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Grey matter morphological anomalies in the caudate head in first-episode psychosis patients with delusions of reference

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ABSTRACT

Delusions of reference (DOR) are theoretically linked with aberrant salience and associative learning. Previous studies have shown that the caudate nucleus plays a critical role in the cognitive circuits of coding prediction errors and associative learning. The current study aimed at testing the hypothesis that abnormalities in the caudate nucleus may be involved in the neuroanatomical substrate of DOR. Structural magnetic resonance imaging of the brain was performed in 44 first-episode psychosis patients (with diagnoses of schizophrenia or schizophreniform disorder) and 25 healthy controls. Patients were divided into three groups according to symptoms: patients with DOR as prominent positive symptom; patients with prominent positive symptoms other than DOR; and patients with minimal positive symptoms. All groups were age-, gender-, and education-matched, and patient groups were matched for diagnosis, duration of illness, and antipsychotic treatment. Voxel-based morphometric analysis was performed to identify group differences in grey matter density. Relationships were explored between grey matter density and DOR. Patients with DOR were found to have reduced grey matter density in the caudate compared with patients without DOR and healthy controls. Grey matter density values of the left and right caudate head were negatively correlated with DOR severity. Decreased grey matter density in the caudate nucleus may underlie DOR in early psychosis.

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1. Introduction

Delusions of reference (DOR) are one of the most common psychotic symptoms in early schizophrenia (World Health Organization, 1975). Its roles as both a prodromal sign (Yung et al., 2005) and signal of relapse (Birchwood et al., 1989) suggest a close linkage with the psychotic state. Importantly, DOR are found in many delusional themes (Kraepelin, 1921) and may be particularly involved in the early delusion-formation stage (Corlett et al., 2006). Some investigators also speculate that different types of delusions such as paranoid ideation, delusions of misidentification and cotard delusion may have different pathological bases (Corlett et al., 2010). Investigation into the neural substrates of DOR may provide insight into understanding delusion formation in psychosis.

In DOR, subjects find their attention drawn toward irrelevant stimuli and events in the environment and impute personal meaning to them (Corlett et al., 2010). Theoretically, aberrant salience and associative learning may be involved. It has been proposed that dopamine mediates the conversion of the neural representation of an external stimulus from neutral information into its appropriate significance (Berridge and Robinson, 1998). In particular, the dopamine system plays a critical role in salience attribution. Authors such as Kapur (2003) and Corlett et al. (2006) have proposed that delusions are the cognitive effort by the patient to make sense of these aberrantly salient experiences which may have resulted from abnormal mesocorticolimbic dopamine system through disrupted prediction-error signalling. Prediction errors, signalled by midbrain dopamine neurons that are densely connected with the prefrontal cortex and basal ganglia, are considered to play a direct role in forming and strengthening

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associations (Schultz and Dickinson, 2000). Converging neurobiological evidence has shown a central role of the caudate nucleus in perception and prediction errors coding, associative learning, and working memory (Levy et al., 1997; Williams and Eskandar, 2006; Schiffer and Schubotz, 2011). Studies have showed that the caudate nucleus, which has dense fibre projections from the prefrontal lobe, is the primary target of the cognitive/limbic association cortex (Alexander et al., 1990; Levy et al., 1997). A functional imaging study has provided initial evidence of the association of DOR with abnormal brain activity in the frontal cortex, insula, and striatal areas (Menon et al., 2011). In theory, therefore, abnormality in the caudate nucleus may also be involved. However, very few research studies have been done on the neuropathology of DOR and their neuroanatomical substrate remains unclear.

In the current study, we studied the neuropathology of DOR in patients with schizophrenia using the voxel-based morphometry (VBM) technique in magnetic resonance imaging (MRI). We hypothesized that an abnormality of the caudate nucleus may be involved in the neuroanatomical substrate of DOR. Considering that structural heterogeneity may be correlated with psychopathological dimensions in psychosis (Koutsouleris et al., 2008), we investigated neuropathology in the following three groups of patients with different symptom profiles: (1) patients with DOR as prominent positive symptom, (2) patients with prominent positive symptoms other than DOR, and (3) patients with minimal positive symptoms. To determine the severity of DOR, we used a recently validated instrument, the Ideas of Reference Interview Scale (IRIS), which provides a theoretically based assessment tool to quantify the amount of aberrant salience in DOR (Wong et al., 2012). The IRIS has been validated in a Chinese patient population with demonstrated sensitivity, specificity, and reliability. We also explored possible relationships between grey matter density and DOR severity.

2. Methods

2.1. Participants and measures

Sixty-nine subjects (44 first-episode psychosis patients and 25 healthy controls) participated in the study. All participants were right-handed Han Chinese aged 18–45 years old, who had at least 9 years of formal education to ensure adequate understanding and expressive capacity, with no history of substance abuse or dependence, brain trauma or neurological disease, or contraindications to MRI. Participants' IQ was estimated using the information and digit-symbol coding subscales of the Wechsler Adult Intelligence Scale (WAIS), Chinese version (Gong, 1983). Handedness was assessed using the Annett Hand Preference Questionnaire (Annett, 1970). The ethics committee of the Second Xiangya Hospital, Central South University approved the study, and all participants gave written informed consent.

Patients diagnosed with schizophrenia or schizophreniform disorder within 18 months with no previous episodes of psychosis, as determined using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P) (First et al., 1996), were recruited from an inpatient unit at the Second Xiangya Hospital, Central South University, Changsha. To minimize the effects of neuroleptic medications on brain structure, only patients who had antipsychotic treatment for less than 12 weeks were recruited. Current and previous antipsychotic regimens (medication and duration of use) were recorded. Forty patients had only one (current) antipsychotic trial, and the remaining four patients had more than one antipsychotic trial (all less than 12 weeks and with more than 2 weeks of washout period). One patient was receiving a typical antipsychotic (sulpiride), 38 patients were receiving atypical antipsychotics (clozapine, risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone), and five patients were receiving both typical and atypical antipsychotic therapy. Mean current treatment duration was 10.48 (S.D.=8.54) days and mean lifetime exposure to antipsychotics was 15.73 (S.D.=21.90) days among the 44 patients. The three patient groups were matched by age (F (2, 41)=0.827, p=0.444), gender (χ^2=0.818, p=0.366) and years of education (F (2, 41)=0.704, p=0.500).

Healthy controls (HC) were evaluated by the Structured Clinical Interview for DSM-IV (SCID), Non-Patient Edition (First et al., 2002). Healthy controls with no lifetime history of any psychiatric disorders and no first-degree relatives with a history of psychiatric disorders were recruited from Changsha city.

2.2. Screening assessments and symptom profiling

Patients were first screened for symptom profile subgroup allocation using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984a). Patients with significant DOR but few other prominent positive symptoms (defined as scores of <3 on all items except the DOR item [item 14]) were defined as the "DOR" group (n=15); those with positive symptoms other than DOR (defined as a score of ≥ 3 on any item except item 14) were defined as the "non-DOR" group (n=14); and those with no prominent positive symptoms (defined as a score of <3 on all items) were defined as the "non-Pos" group (n=15). Patients not fulfilling any of the group criteria (i.e., having prominent DOR and other positive symptoms) were not enroled. The three patient groups and the HC group were matched for age, gender, and years of education. Patient groups were matched for diagnosis, duration of illness, and chlorpromazine-equivalent dosage (Woods, 2003) of antipsychotic treatment.

DOR were then assessed in detail in all participants using the IRIS (Wong et al., 2012). The IRIS contains 15 items on different self-referential themes (e.g., being looked at, being talked about, others dropping hints, messages in media). Each item is rated for endorsement and along three dimensions – severity ("self-referential discrepancy"), conviction, and frequency – according to operationalized criteria. The entire scale has a total score range from 0 to 240.

Negative symptoms were measured using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984b). All symptom assessments were carried out by psychiatrists (H.T., H.Z.) during a study interview within 2 weeks before the MRI session.

2.3. Structural image acquisition

High-resolution structural images were acquired sagittally using T1-weighted 3D turbo field echo (T1W-3D-TFE) on a 3.0-Tesla Philips Achieva whole-body MRI scanner (Philips, The Netherlands) with the following parameters: repetition time=7.5 ms, echo time=3.7 ms, flip angle=8°, field of view=240 × 240 mm^2, acquisition matrix=256 × 200, slice thickness=1 mm, gap=0, number of slices=180. Head motion was minimized with foam pads provided by the manufacturer.

2.4. Image processing and statistical analysis

Structural image processing was carried out using the VBM5 toolbox version 1.19 (http://dbm.neuro.uni-jena.de/vbm), an extension of the Statistical Parametric Mapping 5 (SPM5) software package (http://www.fil.ion.ucl.ac.uk/spm). The VBM technique offers advantages of comprehensive assessment of brain morphometric features by avoiding biases due to structural differences (Ashburner and Friston, 2000). Default parameters were used in the image preprocessing. VBM5 uses a segmentation algorithm from SPM5 and the extension of Hidden Markov Random Field method. Study-specific T1-weighted template, priors of grey matter, white matter, and cerebral spine fluid images were used for segmentation of raw images. Unmodulated grey matter images were then smoothed with a Gaussian kernel of 8-mm full-width at half-maximum (FWHM) and taken to a second level random effects analysis.

Statistical analysis was carried out with the voxel-wise comparison of the grey matter density in whole brain across the four subject groups. Areas showing group differences in grey matter density were first identified using analysis of covariance (ANCOVA) co-varying for age, gender, years of education, and total intracranial volume. A combined threshold at $p<0.001$ (uncorrected) and extent threshold at cluster size >200 was set to identify significant voxels among the four groups. The significant voxels were superimposed onto a T1-weighted brain template of SPM5 for visualization of regions showing group differences. Identified significant clusters showing group differences were created as binary masks in the standard Montreal Neurological Institute (MNI) space. The average grey matter density value in each area corresponding to the mask was obtained from each participant using self-developed software (Wei et al., 2012). Post-hoc least significant difference tests ($p<0.05$) were then used to compare differences in grey matter densities between any two groups using SPSS 11.5 (SPSS, Chicago, IL).

Spearman's correlation coefficient was calculated between grey matter density values of regions identified in the above analysis and IRIS total score, chlorpromazine-equivalent antipsychotic dosage, and duration of treatment to explore relationships between brain structure anomalies, DOR, and antipsychotic treatment.

3. Results

3.1. Demographic and clinical characteristics

Analysis of variance (ANOVA) and chi-square tests showed no significant differences in the age, years of education and gender

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