Clinical Neurophysiology 126 (2015) 2276–2281

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Dissociation of anatomical and functional alterations of the default-mode network in first-episode, drug-naive schizophrenia

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ARTICLE INFO

Article history:
Accepted 27 January 2015
Available online 16 February 2015

Keywords:
First-episode schizophrenia
Default-mode network
Voxel-based morphometry
Fractional amplitude of low-frequency fluctuation

HIGHLIGHTS

- A dissociation pattern indicated that brain functional and anatomical abnormalities of the default-mode network (DMN) might be present independently in schizophrenia.
- The recruitment of first-episode, drug-naive schizophrenia patients offers insight into the pathophysiology of schizophrenia independently of treatment issues.
- Functional and structural abnormalities highlight the importance of DMN in the pathophysiology of schizophrenia.

ABSTRACT

Objective: Anatomical and functional alterations of the default-mode network (DMN) have been implicated in the pathophysiology of schizophrenia. However, no study is engaged to explore whether structural and functional abnormalities of the DMN overlap in schizophrenia. This study was undertaken to examine whether anatomical and functional abnormalities are present in similar or different brain regions of the DMN in first-episode, drug-naive schizophrenia.
Methods: Forty-nine first-episode, drug-naive schizophrenia patients and 50 age-, sex-, and education-matched healthy controls underwent structural and resting-state functional magnetic resonance imaging (fMRI) scanning. The voxel-based morphometry (VBM) and fractional amplitude of low-frequency fluctuation (fALFF) methods were used to analyze imaging data.
Results: The patients exhibited significantly decreased gray matter volume (GMV) in the left medial prefrontal cortex (orbital part) and increased fALFF in the left posterior cingulate cortex compared with the controls. No overlap of brain regions with anatomical and functional abnormalities was observed in the patient group. There was also no correlation between decreased GMV/increased fALFF and clinical variables in patients.
Conclusions: A dissociation pattern of brain regions with anatomical and functional changes within the DMN is revealed in schizophrenia patients.
Significance: Our findings suggest that brain functional and anatomical abnormalities within the DMN might contribute independently to the pathophysiology of schizophrenia.

1. Introduction

Neuroimaging data support that the pathophysiology of schizophrenia is related to alterations of anatomical and functional connectivity of distributed networks (Friston, 1998; Stephan et al., 2009). One of the most examined networks, the default-mode net-

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http://dx.doi.org/10.1016/j.clinph.2015.01.025
1388-2457/

work (DMN), has been implicated in schizophrenia (Zhou et al., 2007; Broyd et al., 2009; Guo et al., 2014d), which includes medial prefrontal cortex (MPFC), posterior cingulate cortex/precuneus (PCC/PCu), lateral temporal cortex, and lateral parietal cortex (Raichle et al., 2001). The DMN is particularly active during "rest" and is deactivated during task-related cognitive process (Garrity et al., 2007), which is related to self-referential or introspective mental activity (Raichle and Snyder, 2007).

Evidence has been accumulated that regional activity of the DMN is disrupted in schizophrenia with inconsistent findings, such as increased and decreased regional activity in the MPFC (Hoptman et al., 2010; Huang et al., 2010). The inconsistent findings of increased and decreased MPFC activity may result from analysis methods and sample heterogeneity. When Hoptman et al. (2010) repeated their analysis using the same method (amplitude of low-frequency fluctuation, ALFF) as that of Huang et al. (2010), their finding of increased fractional ALFF (fALFF) in the MPFC did not exist. Although ALFF seems effective to identify regional activity, it has been criticized for its being sensitive to physiological noise, and fALFF, an improved method, is recommended in analyzing neuroimaging data (Zou et al., 2008). In addition, Hoptman et al. recruited a sample of medicated patients with schizophrenia and schizoaffective disorder. Treatment issues and sample heterogeneity might have biased their findings. Hence, it is meaningful to conduct a fALFF analysis in first-episode, drug-naive patients with schizophrenia to reduce the possible effect of medication use and sample heterogeneity. Of particular importance is that abnormalities of the DMN may act as a role in generating certain symptoms of schizophrenia. For example, significantly negative correlation between negative symptoms and DMN activity in the frontal polar is observed (Mingoia et al., 2012). Specific correlation is also reported between increased MPFC activity and improved illness insight and social functioning in patients with schizophrenia after recovery (Lee et al., 2006). These correlations suggest that altered DMN connectivity bears significance for the core symptoms of schizophrenia.

Investigations of brain structure in schizophrenia have been frequently done to explore the whole-brain differences by a voxel-based morphometry (VBM) method. The VBM findings have revealed decreases of gray matter volume (GMV) mainly in the thalamus and the frontal and temporal gyrus (Honea et al., 2005; Cronenwett and Csernansky, 2010; Levitt et al., 2010), perhaps most predominantly in the temporal gyrus in first-episode schizophrenia (Meisenzahl et al., 2008; Lui et al., 2009; Hu et al., 2013; Guo et al., 2014a). Previous anatomical studies, designed to explore the whole-brain differences, have also observed gray matter abnormalities within the DMN, such as MPFC (Honea et al., 2005) and PCC (Fornito et al., 2009).

Obviously, the DMN has been linked to the pathophysiology of schizophrenia with findings using multimodal neuroimaging techniques, such as resting-state functional magnetic resonance imaging (fMRI) and structural MRI (Broyd et al., 2009; Guo et al., 2014d). However, one important question that remains to be settled is whether anatomical and functional brain alterations in the DMN are present in similar or different brain regions in first-episode, drug-naive schizophrenia. Previously, few studies designed to examine functional and structural abnormalities in the same sample of schizophrenia patients (Lui et al., 2009; Rubinov and Bassett, 2011; Ren et al., 2013) and their unaffected siblings (Guo et al., 2015), and found that functional and structural abnormalities were present in different brain regions. However, no studies have identified anatomical and functional brain alterations of the DMN in the same population to examine whether and how the functional abnormalities are related to anatomical abnormalities within the DMN in schizophrenia. Another important question is that most previous studies have recruited medicated and/or chronic schizophrenia patients. This recruitment criterion may introduce confounding factors such as medication use and long illness duration. For example, medication use can significantly confound the functional and anatomical findings in schizophrenia (Lieberman et al., 2005; Lui et al., 2010). Prolonged illness duration is observed to have a neurotoxic effect on gray matter (Marshall et al., 2005; Perkins et al., 2005). Therefore, it is meaningful to choose first-episode, drug-naive schizophrenia as a starting point for fMRI studies to provide the naive topological information to the pathophysiology of schizophrenia.

In the present study, we used VBM to investigate the anatomy of the DMN in schizophrenia, and the fALFF method was performed to detect regional functional alterations of the DMN. VBM is capable of assessing structural differences in the whole brain and avoids operational bias toward particular brain regions (Honea et al., 2005; Meisenzahl et al., 2008; Ma et al., 2012; Hu et al., 2013; Guo et al., 2014a), and fALFF is designed to detect the regional intensity of spontaneous of blood oxygen level-dependent (BOLD) signals and provides a specific measure of low-frequency oscillatory phenomena (Zou et al., 2008). Increased fALFF might reflect neural hyperactivity in the area and vice versa (Guo et al., 2013; Liu et al., 2013; Su et al., 2014). The two approaches have been widely used to explore anatomical and functional abnormalities in a bulk of psychiatric disorders, including schizophrenia. Our aim in the present study was to identify whether and how the functional abnormalities were related to anatomical abnormalities within the DMN in schizophrenia. Based on the above-mentioned studies (Lui et al., 2009; Rubinov and Bassett, 2011; Ren et al., 2013; Guo et al., 2015), we hypothesized that functional and anatomical abnormalities within the DMN would be observed in different brain regions in first-episode, drug-naive schizophrenia patients. We also examined the relationship between these abnormalities and clinical factors, such as duration of untreated psychosis (DUP) and symptom severity.

2. Methods and materials

2.1. Subjects

A total of 110 right-handed subjects were recruited for the study. Four subjects (3 patients and 1 control) withdrew the consent, and the data from 7 subjects (4 patients and 3 controls) were discarded due to excessive head motion. The final sample include 49 first-episode, drug-naive schizophrenia patients and 50 healthy controls. The study was approved by the ethics committee of the First Affiliated Hospital, Guangxi Medical University, and written informed consent was obtained from all participants. Diagnosis of schizophrenia was determined by using the Structured Clinical Interview of the DSM-IV (SCID), patient edition (First et al., 1997). The DUP for the patients was less than 3 years. Symptom severity was rated with the Positive and Negative Symptom Scale (PANSS) at the scan time. Healthy controls were recruited from the community. All controls were interviewed to exclude individual with psychiatric disorders or with a first-degree relative having psychiatric disorders. The following exclusion criteria were applied to all subjects: neurological or other psychiatric disorders, clinical comorbidities (i.e., anxiety disorders), severe medical disorders, substance abuse, or any contraindications for MRI.

2.2. Scan acquisition

Scanning was conducted on a Siemens 3T scanner. Subjects were instructed to lie still, keep their eyes closed, and remain awake. Foam padding and earplugs were used to minimize head movement and scanner noise. High-resolution T1-weighted