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Research paper

Analysis of voxel-mirrored homotopic connectivity in medication-free, current major depressive disorder

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ABSTRACT

Background: Recent neuroimaging studies suggest that abnormal function connectivity exists in patients with major depressive disorder (MDD). The aim of this study was to further analyze the underlying neural mechanism of MDD and explore whether clinical characteristics are correlated with the alerted homotopic connectivity in patients with MDD.

Methods: Using voxel-mirrored homotopic connectivity (VMHC) during resting state, we compared 80 medication-free patients having current episodes of MDD and 124 never-depressed healthy controls (HCs) matched for age and gender.

Results: We found decreased VMHC in patients with MDD in bilateral posterior cingulate cortex (PCC) extending to precuneus (Pre) compared with the HCs, which provided strong support for the potential role of PCC/Pre in recognizing interhemispheric connectivity deficits of MDD. Negative correlation between illness course and VMHC in PCC was observed as well.

Limitations: First, we just compared the functional connectivity at a rest state but not under a specific task. Second, we did not mitigate the delayed effect on the measurable alterations in homotopic brain activity. Third, we did not make a longitudinal comparison after patients receiving therapeutic drugs.

Conclusions: These findings that linking illness course with functional brain changes in depression help us understand the neural architecture of MDD.

1. Introduction

Major depression disorder (MDD) has been attracting increasing attention from the public owing to its high prevalence, recurrence, and amounting danger of morbidity and mortality that have led to heavy burden on social economy and its great influence on life quality of individuals. Generally speaking, excessive self-blaming or low self-worth, feelings of hopelessness, loss of enjoyment and energy are regarded as part of the core depressive symptoms (Zahn et al., 2015). Although significant progress has been made in understanding the mechanism of MDD and developing optimal treatments, the exact neuro- physiological basis of MDD remains largely unclear. Neuroimaging studies have offered insights into functional changes across brain regions and altered neural circuits in patients with depression to explore the neuropathology of this physiological disorder.

The anatomical relationship between brain structure does not always accurately predict the function and interaction between brain regions. For instance, functional connectivity of posterior cingulate cortex and anterior cingulate cortex is found to be weak despite the fact that their anatomical location is actually very close; by contrast, functional connectivity of left and right cerebral hemisphere was stronger whereas they were far apart at the anatomic distance (Salvador et al., 2005). Strong correlations between bilaterally homologous brain regions have been demonstrated. As the main commissural fiber bundle mediating interhemispheric transfer, the corpus callosum may play a causal role in coordinating homotopic connectivity. Diffusion tensor imaging analysis of the corpus callosum detected significant differences between MDD and control groups in fractional anisotropy and radial dissfusivity values (Won et al., 2016). Moreover, structural and functional studies revealed alterations in bilateral hippocampus and amygdala among MDD patients (Frodl et al., 2008; Wang et al., 2017). Positron-emission tomography (PET) studies investigated alerted

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activity in bilateral prefrontal cortex as well as the dorsal anterior cingulate gyrus in depressive patients (Mayberg et al., 1999; de Asis et al., 2001). These observations, if replicable, could potentially raise the possibility that MDD may represent a disorder of long-distance alerted connectivity within the limbic-cortical circuit (Wang et al., 2012; Siegle et al., 2007), which give rise to the necessity to detect symmetric regional connectivity in MDD.

In contrast to more commonly used rs-fMRI analysis based on the correlation between a prior seed point and other brain regions, a recently validated methodology called voxel-mirrored homotopic connectivity (VMHC) calculates synchronized patterns of low-frequency (0.01–0.08 Hz) BOLD signals within spatially homotopic regions of the brain (Zuo et al., 2010; Fox and Raichle, 2007). Impaired inter-hemispheric functional coordination in several regions that are involved in clinical features and impairment of cognitive performance in MDD have been investigated and the results are not exactly consistent (Lai and Wu, 2014; Wang et al., 2013; Guo et al., 2013a). Reasons might be that previous studies all had relatively small sample sizes, lacked in consensus on cognitive assessment metrics, and were focused on first-episode depression or never-medicated types of depression. This, however, highlights the need for investigations focused on VMHC alterations in current episode patients so that the specific regions involved in the clinical characteristics and cognitive decline in patients having MDD could be explored using well-validated measurements (Bortolato et al., 2014).

Motivated by the question of how VMHC changes in specific regions in patients having current MDD, we analyzed resting-state functional connectivity in both MDD patients and matched healthy controls. Based on prior evidences, we hypothesized that the patient group would show reduced VHMC in several cortico-limbic regions. We used IQ scores to assess the potential cognition deficits of MDD patients. To minimize the effect of antidepressants, only medication-free patients with MDD were recruited in the present study. Furthermore, VMHC was also hypothesized to be related with clinical features and cognitive disturbance.

2. Methods

2.1. Participants

We recruited 204 participants, consisting of 80 current-episode drug-free patients with MDD and 124 age-, gender-matched healthy controls (HCs), from the Mental Health Centre of West China Hospital, Sichuan University, People's Republic of China. The HCs were recruited locally by advertisement and were screened for a lifetime absence of neuropsychiatric illness and a history or current depressive episode using the structured clinical interview (SCID-NP) in the DSM-IV non-patient edition (Stone et al., 2000). All participants were 18–60 years old, right-handed Han Chinese. We also excluded the controls having any psychiatric illness in their first-degree relatives or having a current or history of depression or other axis I disorders.

2.2. Assessments

All patients met the criteria for major depressive disorder according to DSM-IV (Diagnostic and statistical manual of mental disorders, fourth edition) – patient Version (SCID-P) (First et al., 1997) as diagnosed by two professional psychiatrists. The severity of depression was assessed using a 17-item Hamilton Depression Rating Scale (HAMD). Patients who did not receive any treatment during the past three months or more were defined as drug-free and all of them were undergoing a major depressive episode, with their HAMD 17-item scores being at least 17 on the day of scanning. In addition, participants were excluded if they (1) were younger than 18 years or older than 60 years, pregnant or breast feeding, or mentally retarded; (2) had major physical diseases, such as traumatic brain injury, encephalitis, epilepsy, or endocrine disease; (3) had other axis I disorders, such as generalized anxiety disorder, obsessive-compulsive disorder, or drug or alcohol abuse; and (4) had any difficulty in completing an MRI scanning or baseline interview. All patients were assessed immediately if recruited in our study.

Intelligence Quotient (IQ) scores of participants were assessed using the short version of the seven-subtest (information, arithmetic, digital symbol, digital span test, block design, picture completion, and similarities) revised in China of the Wechsler adult intelligence scale (Wechsler, 1981). The estimated sums of IQ scores were described in detail in our previous study (Liang et al., 2016).

This study was approved by the Institutional Review Board of West China Hospital, Sichuan University. At the beginning of the study, all participants provided written informed consent. All the study procedures were carried out according to the Helsinki Declaration.

2.3. fMRI scan acquisition

Participants were instructed to lie inside the scanner, close their eyes, be relaxed, think about nothing specific, stay awake, and minimize head motion with prepared fixation inside the head coil. They then underwent resting state scanning using a 3-Tesla whole body MR scanner (Achieva, Philips, Netherlands). fMRI images were scanned for more than 8 min and 6 s with a gradient- echo-planar imaging (EPI) sequence: repetition time/echo time = 2000/30 ms; flip angle = 90°; slice thickness = 5 mm (no slice gap), 30 axial slices; 64*64 matrix size; field of view = 240*240 mm^2; voxel size = 3.75*3.75*5 mm^3. Two experienced neuro-radiologists inspected the raw image data qualitatively. All participants were asked whether they were able to stay fully awake and think about nothing in particular throughout the whole scanning process.

2.4. Image processing and analysis

Resting-state imaging data were obtained using the data processing assistant for resting-state fMRI (DPARSF) with statistical parametric mapping (SPM8, http://wwwfil.ion.ucl.ac.uk/spm) (Chao-Gan and Yu-Feng, 2010). The initial ten images were discarded to guarantee the stability of the fMRI signals. Processing steps included slice time correction, 3D motion detection and correction, spatial normalization to the Montreal Neurological Institute (MNI) template in SPM, and spatial smoothing using an isotropic Gaussian kernel (6 mm full width at half maxi- mum). Motion-correction results showed no significant difference between the patient and the control groups in any of the six motion parameters (Van Dijk et al., 2012). Nuisance covariates including six motion parameters, cerebrospinal fluid (CSF), and white matter signals were regressed out and were used for the next functional connectivity analysis. To eliminate high-frequency physiological noise, we conducted temporal band-pass filtering (0.01–0.08 Hz) through a band-pass-filter.

2.5. Statistical analysis

The VMHC was processed with DPARSF software. First, Pearson correlations (Fisher z-transformed) between each voxel and its mirrored counterpart in the opposite hemisphere were computed for each participant to generate VMHC maps. The resultant values constituted the VMHC and were used for a voxel wise two-sample *t*-test analysis between the patient and healthy groups with the resting state fMRI data analysis toolkit (REST, http://restfmri.net/forum/REST_V1.8) (Zuo et al., 2010). Statistical inferences were made with a voxel-level threshold of uncorrected p value < 0.001; after cluster-level threshold family-wise error (FWE) was adjusted, the p value was < 0.05 for multiple comparisons. In order to eliminate the inference between variables, we peformed a multiple regression model in which all the variables may account for VMHC were tested in the patient group (see supplementary Table 2). Using the Pearson's correlation analysis, we