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Resting-state Brain Activity Changes Associated with Tardive Dyskinesia in Patients with Schizophrenia: Fractional Amplitude of Low-frequency Fluctuation Decreased in the Occipital Lobe

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Abstract—We explored resting-state brain activity and its potential links to clinical parameters in schizophrenic patients with tardive dyskinesia (TD) using fractional amplitude of low-frequency fluctuations (fALFF). Resting-state functional magnetic resonance imaging data were acquired from 32 schizophrenic patients with TD (TD group), 31 without TD (NTD group), and 32 healthy controls (HC group). Clinical parameters including psychopathological symptoms, severity of TD, and cognitive function were assessed using the Positive and Negative Syndrome Scale, Abnormal Involuntary Movement Scale (AIMS), and Repeatable Battery for the Assessment of Neuropsychological Status, respectively. Pearson correlation analyses were performed to determine the relationship between the regions with altered fALFF values and clinical parameters in TD patients. The TD group showed decreased fALFF in the left middle occipital gyrus (MOG) and the right calcarine sulcus (CAL) compared to the HC group, and decreased fALFF in the left cuneus compared to the NTD group. In the TD group, fALFF values in the left MOG and the right CAL were correlated separately with the delayed memory score ($r = 0.44$, $p = 0.027$; $r = 0.43$, $p = 0.028$, respectively). The AIMS total score was negatively correlated to the visuospatial/constructional score ($r = -0.53$, $p = 0.005$). Our findings suggested that resting-state brain activity changes were associated with TD in schizophrenic patients. There was an association between the decreased brain activity in the occipital lobe and the delayed memory cognition impairment in this population.

Key words: schizophrenia, tardive dyskinesia, resting-state functional magnetic resonance imaging, fractional amplitude of low-frequency fluctuation.

INTRODUCTION

Tardive dyskinesia (TD) is a serious and potentially irreversible motor syndrome whose development is associated with the use of a neuroleptic medication for at least a few months. It is characterized by involuntary, athetoid, or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic or trunk muscles) (American Psychiatric Association). As no efficacious treatment has yet been made available for TD (Lockwood and Remington, 2015; Hatcher-Martin et al., 2016), identifying the neural processes associated with TD may advance our understanding of its etiology and facilitate the development of therapeutic strategies.

Over the years, several hypotheses have been proposed to account for the development of TD, focusing on dopamine-receptor hypersensitivity, γ-aminobutyric acid deficiency, oxidative stress, and neurotoxicity (Kulkarni and Naidu, 2003; Lerner et al., 2015). However, none could explain the full spectrum of clinical symptoms of TD (Bhidayasiri and Boonyawairoj, 2011). Another avenue of research on TD has focused on systems neuroscience and has investigated its association with structural brain changes (Sarró et al., 2013).

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Abbreviations: AIMS, Abnormal Involuntary Movements Scale; ALFF, amplitude of low-frequency fluctuations; BA, Brodmann area; CAL, calcarine sulcus; CPZ, chlorpromazine; CUN, cuneus; FA, flip of angle; fALFF, fractional amplitude of low-frequency fluctuations; FD, framewise displacement; FOV, field of view; GM, gray matter; HC group, the group of healthy controls; ICC, inter-rater correlation coefficient; MOG, middle occipital gyrus; NEX, number of excitations; NTD group, the group of schizophrenic patients without tardive dyskinesia; PANSS, Positive and Negative Syndrome Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; REST, Resting-State fMRI Data Analysis Toolkit; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; SPM, Statistical Parametric Mapping; TD group, the group of schizophrenic patients with tardive dyskinesia; TD, tardive dyskinesia; TE, echo time; TI, inversion time; TR, repetition time.

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For example, schizophrenic patients with TD reportedly have significantly reduced gray matter (GM) volume in numerous brain areas compared to patients without TD (Telfer et al., 2011; Li et al., 2013; Sarró et al., 2013). Though the pertinent findings have been less than consistent, the studies have suggested potential cerebral bases for the development of TD.

Nevertheless, no studies have examined functional brain abnormality in this population. Resting-state functional magnetic resonance imaging (rs-fMRI) has been widely used to characterize cerebral functional organization in health and illness. In rs-fMRI, the amplitude of low-frequency fluctuation (ALFF) represents a measure of spontaneous neural activity. ALFF quantifies the total power of a given fMRI time course within the low-frequency range (Zang et al., 2007; Zou et al., 2008). Investigators have used ALFF to characterize altered brain activities in many neuropsychiatric conditions including attention deficit hyperactivity disorder (Zang et al., 2007), schizophrenia (Turner et al., 2013), and depression (Wang et al., 2016). For instance, lower resting-state ALFF in the parietal cortex may represent working memory dysfunction in patients with schizophrenia (Turner et al., 2013). Findings from these functional imaging studies complement structural brain imaging in advancing our understanding of cerebral dysfunction of many clinical conditions (Tang et al., 2015). More recent studies have suggested that ALFF could easily be influenced by physiological noise (Zou et al., 2008), and that fractional ALFF (fALFF), a normalized index of ALFF, could provide a more specific measure of low-frequency oscillations. Similar to ALFF, fALFF showed good to moderate test–retest reliability in a sample of healthy subjects (Zuo et al., 2010).

It is well known that schizophrenic patients with TD experience more severe cognitive impairment compared to those without TD (Waddington et al., 1987; Wu et al., 2013; Hui et al., 2017). In a positron-emission tomography imaging study, TD was related to abnormal metabolic activity in the parietal and cingulate cortices (Szymanski et al., 1996), but it is not clear whether these metabolic changes are associated with cognitive impairment in TD.

Here, we aimed to contribute to this line of research and explore resting-state brain activity and its potential relationships with clinical ratings, including the severity of involuntary movement, psychotic symptoms, and cognitive performance, in schizophrenic patients with TD. Our hypothesis was that patients with TD might have exclusively altered resting-state brain activity in some brain regions, and the alteration might be related to the clinical manifestations and cognitive function in this population.

EXPERIMENTAL PROCEDURES

Participants

Sixty-three inpatients meeting the DSM-IV criteria for schizophrenia were recruited from Beijing HuiLongGuan Hospital, a city-owned psychiatric hospital. According to the criteria of Schooler and Kane (1982), 32 of the 63 patients were determined to have TD (TD group) and the other 31 to not have TD (NTD group) by two experienced psychiatrists. The severity of abnormal involuntary movement in the TD group was measured with the Abnormal Involuntary Movements Scale (AIMS). Each item on the AIMS ranges from 0 to 4, and the AIMS total score was calculated by adding items 1–7. The two independent raters had a 1.0 inter-rater correlation coefficient (ICC) for the diagnosis of TD, and at least 0.85 for the severity of TD. Two other psychiatrists assessed the psychopathological symptoms of all patients using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) after scale training, with an ICC > 0.90. A group of 32 healthy controls (HC group) demographically matched for age, sex, and education was recruited from the local community. The Chinese version (Zhang et al., 2008) of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A) (Randolph et al., 1998) was used to evaluate cognitive functions. The RBANS examines five domains, including immediate memory, visuospatial/constructional function, language, attention, and delayed memory. Two psychiatrists evaluated all participants with the RBANS with an ICC > 0.88. The total score and five subscores were standardized (using 100 as the normal mean scores and 15 as the standard deviation) for subsequent analyses.

This study was approved by the Ethics Review Board of the Beijing HuiLongGuan Hospital, and all subjects provided written informed consent after a detailed explanation of the study prior to participation.

Image acquisition

Imaging data were collected using a 3 T MR scanner (Magnetom Trio, Siemens, Germany). Each participant lay supine with the head snugly fixed by a belt and foam pad, and wore earphones to reduce the MRI noise. High resolution structural T1-weighted images were acquired covering the whole brain with a magnetization prepared rapid acquisition gradient echo sequence: repetition time (TR) = 2300 ms, echo time (TE) = 2 ms, inversion time (TI) = 900 ms, matrix size = 512 $\times$ 256, flip angle (FA) = 9°, field of view (FOV) = 220 mm $\times$ 220 mm, number of excitations (NEX) = 1, thickness/gap = 1/0.5 mm, 176 slices. A 7-minrs-fMRI scan was collected using a gradient echo planar imaging sequence: 210 time points, TR = 2000 ms, TE = 30 ms, matrix size = 64 $\times$ 64, FA = 90°, FOV = 210 mm $\times$ 210 mm, NEX = 1, thickness/gap = 4/0 mm, 32 axial slices. During rs-fMRI scanning, all participants were instructed to keep their eyes closed, to remain awake, and not to think about anything in particular.

Data preprocessing

The preprocessing was carried out using the Data Processing Assistant for Resting-State fMRI (DPARSF, Yan and Zang, 2010. http://www.restfmri.net), which is based on Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST, Song et al., 2011. http://www.restfmri.net). These steps included: remove the first 10 time points to allow for magnetic saturation; slice timing

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