design, and Digit Symbol subtests) (Schopp et al., 1998) of the Wechsler Adult Intelligence Scale -revised in China (WAIS-RC) (Gong, 1992).

All subjects were Han Chinese, and right-handed as assessed by the Annett Handedness Scale (Annett, 1970). After a complete description of the study, written informed consent was obtained from patients and patients' guardians and all healthy subjects. The study was approved by the Institutional Review Board of West China Hospital, Sichuan University.