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Research report

Aberrant connectivity within the default mode network in first-episode, treatment-naïve major depressive disorder

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ABSTRACT

Background: Convergent studies have highlighted the dysfunction of default mode network (DMN) in major depressive disorder (MDD). The altered connectivity in posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) was especially found to be of interest in the resting state functional connectivity analysis. Recently, more attention has turned to the internal functional connectivity within the DMN. However, the internal connection patterns within the DMN remain unclear at the initial onset of MDD.
Methods: Resting-state fMRI was performed on 38 first-episode, treatment-naïve MDD patients along with 38 matched healthy controls. Seed-based analysis was used to define the DMN and then a region-to-region connectivity analysis was performed to inspect the functional connectivity within the DMN. Spearman's rank correlation analysis was performed between significantly abnormal connectivities in MDD patients and clinical measurements.
Results: Decreased region-to-region connectivities within DMN were found between the PCC and dorsal medial prefrontal cortex (dmPFC), between PCC and the right inferior parietal gyrus/angular, as well as between the left thalamus and cerebellar tonsil. No significant increase in connectivity was found. Moreover, functional connectivity between the left thalamus and cerebellar tonsil revealed a marginal significant negative correlation with clinical Hamilton Depression Rating Scale (HDRS) scores.
Limitations: Noteworthiness in morbidity, a high risk of mortality, and a high rate of medical service utilization of MDD make the current results uncertain to apply to the more complicated situations.
Conclusions: Each region within DMN may have a specific, individual functional role. The reason to identify the pathological mechanism of MDD may not lie in the abnormal DMN functional connectivity, but rather in the abnormal functional connectivity within DMN.

1. Introduction

Major depressive disorder (MDD) is a common mental disorder, typically characterized by pervasive despondency and failure to suppress negative thoughts, as well as specific cognitive and behavioral alterations (First et al., 2001). The complexity of the disease itself causes the underlying pathophysiology of this disorder to remain unclear. Functional connectivity studies based on resting-state functional magnetic resonance imaging (fMRI) have been established as a technique for unbiased analysis of the brain's functional connectome (Gorges et al., 2013; Lang et al., 2012). Therefore, the investigation of objective neurobiological markers of the core MDD symptoms may be associated with brain network dysfunction (Drevets et al., 2008; Mayberg, 2003; Van Dijk et al., 2010), and a wealth of resting-state fMRI functional connectivity studies has been prompted (Zeng et al., 2014).

Numerous past neuro-imaging researches have accumulated and extracted a distinct functional system of brain regions that can be activated to a greater extent during passive cognitive modes. Consequently, Raichle et al. termed it default mode network (DMN) (Raichle et al., 2001; Raichle and Snyder, 2007). The DMN distributed largely across brain regions including the precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC) as well as in the medial, lateral, and inferior parietal cortex (van Wingen et al., 2013; Zhu et al., 2012). Sestieri et al. (2011) found a robust functional dissociation within the DMN that DMN parietal regions directly supported memory retrieval, whereas non-DMN parietal regions were more involved in post-retrieval processes such as memory-based decision making. Uddin et al. (2009) found

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ventral medial prefrontal cortex (vmPFC) and PCC as the two major nodes comprising the DMN are differentiated with respect to the specific brain systems with which they interact. Altered functional connectivity within these brain regions is characteristic of altered network integrity, and is affiliated with mental disorder functions in the resting state (Gorges et al., 2013; Luo et al., 2011).

Converging findings suggested DMN as a potentially valuable biomarker for MDD (Broyd et al., 2009; Silbersweig, 2013; Tahmasian et al., 2013; Wu et al., 2013), although not all outcomes of the experiments are consistent (Kerestes et al., 2014). One study showed extensively increased network connectivity within the posterior, ventral, and core DMN subsystems in MDD patients, while reduced interplay emerged from the anterior to the ventral DMN sub-systems (Sambataro et al., 2013). Another study observed totally opposite results that showed increased connectivity in the anterior node of the DMN and reduced connectivity in the posterior node of the DMN (Zhu et al., 2012). Besides, Li et al. (2013) reported that two spatially independent default mode subnetworks were detected in MDD and suggested a dissociation of the DMN into subnetworks. Guo et al. (2013b) found that patients with MDD exhibited a dissociation pattern of resting-state amplitude of low-frequency fluctuation (ALFF) in the DMN, with increased ALFF in the left dorsal medial prefrontal cortex (dmPFC) and decreased ALFF in the left parahippocampal gyrus. These findings, that have been commonly appreciated, suggest a greater heterogeneity within this network. To date, few studies have directly elaborated the definite results to indicate depression-related changes within resting-state DMN nodes. Great importance should be attached to that the DMN changes in MDD may present in a complex way, not as sole increases or decreases (Broyd et al., 2009; Northoff et al., 2006).

The DMN has been connected to episodic memory (Greicius and Menon, 2004) and self-related processes (Buckner and Carroll, 2007; Wicker et al., 2003), memory consolidation (Miall and Robertson, 2006), and others associating default mode function with more general processes such as stimulus-independent (Mason et al., 2007) or task unrelated thought (McKiernan et al., 2006). Though this may be explained to the network's ability to support such a diverse array of functions, the greater likelihood is that the DMN consists of functionally differentiable subdivisions or sub-networks (Uddin et al., 2009). Also, it still remains unknown whether the entire DMN functions as a single unit, or whether each DMN node has a specific functional role (Uddin et al., 2009). The aim of this study was to verify functional connectivity changes within the DMN in the first-episode, treatment-naïve MDD patients compared with the matched healthy controls along with a within DMN region-wise method. We hypothesized that each major node of the DMN may be differentially involved in these processes, and that analyzing each individually will lead to a richer understanding of the functions of the network and furthermore, the physiopathology of MDD.

2. Subjects and methods

2.1. Subjects

This study was approved by the local medical research ethics committee, and written informed consent was obtained from all participants prior to participation. A total of 76 participants took part in the study. Thirty-eight outpatients were matched with an equal number of healthy controls (HCs). Groups were pairwise matched according to gender, age and level of education. All participants were recruited from the Department of Medical Psychology of Affiliated Nanjing Brain Hospital of Nanjing Medical University in Nanjing, Jiangsu, PR China. The patients were clinically diagnosed as major depressive disorder according to the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001) by independent assessments of two qualified psychiatrists (C. Wang. and Y. Tan). Inclusion criteria for the MDD group were: (a) first-episode major depression as primary diagnosis, (b) unipolar subtype, (c) psychotropic drug-naïve, and (d) a score from 18 to 35 on the 24-item Hamilton Depression Rating Scale for Depression (HDRS) and duration of depression less than a year. Exclusion criteria were a history of antidepressant treatment including pharmacotherapy or psychotherapy, any history of serious medical or neurological illness, lifetime history psychiatric disorder, substance abuse or mental retardation, a significant life change within 6 months, current high risk of suicide and any contraindication to MRI scan, a history of loss of consciousness, head trauma, pregnancy, or breast-feeding. The HCs with HDRS scores less than 8 and no history of any psychiatric disorder, neurological disorder and serious somatic disease were recruited from the community samples. HCs were also assessed with SCID. All subjects were right-handed.

2.2. Data acquisition

All magnetic resonance imaging (MRI) data were obtained using a 3.0T MR scanner (Magnetom Symphony; Siemens, Erlangen, Germany) with a standard head coil. During scanning, all the subjects were asked to rest with their eyes closed and try not to think of anything systematically. A foam pad was used to minimize the head motion of all participants. The resting-state fMRI data was obtained using a single-shot, gradient-recalled echo-planar imaging (EPI) sequence. The orientation of slices was consistent with anterior commissure–posterior commissure (AC–PC) line. The imaging parameters were as follows: repetition time=3000 ms; echo time=40 ms; flip angle=90°; field of view (FOV)=24×24 cm^2; matrix=64×64; 32 slices; slice thickness/gap=4.0 mm/4.0 mm; acquisition time=5 min 06 s. Structural MRI were acquired by using a sagittal magnetization prepared rapid gradient echo (MP-RAGE) three-dimensional T1-weighted sequence (repetition time/echo time (TR/TE)=1900 ms/2.48 ms, flip angle=9°, thickness/gap=1.0 mm/0.5 mm, 176 slices, matrix=256×256, FOV=24×24 cm^2, acquisition time=4 min 18 s). The parameters were set corroding to the previous publications (Zhang et al., 2011; Zhu et al., 2012).

2.3. Data preprocessing

Pre-processing of functional images was performed using the software package of SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Slice-timing adjustment and realignment for head motion correction were performed. Two patients were excluded from further analysis because of excessive movement (translation exceeded 1.0 mm or rotation exceeded 1.0°). We also evaluated the group differences in translation and rotation of head motion according to the following formula: head motion/rotation$=\frac{1}{L-1}\sum_{i=2}^{L}\sqrt{|x_i-x_{i-1}|^2+|y_i-y_{i-1}|^2+|z_i-z_{i-1}|^2}$, where L is the length of the time series ($L=100$ in this study), x_i, y_j and z_j are translations/rotations at the ith time point in the x, y and z directions, respectively. The results showed that the two groups had no significant differences in image quality (two sample t test, $t=1.079$, $P=0.284$ for translational motion, and $t=0.810$, $P=0.420$ for rotational motion). The standard Montreal Neurological Institute (MNI) template provided by SPM8 was used in normalization with resampling voxel size of 3×3×3 mm^3. The normalized images were then smoothed by convolution with an isotropic Gaussian kernel of 6 mm full-width at half-maximum (FWHW) to decrease spatial noise. To further reduce the effects of confounding factors unlikely to be involved in specific regional correlation, we also removed several sources of spurious variance by linear regression, including six head motion parameters obtained by rigid body head motion correction, and average signals from cerebrospinal fluid and white matter. A temporal filter ($0.01\ \text{Hz} < f < 0.08\ \text{Hz}$) was applied to remove low-frequency drifts and physiological high-frequency noise using finite impulse response (FIR) filter (Zhong et al., 2015).