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Research paper

Functional network-based statistics in depression: Theory of mind subnetwork and importance of parietal region

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A R T I C L E I N F O

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A B S T R A C T

Objective: The functional network analysis of whole brain is an emerging field for research in depression. We initiated this study to investigate which subnetwork is significantly altered within the functional connectome in major depressive disorder (MDD).
Methods: The study enrolled 52 first-episode medication-naïve patients with MDD and 40 controls for functional network analysis. All participants received the resting-state functional imaging using a 3-Tesla magnetic resonance scanner. After preprocessing, we calculated the connectivity matrix of functional connectivity in whole brain for each subject. The network-based statistics of connectome was used to perform group comparisons between patients and controls. The correlations between functional connectivity and clinical parameters were also performed.
Results: MDD patients had significant alterations in the network involving "theory of mind" regions, such as the left precentral gyrus, left angular gyrus, bilateral rolandic operculums and left inferior frontal gyrus. The center node of significant network was the left angular gyrus. No significant correlations of functional connectivity within the subnetwork and clinical parameters were noted.
Conclusion: Functional connectivity of "theory of mind" subnetwork may be the core issue for pathophysiology in MDD. In addition, the center role of parietal region should be emphasized in future study.

1. Introduction

The brain pathophysiology of major depressive disorder (MDD) is an entry to understand the biological origin of depression. The initial theory of "limbic-cortical-striatal-pallidal-thalamic tract" (Sheline, 2000) suggested possible existence of network-based alterations for MDD. The previous studies also demonstrated the possible involvement of network (de Kwaasteniet et al., 2013; Lai et al., 2010; Lai and Wu, 2014b). However, the study of whole brain network-based statistics in MDD is very limited. It would be a possible obstacle for the further resolution of network pathophysiology in MDD.

The network of "theory of mind" has been discovered in healthy participants. It includes cognitive subnetwork, such as the precuneus, occipital lobe and temporal lobe, combined with affective subnetwork, such as the frontal lobe (Schlaffke et al., 2015). The network is important for implicit and explicit mental activities, such as self monitoring and reflections. They are crucial for social cognition (Frith and Frith, 2012). The frontal lobe serve as the center of human mental processing and control the self thoughts, which is derived from the gateway hypothesis (Burgess et al., 2007). The "theory of mind" is a possible theory for many mental illnesses, including MDD. Impaired domains of "theory of mind", such as social-perceptual and social-cognitive components, have been discovered in patients with MDD (Wang et al., 2008). The patients with MDD have difficult in reading social interactions (Zobel et al., 2010), which would be associated with chronicity and functional decline. In the system of "theory of mind", major parts include language processing regions and cognitive regions, such as the angular gyrus (ANG), inferior frontal gyrus (IFG) and temporal gyrus (Mason and Just, 2011). These regions could cooperate with language and emotional processing networks to modulate the perception of emotional content for sentences in speech (Herve et al., 2012). In the condition of natural social interaction, a mentalizing network also involves the precentral gyrus (PreCG) and other sensory regions, which could process the social stimuli and play an important role in social cognition (Saggar et al., 2014). A recent functional connectivity study showed that alterations in connections between the regions of "theory of mind", such as the parietal, frontal and temporal regions. In addition, the alterations were associated with

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emotional dysregulation and extensive processing of self-referential information (O'Neill et al., 2015). The literature suggests the crucial role of "theory of mind" regions in the pathophysiology of depression. However, the study was derived from borderline personality disorder to obtain the results. Therefore the importance of "theory of mind" hypothesis still needs further study with improvements in methodology to be proved.

The whole-brain functional connectome has been an emerging area for the investigation of pathophysiology in mental illnesses. Recently a new method, network-based statistics (NBS), has been applied in the field of connectome analysis. It uses the graph theory concept to derive the large-scale brain connectivity with the control of family wise error due to mass-univariate testing for each connection of the functional or structural connectome (Zalesky et al., 2010). It has been applied in several psychiatric illnesses, such as functional connectome in schizophrenia (Zalesky et al., 2010) and structural connectome in MDD (Korgaonkar et al., 2014; Long et al., 2015). The two reports of structural connectome found alterations of default mod network and other fronto-limbic networks for emotional and cognitive functions in depression. One functional connectome analysis using graph theory found similar disturbances in the network involving mood and cognition (Zhang et al., 2011).

From the above literature, we designed this study using resting-state functional magnetic resonance imaging (Rs-FMRI) technique to survey the brain connectivity in MDD patients. In addition, we applied the connectivity matrix analysis and NBS analysis of Rs-FMRI signals in MDD. Based on the "theory of mind" model, we hypothesized that patients with MDD would have reductions in the functional connectome of "theory of mind" network, such as the ANG, PreCG, IFG and temporal lobe, using a relatively unbiased method.

2. Participants

All patients with MDD were met for the following criteria: (1) first-episode patients with a pure MDD diagnosis (DSM-IV criteria) made by the Structured Clinical Interview for DSM-IV; (2) severity of MDD was at least moderate: Clinician Global Impression of Severity > 4, Hamilton Rating Scales for Depression (HDRS) score > 20, Hamilton Rating Scales for Anxiety (HARS) score < 5; (3) no co-morbid psychiatric illnesses or medical illnesses; (4) no previous cognitive behavioural therapy or other psychotherapies; (5) medication-naïve; (6) no abuse of or dependence on alcohol or other substances; and (7) no past history of claustrophobia or discomfort while receiving MR scanning. The healthy controls had no psychiatric illnesses or significant medical illnesses. All of the patients and part of healthy subjects signed the informed consent that was approved by the three Institutional Review Boards at Taipei Tzu Chi Hospital, Cheng Hsin General Hospital and National Yang-Ming University according to the institute where they were recruited. The patients were enrolled at Taipei Tzu Chi Hospital and Cheng Hsin General Hospital. The controls were enrolled from Taipei Tzu Chi Hospital, Cheng Hsin General Hospital and National Yang-Ming University. At the time of the MR imaging, none of the participants in the control group received psychotropic treatment. Handedness was determined by using the Edinburgh Inventory of Handedness (Oldfield, 1971). The sample of participants has some overlaps of our previous reports (Lai and Wu, 2013, 2014a). In this study, we enrolled 52 patients with MDD (26 men and 26 women; 40.26 ± 8.97) and 40 controls (20 men and 20 women; 39 ± 11.81) (Table 1). 44 of the 52 patients and 27 of the controls have been previously reported (Lai and Wu, 2015). This prior article dealt with regional homogeneity alterations in depression patients whereas in this manuscript we report on the whole-brain functional connectome analysis in depression patients.

2.1. Rs-FMRI data acquisition and pulse sequence

Echo planar imaging (EPI) sequence were acquired in 20 axial slices (TR = 2000 ms, TE = 40 ms, flip angle = 90°, field of view = 24 cm; 5 mm thickness and 1 mm gap; the sequence duration was 300 s for each subject, 150 time points were acquired, voxel dimension: 64x64 × 20) at baseline visit (3 T Siemens scanner housed at MRI (magnetic resonance imaging) center of National Yang Ming University) in patients and controls. All the patients and controls were requested to close their eyes with relaxing manner and not sleepy while scanning. The participating subjects were instructed to move as little as possible and stay fully awake while scanning. All these patients and controls reported that they could be fully awake while MRI scanning.

Table 1
Demographic data of participating patients and controls.

	Patients (N = 52)	Controls (N = 40)	Sig p (2-tailed), Z df = 63
Age, mean (SD), years old	40.26 (8.97)	39 (11.81)	0.238, −1.17
Gender (number)	F(26), M(26)	F(20), M(20)	0.835
Duration of illness, mean (SD), months	4.52 (1.60)	0 (0)	N/A
Educational years, mean (SD)	15.78 (0.80)	15.90 (0.59)	0.752, −0.316
Handedness	R (51)	R (39)	0.131
HDRS, mean (SD)	22.38 (2.33)	1.92 (0.97)	< 0.001, −8.246
HARS, mean (SD)	2.23 (1.02)	2.20 (1.15)	0.316, −0.195

N: number; SD: standard deviation; F: female, M: male; HDRS: Hamilton rating scales for depression; HARS: Hamilton rating scales for anxiety; N/A: not applicable; Sig p (significance of p-value) was from Mann-Whitney *U* test for nonparametric independent 2-sample *t*-test; df: degree of freedom.

2.2. Rs-FMRI data preprocessing

EPI data was first preprocessed by DPARSF (Data Processing Assistant and Resting-State FMRI, version 2.2; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China.) (Chao-Gan and Yu-Feng, 2010) working with the statistical parametric mapping 8 (SPM8) on the Matlab platform, which included the removal of first 10 time points due to the consideration for instability of initial MRI signal and patients' difficult to adapt at first about MRI acquisition circumstance, slice timing with 20th slice as reference slice, realignment, normalization to standard MNI spaces by using EPI templates and re-sampling with 3 × 3 x 3 mm3, smoothing by Full Width at Half Maximum (FWHM) 4x4 × 4 kernel, to detrend and filter data with residual signals within 0.01–0.08 Hz to discard the bias from high-frequency physiological noise and low-frequency drift. As all subjects' head movements were less than 0.5 mm in translation and 1° in rotation by obtaining the motion time courses of all subjects, no subject was excluded due to no excessive motions were observed. The filtered Rs-FMRI data were registered (nonlinear elastric registration) to the EPI template. The estimated motion parameters were obtained for each subject regressed on each voxel. Besides, the effects of "micro-movements" and the nuisance correlation caused by head motion were removed by checking covariates in nuisance regressors in DPARSF (Power et al., 2012; Yan et al., 2013a). Several sources of spurious covariates were removed except global signals due to the controversy about removing the global signal in the resting-state functional connectivity data (Fox et al., 2005; Murphy et al., 2009). The individual-level covariates of motion included Friston-24 parameter model (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) and group-level covariates of motion included framewise displacement motion regression model (Yan et al., 2013b).

2.3. Connectivity matrix measures

We used the GRETNA toolbox (https://www.nitrc.org/projects/