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Disrupted structural connectivity network in treatment-naive depression

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ABSTRACT

Background: Neuroimaging studies suggest that treatment-naive depression (TD) is characterized by abnormal functional connectivity between specific brain regions. However, the question surrounding the structural basis of functional aberrations in TD patients still remains.
Methods: In the present study, diffusion tensor imaging tractography was employed to construct structural connectivity networks in 22 early adult-onset, first-episode TD patients and 19 healthy controls (HC). Graph theory and network-based statistic (NBS) were then employed to investigate systematically the alteration of whole brain structural topological organization and structural connectivity in TD patients.
Results: Graph theoretical analysis revealed that, compared with HC, TD patients exhibited altered structural topological measures, including decreased shortest path length, normalized clustering coefficient, normalized shortest path length, and small-worldness, as well as increased global and local efficiency. NBS results further revealed that TD patients showed two altered structural sub-networks. One sub-network mainly involved connections between the right orbitofrontal cortex (OFC) and the right insula, putamen, caudate, hippocampus, fusiform gyrus, inferior temporal gyrus and lingual gyrus. The other sub-network mainly included connections between the left OFC and the left gyrus rectus, insula, putamen, caudate, thalamus, pallidum and middle occipital gyrus.
Conclusions: The findings suggest that TD patients exhibit a disruption in the topological organization of structural brain networks. The altered orbitofrontal connectivity may particularly contribute to the manifestation of symptoms in TD patients. The abnormalities may facilitate understanding of the functional disturbances of mood and cognition in the disease.

1. Introduction

Depression is a common psychiatric disease characterized by feelings of sadness, guilt, worthlessness, and hopelessness, followed by a high chance of suicide (Jia et al., 2010; Petersen et al., 2001). The emerging functional magnetic resonance imaging (fMRI) technique has recently deepened the understanding of the pathogenesis of the disorder. For instance, Hooley et al. (2009) reported that participants recovered from depression have increased activation in the amygdala and decreased activation in the dorsolateral prefrontal cortex when they responded to criticism from their mothers. Hypoactivation of prefrontal cortex was also observed in depression when they were shown pictures of sad faces (Lee et al., 2008). However, these studies usually recruited depressive subjects taking antidepressant medication, and the findings might be confounded by medication effects. For example, Lui et al. (2011) found distinct functional deficits in the distributed brain networks between depressed patients who show response to antidepressant treatment and those who exhibit no such response, which indicates different pathogenesis between the two clinical subtypes. Thus, a study of treatment-naive depression (TD) may facilitate understanding of the underlying pathophysiological mechanisms in depression, which could improve early diagnosis and therapy.

A number of neuroimaging studies have revealed that abnormal functional cortico-limbic circuits were associated with the pathophysiology of TD patients. For instance, an fMRI study employing a face-matching task (Frodl et al., 2010) reported a functional connectivity bias of the orbitofrontal cortex (OFC) with precuneus and dorsolateral prefrontal cortex in drug-free patients with depression, representing a neural mechanism of processing bias in the disease. Anand et al. (2009) found decreased cortico-limbic functional connectivity in

Abbreviations: TD, treatment-naive depression; HC, healthy controls; DTI, diffusion tensor imaging; SCN, structural connectivity network; MNI, Montreal Neurological Institute; AAL, automated anatomical labeling; NBS, network-based statistic; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; HRSD, Hamilton Rating Scale for Depression; FACT, Fiber Assignment by Continuous Tracking; ROI, regions of interest; FDR, false discovery rate; OFC, orbitofrontal cortex; DMN, default mode network.

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unmedicated unipolar depression at rest by using an analysis based on regions of interest (ROI). Altered functional connectivity between the amygdala and prefrontal cortex was observed in TD patients during emotional face processing task (Kong et al., 2013) and also under the resting-state condition (Yue et al., 2013). In addition, resting-state fMRI studies reported that TD patients exhibit altered functional connectivity within the default mode network (DMN) (Guo et al., 2013a; Zhu et al., 2012), and between the DMN and the middle temporal gyrus (Ma et al., 2012), anterior cingulate cortex and thalamus (Guo et al., 2013a). Furthermore, neuroimaging studies revealed increased cerebellar functional connectivity with the temporal poles (Liu et al., 2012) and visual recognition network (Guo et al., 2013b), along with decreased functional connectivity with regions within the DMN (Guo et al., 2013b; Liu et al., 2012) in TD patients. Functional abnormalities of these circuits or networks suggest that TD patients possess a multidimensional and system-level disorder rather than a disease of dysfunction in a single brain region. However, the question surrounding the structural connectivity basis of these functional changes in the disease still remains.

The functional circuit integration has been suggested to be significantly constrained by the large-scale structural pathways interconnecting the human functional brain regions (Hagmann et al., 2008; Honey et al., 2009; van den Heuvel et al., 2008). Therefore, the structural connectivity substrate of distributed functional interactions among brain regions should be studied to gain full understanding of the functional disturbances in TD patients. Diffusion tensor imaging (DTI) tractography, which is capable of reconstructing white matter tracts of the human brain, provides powerful strength for the comprehension of the structural connectivity patterns of brain. To the best of our knowledge, only three studies have investigated the structural connectivity in TD patients by employing DTI tractography. The first study (Korgaonkar et al., 2012) reported that several inter-cortical connections have the most discriminative power for classification between treatment-free depression and healthy controls (HC). This study, however, did not investigate structural connectivity of subcortical areas, for example, the basal ganglia, which has been demonstrated critical in depression (Chantiluke et al., 2012; Marchand, 2010). The second study (Fang et al., 2012) found increased structural connectivity within the cortical-limbic circuit in TD patients. The altered connections were further identified as the most discriminating features. This study, however, did not examine structural abnormalities at the network level. A study of TD patients at network level might provide new insights into the disease. The third study (Korgaonkar et al., in press) demonstrated decreased structural connectivity within the DMN and the network which comprises the frontal cortex, thalamus and caudate regions in a large sample of depression. Results of this study, however, might be affected by antidepressant effects. In brief, these previous structural studies 1) mainly focused on the structural connectivity between cortical and limbic regions, or 2) might have results confounded by medication effects. The question of whether TD patients have deficits of structural connectivity across the whole brain, as well as alterations of structurally topological organization at the network level, still remains.

Graph theory, which is capable of investigating the topological organization of the human brain, has attracted considerable attention in studies of healthy subjects (Achard and Bullmore, 2007; Li et al., 2014; Sporns and Zwi, 2004). This technique conceptualizes the brain as a network consisting of a set of nodes and the edges linking these nodes, and has been increasingly applied to brain diseases such as mild cognitive impairment (Bai et al., 2012), Alzheimer's disease (Lo et al., 2010), post-traumatic stress disorder (Long et al., 2013), and multiple sclerosis (Shu et al., 2011). Two fMRI studies have used graph theory to reveal disruptions of the topological organization of the functional brain network in TD patients, which may contribute to disturbances in mood and cognition in the disease (Jin et al., 2011; J. Zhang et al., 2011). However, the structural topological abnormalities of the brain network in TD patients remain unclear.

The principal aim of the present study was to test whether structurally connectional architecture demonstrates abnormality in TD patients by employing DTI tractography and graph theory. Based on previously reported results, we hypothesized that TD patients might exhibit disruption of the topological organization of the whole-brain structural network, as well as connectivity strength within specific sub-networks.

2. Materials and methods

2.1. Participants

Twenty-two right-handed outpatients with early adult-onset, first-episode TD (10 females; age [mean ± SD]: 28.09 ± 9.91 years; education: 12.23 ± 2.62 years; HRSD score: 25.89 ± 6.26) were recruited from the Mental Health Institute, of the Second Xiangya Hospital, Central South University, China. TD patients were diagnosed using the Structured Clinical Interview according to the DSM-IV criteria (Runeson and Rich, 1994). The severity of depression was quantified by using the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). Only patients with HRSD score larger than 18 were eligible for the present study. Thus, all patients in our current study are diagnosed to have severe depression. Exclusion criteria included any history of neurological diseases or other physical diseases, as well as comorbidities with other disorders (no evidence of schizoaffective disorder, bipolar disorder or Axis II, personality disorders and mental retardation). Patients younger than 18 years or older than 50 years were also excluded. Additionally, the current illness duration was no more than six months.

Nineteen right-handed HC (9 females; age [mean ± SD]: 24.37 ± 4.18 years; education [mean ± SD]: 13.11 ± 2.47 years) were recruited from the community. The participants were interviewed by the same psychiatrists using the Structured Clinical Interview for DSM-IV, non-patient edition (Runeson and Rich, 1994). None of the participants had a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness among first-degree relatives. No significant differences in age, gender, and education were found between TD patients and HC. The clinical and demographic data are shown in Table 1.

The present study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. All participants were given information about the procedure, and participated in the research willingly and without coercion. Written informed consents were obtained from all participants.

2.2. Data acquisition

All participants were scanned by using a 1.5T GE scanner (General Electric, Fairfield, Connecticut, USA). The participants were asked to use a prototype quadrature birdcage head coil fitted with foam padding to minimize head movement. The participants were instructed to remain motionless, keep their eyes closed and not think of anything in particular. T1 and DTI images were acquired using the following sequences respectively: 1) T1-weighted volumetric 3D Spoiled Gradient Recall sequence (repetition time/echo time [TR/TE] = 12.1/4.2 ms,

Table 1
Demographic information and disease severity in TD patients and HC.

Demographic data	TD (n = 22)	HC (n = 19)	p value
Gender (male/female)	12/10	10/9	0.902[a]
Age (years)	28.09 ± 9.91	24.37 ± 4.18	0.119[b]
Years of education (years)	12.23 ± 2.62	13.11 ± 2.47	0.278[b]
HRSD score	25.89 ± 6.26	–	
Illness duration (months)	2.95 ± 1.73	–	

TD, treatment-naive depression; HC, healthy control; HRSD, Hamilton Rating Scale for Depression.
[a] The p value was obtained by chi-square test.
[b] The p value was obtained by two-tailed two-sample t-test.