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Research paper

Reconfiguration of hub-level community structure in depressions: A follow-up study via diffusion tensor imaging

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ABSTRACT

Background: The role of abnormal communications among large-scale brain networks have been given increasing attentions in the pathophysiology of major depressive disorder (MDD). However, few studies have investigated the effect of antidepressant medication treatment on the information communication of structural brain networks, especially converged from the individual analysis.

Methods: Nineteen unipolar MDD patients completed two diffusion tensor imaging (DTI) scans before and after 8-week treatment with selective serotonin reuptake inhibitor. DTI data of 37 matched healthy controls were acquired. We focused on a hub-level community structure network, and investigated whether it had differences on the whole structure and which regions drove these differences in terms of modular affiliation and hub role shift. Data were analyzed by the novel permutation network framework, which appraised the topological consistency of hubs and reserved an individual information.

Results: Compared to the pre-treatment state, post-treatment patients exhibited increasing number of modular members in the modules that included the right medial superior frontal gyrus (SFGmed) or the thalamus. Moreover, the result suggested a hub role shift of the left insula from a *provincial*-hub before treatment to a *connector*-hub after treatment. Additionally, reduced inter-module degree in the right SFGmed was positively correlated with the reduced sum score of 17-item Hamilton depression rating scale at the follow-up.

Conclusions: Antidepressant medication treatment might be associated with modular reconfigurations of hubs within the fronto-limbic circuit. Moreover, increased inter-module connections of the left insula might improve its integration ability, promoting the remission of MDD. The correlation results of the right SFGmed suggested it might be a valuable indicator for treatment response.

1. Introduction

Major depressive disorder (MDD) is a serious mental illness with devastating social, personal, and medical consequences. It is characterized by persistent and overwhelming feelings of guilt, sadness, anhedonia, hopelessness, etc. (APA, 1994; Kessler, 2012). Antidepressant medication is commonly use to treat MDD and one of the typical classes of antidepressants is the class of selective serotonin reuptake inhibitors (SSRIs). It was hypothesized that the effects of antidepressant medication was to enhance functional connectivity between the cortical mood-regulating and the limbic mood-generating regions, coupled with decreased limbic activation in response to negative emotional stimuli (Sneed et al., 2011). Convergent evidence from neuroimaging studies demonstrated that antidepressant medication treatment could reverse the increased activity in the limbic regions such as the insula, the striatum, the anterior cingulated and thalamus (Fu et al., 2013; Wang et al., 2014), coupled with the altered fractional anisotropy (FA), such as in the right cingulum bundle (Bracht et al., 2015), and the altered grey matter volume in the dorsolateral prefrontal cortex, the insula and the hippocampal regions of MDD patients (Arnone et al., 2013; Jung et al., 2014; Smith et al., 2013). The aforementioned findings suggested that the improvement of clinical

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symptoms after using antidepressant medication treatment was associated with the alterations within the fronto-limbic circuit.

An increasing interest is focused on the role of abnormal communication among large-scale brain networks in the pathophysiology of MDD (Gong and He, 2015; Wang et al., 2015). The segregation and integration of neural information are very important aspects of the information communication among the whole brain, and the balance between them is essential for the manipulation of distributed networks underlying cognitive function (Fox and Friston, 2012; Tononi et al., 1994). The hubs and communities can measure these two aspects, respectively. Previous work reported there were abnormalities of hubs and network modules in MDD using both functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) (GadElkarim et al., 2012; Lord et al., 2012; Peng et al., 2014; Qin et al., 2014). However, to the best of our knowledge, few studies have investigated the effect of antidepressant medication treatment on the segregation and integration of information communication in brain network.

Regarding to the between-group comparison of modular analysis, one popular comparison method is conducted on an averaged network of each group, while another method is to assess the consistency of a specific network measure or modular structure across each group (Moussa et al., 2012). Although both methods can yield results, the former fail to characterize complexity of networks. It was demonstrated that brain networks exhibit certain consistent organizations across subjects, and such consistency varied in different groups of subjects (i.e., the healthy and the disease) (Alexander-Bloch et al., 2012; Simpson et al., 2013). Therefore, we utilized the modular consistency of each group to assess the between-group difference.

In the present study, we utilized DTI to appraise the effect of an 8-week treatment with SSRIs on the hub-level community structure (HLCS) network, a sub-network that retained the modular structure of network and removed its non-hub nodes, in a well-defined population with unipolar MDD. DTI could estimate the white matter connectivity patterns (Alexander et al., 2007; Mori et al., 1999), and emerge as a powerful tool to map typical and atypical brain connectivity (Sexton et al., 2009; Simmonds et al., 2014). We obtained the HLCS network for each subject and analyzed it using the permutation network framework (PNF), which permitted to assess the topological consistency of key regions and preserve the individual modular information during the between-group comparisons, rather than analyzing the averaged group-level modular structure. We began at probing whether there was a significant between-group difference in the network-level of HLCS network, and then measured which regions driving this network difference from the two points, modular affiliation and the shift of hub role. Finally, the correlations between the modular metrics and clinical variables were explored.

2. Materials and methods

2.1. Participants

Nineteen unipolar MDD patients from in-patient facilities at Nanjing Brain Hospital and 37 gender- and age- matched healthy controls (HC) were recruited from the local community (Table 1). All recruited volunteers are Han Chinese. Eligibility screening procedures included the Structured Clinical Interview for the DSM-IV (SCID), the 17-item Hamilton depression rating scale (HAMD) and the Brief Psychiatric Rating Scale (BPRS). All patients were drug-free for at least two weeks at the baseline scanning, and then they received the SSRIs single-drug treatment. The patients underwent DTI scans at baseline and at an 8-week antidepressant medication treatment. The MDD patients had a minimum score of 24 rated with the 17-item HAMD on the day of scanning at baseline. Eighteen patients showed a clinical response to the treatment, defined as at least a 50% decrease from the baseline HAMD score. Eleven patients achieved clinical remission, defined as the HAMD score after treatment lower than 7. The exclusion criteria for the patients included serious suicide thought, other psychiatric illness and psychotic symptoms, physical diseases, a history of electroconvulsive therapy and treatment of transcranial magnetic stimulation. Moreover, the controllers with a family history of major psychiatric or neurological illness in their first-degree relatives were excluded. All subjects met the criteria to undergo the MRI scan. This study was approved by the Research Ethics Review Board of Nanjing Brain Hospital, and written informed consents were obtained from all participants.

2.2. Imaging acquisitions

Images were acquired with a GE Signa 1.5T MRI scanner. All participants were obtained both DTI data and high-resolution T1-weighted axial images. The DTI images were obtained with the following parameters: diffusion was measured along 25 non-collinear directions (b value=000 s/mm^2), and an additional image without diffusion weighting (i.e., b=0 s/mm^2), TR/TE=10000 ms/81.2 ms, FOV=240 mm×240 mm, matrix=128×128, number of excitations (NEX)=2, slice thickness=4 mm without gap. The high-resolution T1-weighted axial images were obtained with the following parameters: repetition time/echo time (TR/TE)=500/14 ms, thickness/gap=1.0/0 mm, flip angle=15°, inversion time=400 ms, matrix=256×128, field of view (FOV)=240×240 mm^2, in-plane resolution=256×192.

2.3. Data preprocessing

Image preprocessing was performed using the diffusion toolbox of

Table 1
Demographic information of the participants involved in this study.

Variables	MDD (n=19) Baseline	HC (n=37)	MDD (n=19) After 8 weeks	*p* value
Age (years)	23–53 (39.53 ± 9.22)	23–54 (36.65 ± 11.71)	–	0.36[a]
Gender (male/female)	8/11	13/24	8/11	0.61[b]
Education (years)	5–15 (10.68 ± 3.09)	5–18 (12.78 ± 4.31)	–	0.07[a]
Handedness (R/L)	19/0	37/0	19/0	–
Number of previous episodes	1.53 ± 0.51	–	–	–
Age of onset	19–44 (34.20 ± 7.18)			
Family history of mental illness (Positive/Negative)	1/18	–	–	–
Score of 17-item HAMD	24–42 (32.32 ± 6.00)	–	0–19 (5.47 ± 6.11)	< 0.001[c]
Duration of illness(months)	0.17–22 (5.03 ± 7.20)	–	–	–

Data are presented as the range of minimum-maximum (mean ± SD).
HC, healthy controls; MDD, depressive disorder patients; HAMD, Hamilton Depression Rating Scale.
L, left; R, right.
[a] *p* values were obtained by independent two-sample *t* test.
[b] *p* values were obtained by two-tailed Pearson chi-square test.
[c] *p* values were obtained by paired two-sample *t* test.