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Distance-dependent alterations in local functional connectivity in drug-naive major depressive disorder

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ABSTRACT

Previous studies using resting-state functional magnetic resonance imaging (fMRI) have found abnormal functional connectivity in patients with major depressive disorder (MDD). Yet, effect of distance thresholds on local functional connectivity changes in MDD is largely unknown. Here, we used resting-state fMRI data and functional connectivity strength (FCS) method to test local functional connectivity differences at different distance thresholds between 47 drug-naive patients with MDD and 47 healthy controls. For the distribution of functional brain hubs with high local FCS, the overall changing trend from distance thresholds of 10 mm to 100 mm was from lateral to medial. Compared to controls, MDD patients exhibited decreased local FCS independent of distance threshold in the sensorimotor system (postcentral gyrus, paracentral lobule, and supplementary motor area). MDD Patients exhibited increased local FCS in the inferior temporal gyrus at two lower distance thresholds (20 mm and 30 mm) and a higher distance threshold (100 mm). In addition, MDD patients showed increased local FCS in the putamen at higher distance thresholds (80–100 mm). These findings suggest that local functional connectivity abnormalities in MDD are dependent on distance thresholds and that future studies should take the distance thresholds into account when measuring local functional connectivity in MDD.

1. Introduction

Major depressive disorder (MDD) is a debilitating psychiatric disorder characterized by abnormal brain connectivity (Gong and He, 2015; Hamilton et al., 2013; Kaiser et al., 2015; Mulders et al., 2015; Zhang et al., 2016b). Resting-state functional magnetic resonance imaging (fMRI) is a non-invasive imaging technique which allows researchers to measure spontaneous brain activity based on the blood-oxygen-level-dependent (BOLD) signal (Biswal et al., 1995). Resting-state functional connectivity (rsFC), measured as the temporal coherence of the BOLD signal between discrete brain regions during rest (Fox and Raichle, 2007), is a promising approach to investigate disrupted brain communication in MDD. For example, a recent review has demonstrated that consistent findings in MDD revealed by either seed-based correlation or independent component analysis are altered rsFC within the default mode network (DMN) and altered connectivity between DMN and salience network/central executive network (SN/CEN) (Mulders et al., 2015). A recent meta-analysis has provided evidence for large-scale network dysfunction in MDD, including imbalanced connectivity among networks engaged in regulating attention to internal or external world, and decreased connectivity between networks engaged in regulating or responding to emotion or salience (Kaiser et al., 2015). Recent advances in brain connectomics through the use of graph theory unravel disrupted topological organization (global topology, modular structure, and network hubs) of large-scale functional brain networks in MDD (Gong and He, 2015).

Functional connectivity density (FCD) or functional connectivity strength (FCS), a data-driven method based on graph theory, has been developed to reflect the hub property of a single voxel (Buckner et al., 2009; Liang et al., 2013; Tomasi and Volkow, 2010, 2011a, 2011b). The FCD/FCS is also referred to as the nodal degree centrality of binary/weighted networks (Buckner et al., 2009; Zuo et al., 2012), and brain regions with high FCD/FCS are considered functional hubs. The global FCD/FCS tests the connectivity of a given voxel with all other voxels in the brain, thus its abnormality could be interpreted as the deficit of a voxel's central role in information transmission in the whole brain network. The global FCD/FCS has been shown to be a powerful and replicable biomarker to be disrupted in MDD (Murrough et al., 2016; Wang et al., 2014a; Wu et al., 2016; Zhang et al., 2016a; Zhuo et al., 2016). The most consistent finding is decreased global FCD/FCS in the

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ventral medial prefrontal cortex/subgenual anterior cingulate cortex in patients with MDD. The local FCS is defined as the connectivity between a given voxel and other voxels with an anatomical distance less than a certain threshold (e.g., 75 mm) (Achard et al., 2006; He et al., 2007). The local FCS is also applied to investigate connectivity changes in MDD and has revealed decreased local FCS in the insula and superior temporal gyrus (Guo et al., 2016). However, only an arbitrary distance threshold was used in previous studies and the potential effect of distance thresholds on the local FCS analysis remains unclear.

Here, we used resting-state fMRI data to test local FCS differences between drug-naive patients with MDD and healthy controls. The purpose of the current study was to investigate the effect of distance thresholds on local FCS changes in MDD. We hypothesized that patients with MDD would show distinct local FCS alteration patterns at different distance thresholds.

2. Methods

2.1. Participants

A total of ninety-four right-handed individuals were enrolled in the present study, including 47 drug-naive patients with MDD recruited consecutively from the psychiatric outpatient or inpatient department of the local hospital and 47 healthy controls recruited from the local community via advertisements. The patients and controls were well-matched in terms of age, sex and education (Table 1). The diagnosis of MDD was made according to the Structural Clinical Interview of the DSM-IV(SCID) (First et al., 1997), patient edition. The severity of depression was assessed using the 24-item Hamilton Rating Scale for Depression (HRSD-24) (Williams, 1988). Only those patients with a HRSD-24 score ≥ 20 were eligible for this study. The detailed clinical characteristics of the patients are shown in Table 1, including the HDRS score, illness duration, onset age, episode number, and current episode duration. Healthy controls were carefully screened for a current or lifetime diagnosis of any Axis I and II disorder using the SCID, non-patient edition. Exclusion criteria for all participants were 1) the presence of other Axis I psychiatric disorders such as schizophrenia, bipolar disorder, substance-induced mood disorder, anxiety disorders, substance abuse or dependence; 2) a history of neurological diseases or other physical illness; 3) a history of head injury resulting in loss of consciousness; 4) the inability to undergo an MRI. In addition, all healthy controls reported no psychiatric disorders among their first-degree relatives. This study was approved by the local ethics committee, and written informed consent was obtained from all participants after they had been given a detailed description of the study.

Table 1
Demographic and Clinical Characteristics of the Sample.

Characteristics	MDD	HC	Statistics	*P* value
Number of subjects	47	47		
Age (years)	46.4 ± 13.5	47.0 ± 17.9	t = 0.182	0.856[b]
Sex (female/male)	27/20	23/24	χ^2 = 0.684	0.408[c]
Education (years)	11.2 ± 3.8	11.7 ± 4.1	t = 0.657	0.513[b]
FD	0.141 ± 0.066	0.149 ± 0.073	t = 0.601	0.549[b]
HDRS score	30.3 ± 7.1	–		
Illness duration (months)[a]	23.7 ± 36.1	–		
Onset age (years)[a]	43.4 ± 12.4	–		
Episode number[a]	1.3 ± 0.7	–		
Current episode duration (months)	5.0 ± 6.3	–		

The data are presented as the mean ± SD. Abbreviations: FD, frame-wise displacement; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder.

[a] The data are available for 39 of 47 patients.

[b] The *P* values were obtained by two-sample *t*-tests.

[c] The *P* value was obtained by chi-square test.

2.2. Data acquisition

MRI data were acquired using a 3.0-Tesla scanner (Magnetom Verio, Siemens, Erlangen, Germany). Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. High resolution structural images were acquired sagittally using a 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: repetition time (TR) = 1900 ms; echo time (TE) = 2.48 ms; inversion time (TI) = 900 ms; flip angle (FA) = 9°; field of view (FOV) = 250 mm × 250 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; slice number = 176; and acquisition time = 258 s. Resting-state functional blood-oxygen-level-dependent (BOLD) images were acquired axially using a gradient-echo planar imaging (GRE-EPI) sequence with the following parameters: TR/TE = 2000/25 ms; FA = 90°; FOV = 240 mm × 240 mm; matrix = 64 × 64; slice thickness = 4 mm; no gap; slice number = 36; 240 volumes; and acquisition time = 480 s. Before the scanning, all subjects were instructed to keep their eyes closed, relax, move as little as possible, think of nothing in particular, and not fall asleep during the scans. During and after the scanning, we asked subjects whether they had fallen asleep to confirm that none of them had done so. All MR images were visually inspected to ensure that only images without visible artifacts were included in subsequent analyses.

2.3. fMRI data preprocessing

BOLD MRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes for each participant were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining volumes were corrected for the acquisition time delay between slices. Then, realignment was performed to correct the motion between time points. In resting state fMRI, a common finding is that many long-distance correlations are decreased by subject motion, whereas many short-distance correlations are increased (Power et al., 2012). Therefore, we estimated subject head motion immediately after the fMRI scans to ensure that all participants' BOLD data were within the defined motion thresholds (i.e., translational or rotational motion parameters less than 2 mm or 2°). We also calculated frame-wise displacement (FD), which indexes the volume-to-volume changes in head position. There were no significant group differences in mean FD (t = 0.601, P = 0.549) between patients with MDD (0.141 ± 0.066) and healthy controls (0.149 ± 0.073). Several nuisance covariates (six motion parameters, their first time derivations, and signals of the global brain, white matter, and cerebrospinal fluid) were regressed out from the data. A recent study has reported that the signal spike caused by head motion significantly contaminated the final resting-state fMRI results even after regressing out the linear motion parameters (Power et al., 2012). Therefore, we further regressed out spike volumes when the FD of the specific volume exceeded 0.5. The datasets were then band-pass filtered using a frequency range of 0.01–0.08 Hz. In the normalization step, individual structural images were firstly co-registered with the mean functional image; then the transformed structural images were segmented and normalized to the Montreal Neurological Institute (MNI) space using a high-level non-linear warping algorithm, that is, the diffeomorphic anatomical registration through the exponentiated Lie algebra (DARTEL) technique (Ashburner, 2007). Finally, each filtered functional volume was spatially normalized to MNI space using the deformation parameters estimated during the above step and resampled into a 3-mm cubic voxel.

2.4. Local FCS analysis

We computed Pearson's correlation coefficients between the BOLD time courses of all pairs of voxels within the gray matter mask and obtained a whole gray matter functional connectivity matrix for each