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Altered volume and lateralization of language-related regions in first-episode schizophrenia

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ABSTRACT

Neuroanatomical abnormalities are considered to be related to the pathogenesis of schizophrenia. Reversal or reduction of normal structural cerebral asymmetries in schizophrenia is particularly striking. The current study investigated the alteration of gray matter volume and cerebral asymmetry in early stage of first-episode schizophrenia (FESZ), and their correlations with clinical measures. Magnetic resonance imaging scans were obtained from a total of 89 participants. Thirty-three FESZ patients and 41 matched healthy controls were included in the analysis. Compared to healthy controls, the FESZ patients showed decreased gray matter volume (GMV) in the frontal cortex, anterior cingulate cortex, temporal cortex, parahippocampal, fusiform, insula, and lingual; and increased GMV in cerebellum. Both male and female patients displayed an increased rightward lateralization in frontal and temporal cortex, which was significantly correlated with the severity of symptoms and social functioning. These findings may provide the neurological substrate for the etiology and clinical manifestations of the illness.

1. Introduction

A growing body of evidence suggests that schizophrenia is a severe and complex psychiatric disorder with widespread brain structural alterations (Ellison-Wright et al., 2008; Glahn et al., 2008; Fornito et al., 2009; Ellison-Wright and Bullmore, 2010). Disturbance of cerebral asymmetries, especially in language-related regions is well-documented in schizophrenia (Crow, 1997a; DeLisi et al., 1997; Li et al., 2009). Numerous studies continue to support the notion that deficits in language function are associated with the main symptoms of schizophrenia, such as auditory hallucinations and thought disorders (Crow, 1997b; DeLisi, 2001; Shapleske et al., 2001; Zhang et al., 2008; Ocklenburg et al., 2013). Crow proposed that the nuclear symptoms of schizophrenia could be considered as a failure to establish dominance for the phonological sequence of language in one hemisphere, resulting in disruption of the speaker to distinguish his thoughts from the speech output that he generates and the speech input that he receives and decodes from others (Crow, 2000). The human hemispheric dominance for processing of language is typically located in the left hemisphere in the majority of right-handed individuals, while the accumulating literature suggests that schizophrenia has a reduced normal pattern of left-greater-than-right language processing (Sommer et al., 2001; Kircher et al., 2002; Dollfus et al., 2005; Weiss et al., 2006; Razafimandimby et al., 2007; Dollfus et al., 2008; Angrilli et al., 2009; Bleich-Cohen et al., 2009; Oertel et al., 2010; Li et al., 2012a), but there were also inconsistent reports (Chapple et al., 2004; Hadjulis et al., 2004; Takao et al., 2010). The aim of this current study was to examine whether there is gray matter volume (GMV) alteration in language-related regions in an early phase of first-episode schizophrenia (FESZ), and whether the leftward language lateralization is reduced in FESZ.

Over the past decade, voxel-based morphometry (VBM) has been widely used in neuroanatomical studies of schizophrenia. Increased evidence has showed gray matter changes in patients with FESZ. The earlier study by Ananth et al. (2002) indicated global differences in gray matter volume between schizophrenic patients and healthy controls (HCs), and selective regional gray matter differences noted in the mediodorsal thalamus, and the ventral and medial prefrontal cortices. Another VBM study by Antonova et al. (2005) also found that patients with schizophrenia had smaller total brain volume, and regional gray matter alterations were left-hemisphere specific. A recent study on a large sample by Koutsouleris et al. (2008) showed

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that significant gray matter density (GMD) reductions in schizophrenia compared to controls were involved in the prefrontal, limbic, paralimbic, temporal and thalamic regions. Another large sample study by Honea et al. (2008) also found that patients with schizophrenia had significant regional gray matter volume (GMV) decreases in the frontal, temporal, and parietal cortices compared with HCs. The findings from the two large-sample studies were relatively consistent in gray matter changes. A recent meta-analysis study reported that gray matter concentration (GMC) reductions were more frequent in the insula, medial prefrontal, medial temporal and striatal regions, and GMV reductions were more frequent in dorso-medial frontal cortex, and lateral and orbital frontal areas (Fornito et al., 2009). In the abovementioned studies, the frequently reported regions in the frontal, temporal and parietal cortices play key roles in language processing network (Li et al., 2009).

The human cerebral hemispheres are anatomically and functionally asymmetric, which has been borne out since the middle of the 19th century. In normal adults, the left occipital lobe and the right frontal lobe are larger than their counterparts in the opposite hemisphere (LeMay and Kido, 1978; Pieniadz and Naeser, 1984), known as "cerebral torque", which is most marked in right-handers. Asymmetry of the planum temporal (PT) has been most extensively studied, because it is not only greater than any other asymmetry anywhere else in the human brain, but also plays an important role in the evolution of language ability. In most healthy right-handers, the left PT is larger than the right. Increasing evidence suggests that schizophrenia has less left asymmetry or even rightward asymmetry of PT (Sallet et al., 2003; Chance et al., 2008; Kawasaki et al., 2008; Clark et al., 2010; Oertel et al., 2010; Hasan et al., 2011; Smiley et al., 2011). Altered lateralization in other language functioning regions has been also frequently reported in schizophrenia. Using a verb-generation and a semantic decision task, Sommer et al. measured bilateral activation in the frontal, temporal and temporo-parietal language areas and found less lateralization in schizophrenia than in controls (Sommer et al., 2001). Dollfus et al. reported lower activation in the left middle temporal gyrus, the left angular gyrus, and the pars triangularis of the left inferior frontal gyrus during auditory task in schizophrenia compared with controls (Dollfus et al., 2005). Weiss and her colleagues also utilized a verbal fluency task and found a more bilateral activation of Broca's area in schizophrenia compared with a primarily left hemisphere activation in healthy controls (Weiss et al., 2006). In the study by Bleich-Cohen et al., patients with schizophrenia had significantly smaller lateralization indices in the inferior frontal gyrus (part of Broca's area) and the superior temporal sulcus (part of Wernicke's area) during language tasks of verb generation and passive music listening (Bleich-Cohen et al., 2009), which is consistent with the findings of a recent study by van Veelen et al. (2011).

Our current study focused on the alterations of GMV and lateralization in language-related regions in early stage of FESZ, and their correlations with clinical measures. We hypothesized that (1) FESZ patients would show GMV reduction in the areas of language processing, especially in the frontal and temporal cortices in comparison to HCs; (2) FESZ patients would exhibit a decrease or loss of normal anatomical brain asymmetry in language-related regions; (3) these alterations would be associated with their clinical measures.

2. Methods

2.1. Participants

Eighty-nine participants (43 first-episode schizophrenic patients and 46 healthy controls) were recruited in the study. Due to insufficient image quality for VBM (incomplete brain scan and magnetic interference), 15 cases (10 schizophrenic patients and 5 healthy controls) were excluded from our analysis. All participants were Chinese and right-handed, and were matched for age and gender. The FESZ patients were inpatients recruited from Shanghai Mental Health Center, Shanghai, China, with the following inclusion criteria: age between 16 and 45; a diagnosis of schizophrenia based on the Structured Clinical Interview for DSM (SCID) Patient Edition for DSM-IV (First et al., 1997); illness duration <3 years without more than 3-months of full-dose medication treatment or illness duration between 3 and 4 years without regular treatment. The healthy volunteers were confirmed to have no Axis I or Axis II disorders by using the Structured Clinical Interview for DSM-IV, and no history of Axis I disorders in their first-degree relatives. Participants with a history of neurological or severe somatic illness, head trauma with loss of consciousness over one hour, alcohol dependence or substance abuse within 3 months were excluded. Psychopathological state of FESZ patients was assessed by use of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Social functioning of FESZ patients was assessed with the Personal and Social Performance scale (PSP) (Morosini et al., 2000). All participants provided their written informed consent prior to inclusion, and the study was approved by the local institutional ethics board (Institutional Review Board of Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine).

2.2. Image acquisition

MRI scans were performed on a 1.5 T GE MRI scanner (General Electric, Milwaukee, Wisconsin) at Shanghai Rui Jin Hospital, Shanghai, China. A 3-D structural MRI was obtained for each participant using a spoiled gradient recalled echo (SPGR) sequence with the following imaging parameters: TR = 7.8 ms, TE = 3 ms, TI = 380 ms, flip angle = 13, matrix size = 288 × 256 pixels, and 170 slices. MRI data were saved in DICOM format and converted into the Analyze format using the dcm2nii DICOM converter software (http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html). All images were visually inspected blind to clinical data by using the MRIcron NifTI viewer software (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html).

2.3. Image processing

We analyzed the MRI data following the optimized VBM method (Ashburner and Friston, 2000; Good et al., 2001) using the Statistical Parametric Mapping package (SPM8; The Wellcome Trust Centre for Neuroimaging, London, UK) and VBM8 toolbox (http://dbm.neuro.uni-jena.de), running in Matlab version R2009a (MathWorks, Natick, MA). First, all the structural images were manually reoriented, setting the origin in the anterior commissure. Then, the anatomical 3D data were normalized to the standard Montreal Neurological Institute (MNI) T1 MRI template (ICBM 152, inherent to SPM8). Normalized images were re-sliced to 1 × 1 × 1 mm voxel size and further segmented into probability maps of gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF). The voxel values of each GM segment and WM segment were multiplied by the Jacobin determinants to modulate for volume changes resulting from nonlinear spatial normalization. Finally, the normalized, segmented and modulated images were smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel.

2.4. Statistical analysis

The Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) version 16.0 for Windows was used for statistical analysis of demographic and clinical data. A whole brain VBM analysis was performed by using the normalized and smoothed GM maps, employing the framework of the General Linear Model (Friston et al., 1995), for a two-sample *t*-test between 41 healthy controls and 33 schizophrenic patients. The analysis was conducted by using a General Linear Model repeated-measure analysis of covariance (ANCOVA) model in SPM8, including normalized total intracranial volume (TIV) as covariate. The SPM(t)