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Research paper

Abnormal functional connectivity density in first-episode, drug-naive adult patients with major depressive disorder

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ABSTRACT

Previous studies have found evidence of brain functional connectivity (FC) changes with pre-selected region-of-interest (ROI) method in major depressive disorder (MDD). However, these studies could not completely exclude personal inequality when drawing ROIs manually and did not measure the total number of FC for each voxel. Here, we firstly applied functional connectivity density (FCD) mapping, a voxel-based analysis to locate the hubs with amount changes of FC between 22 first-episode, drug-naive adult MDD patients and 22 healthy control (HC) subjects. Both short-range (local) FCD and long-range (distal) FCD were measured. The relationships of FCD changes with Hamilton Depression Rating Scale (HAMD) scores and illness duration were also explored. Compared with the HC group, MDD patients showed significantly decreased short-range FCD in the left superior temporal gyrus (STG), the right orbital frontal cortex (OFC) and bilateral precuneus, while significantly decreased long-range FCD was found in bilateral middle occipital gyrus (MOG), superior occipital gyrus (SOG) and right calcarine. These results firstly demonstrated both local and distal alterations of connection amount at voxel level, and highlighted that the OFC, the precuneus, the STG and the visual cortex were important brain network hubs for first-episode, drug-naive adult MDD patients. Our findings were complementary for previous structural and functional studies in MDD patients, and provided new evidence of the dysfunction of connection hubs in the pathophysiology of MDD at voxel level.

1. Introduction

Major depressive disorder (MDD) is a consequential public health problem, with a lifetime prevalence as high as 20% worldwide (Kessler et al., 2005). It was the foremost contributor to the global burden of disease as measured by years of health lost to disability, according to the World Health Organization.

It is known to all that brain function depends on the normal work of series networks. Brain networks are defined in graph theory as a set of nodes or vertices and the edges or lines between them, and those nodes with high degree or high centrality are hubs (Bullmore and Sporns, 2009). Hubs play essential roles in the interconnection of distributed functionally specified regions and in coordinating performance across the brain. Research showed that brain networks appeared to have few and well localized hubs for fast integration of neural processing, and their dysfunction could contribute to neuropsychiatric diseases (Tomasi and Volkow, 2011).

Over the last two decades, sophisticated brain-imaging techniques have made us a deep understanding of brain networks. One of the most effective techniques for detecting network function was resting-state functional magnetic resonance imaging (fMRI). It is an established imaging modality specific for investigating the integration of neural networks at rest (e.g. lying still with eyes closed) when no task is performed. To date, resting-state fMRI has been widely used in neuroimaging studies of MDD. In a recent systematic review of resting-state fMRI studies in MDD, it was summarized that though findings of different research groups were somewhat confusing, the current evidence largely suggested abnormal resting functional connectivity (FC) in the cortico-limbic mood regulating circuits (MRC) and the default-mode network (DMN) to be contributing to the pathophysiology of MDD (Wang et al., 2012a).

Because depressive episodes and antidepressant medication might have possible influence to the brain function, to study first-

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episode, medication-free patients maybe better understand the primary functional changes of MDD. There were a few resting state fMRI research focus on first-episode or medication-naive adult patients with MDD so far, the approaches they used including region-of-interest (ROI) analysis (Anand et al., 2009; Cao et al., 2012; Ma et al., 2012; Tao et al., 2013; Zhang et al., 2011), regional homogeneity (ReHo) approach (Guo et al., 2011), independent component analysis (ICA) (Veer et al., 2010; Zhu et al., 2012), and amplitude of low-frequency fluctuation (ALFF) (Wang et al., 2012b). These methods were constrained by the fact that they relied strongly on a priori selection of specific seed regions rather than allowing for the characteristics of the network to identify and locate the node regions; what is more, these methods were also computationally demanding (Tomasi and Volkow, 2010). And, previous methods calculated FC between brain regions, but they did not measure the total number of FC per voxel. Thus, it reminded us to use a new method to overcome these limitations. Functional connectivity density (FCD) mapping is such a new method. It is a voxel-wise data-driven method for identifying brain hubs and is an ultrafast technique that can speed up the computation of the number of functional connections (Tomasi and Volkow, 2010). Namely, it can measure the amount of FC for each voxel. FCD mapping can calculate short-range FCD and long-range FCD respectively. The short-range FCD was considered to indicate central roles of voxels in the functional specialization, and mainly located in the posterior cingulate/ventral precuneus; the long-range FCD, representing functional integration of the whole-brain networks and mostly distributed in the visual cortex (Tomasi and Volkow, 2010, 2012). Compared with previous FC approaches, it is a good method for identifying hubs with connection number changes at voxel level, and, it avoids artificial factors to a great extent. As far as we know, no study to date has uncovered FC changes at voxel level in first-episode, drug-naive adult MDD patients.

Therefore, we performed FCD mapping method with resting-state fMRI data to locate the hubs with amount changes of FC between first-episode, drug-naive adult MDD patients and healthy controls. Then, correlation analysis was performed to explore the relationship between the neuronal connectivity changes and symptom severities and illness duration in patient group. According to Tomasi and Volkow's studies, we hypothesized that FCD changes might be located in certain regions of the DNM and the visual cortex.

2. Materials and methods

2.1. Participants

Twenty-five first-episode, drug-naive patients were recruited from the Mental Health Center, West China Hospital of Sichuan University. They all met DSM-IV criteria for MDD according to the diagnostic assessment by the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-P) and were with scores of 18 or greater on the 17-item Hamilton Depression Scale (HAMD). Patients comorbid with other Axis I and Axis II psychiatric disorders such as schizophrenia, bipolar affective disorder, personality disorders and substance abuse or dependence were excluded according to the SCID-I and SCID-II assessment. Twenty-four healthy controls (HC) were also recruited from the 5 city districts of Chengdu, China. They were screened through a diagnostic interview, the Structured Clinical Interview for DSM-IV Nonpatient Edition (SCID-NP), to rule out current or past DSM-IV Axis I disorders. They were also interviewed to affirm that there was no history of psychiatric illness in their first-degree relatives. All subjects were right-handed and without severe or acute medical conditions physically based on clinical evaluations and medical records. The ethical committee of the West China Hospital of Sichuan University approved this study, and all participants provided written informed consent.

2.2. MRI acquisition

Participants underwent scanning using a GE Signa EXCITE 3-T MR system (GE Healthcare, Milwaukee) with an 8-channel phased array head coil. Foam padding was used to minimize head motion for all subjects. First, high-resolution T1-weighted images were acquired using a 3D spoiled gradient-recalled (SPGR) sequence, producing 156 contiguous coronal slices with a slice thickness of 1.0 mm (TR=8.5 ms, echo time=3.4 ms, flip angle=12°). The final matrix size of T1-weighted images was automatically interpolated in-plane to 512×512, which yielded an in-plane resolution of 0.47×0.47 mm^2. Then, BOLD signal levels (TR=2000 ms, echo time=30 ms, flip angle=90°) were obtained via a gradient-echo echo-planar imaging (EPI) sequence. Five dummy scans were collected before fMRI scans were performed, and the first two volumes of fMRI time series were discarded for magnetization stabilization (slice thickness=5 mm [no slice gap]; matrix=64×64; field of view=240×240 mm^2; voxel size=$3.75 \times 3.75 \times 5$ mm^3). Each brain volume comprised 30 axial slices, and each functional run contained 200 image volumes finally. During the scan, subjects were asked to lie still with their eyes closed and to avoid falling asleep. After scanning, all subjects were asked whether they fell asleep during the scan, and all subjects confirmed that they were awake.

2.3. Data processing and analysis

Data preprocessing was performed using the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). First, the resting-state fMRI images were first corrected by the acquisition time delay among different slices, and then realigned to the first volume for head-motion correction. The dataset with translational or rotational parameters exceeding ± 1.5 mm or $\pm 1.5°$ would be excluded, so two HC subjects and three patients have been excluded for head-motion. Accordingly, 22 MDD patients and 22 HC subjects were remained for further analysis. Second, the images were spatially normalized into a standard stereotaxic space at $3 \times 3 \times 3$ mm^3, using the Montreal Neurological Institute (MNI) template in SPM8. No spatial smoothing was applied in order to avoid artificially introducing local spatial correlation (Achard and Bullmore, 2007). Since functional connectivity analysis is sensitive to gross head motion effects, we further evaluated the framewise displacement (FD) (Power et al., 2012) with the suggested threshold of 0.5 to express instantaneous head motion. The largest FD of all subjects was less than 0.2 mm. Two-sample t-test showed there was no significant difference of FD between the two groups (0.057 ± 0.031 for HC and 0.048 ± 0.022 for MDD; $p=0.301$).

Images were then corrected by linear regression to remove the possible spurious variances including six head motion parameters, the white matter (WM), and the ventricular signals averaged from a WM mask and a ventricular mask respectively. The residuals of these regressions were temporally band-pass filtered ($0.01 < f < 0.08$ Hz) to reduce low-frequency drifts and physiological high-frequency respiratory and cardiac noise, and linearly detrended for further analysis.

2.4. Whole brain FCD mapping

We limited the procedure within a whole brain gray matter mask including cerebellum ($N_{voxels}=$ 54,837) that was created based on the automated anatomical labeling (AAL) atlas. The Pearson's correlation r_{ij} was calculated on a voxel-based level to build the whole brain FC network for each subject. A Fisher's r-to-z transformation was then applied to the correlation matrices to improve normality. To ensure that differences between groups could not be attributed to differences in network sparsity (cost), we thresholded network matrices by cost. To do this, the correlation matrices were firstly thresholded