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Prognostic value of imbalanced interhemispheric functional coordination in early therapeutic efficacy in major depressive disorder

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ABSTRACT

This study aims to explore the early response of antidepressant therapy by measuring the voxel-mirrored homotopic connectivity (VMHC) in major depressive disorder (MDD). Eighty-two MDD patients [n=42 treatment-responsive depression (RD) and n=40 non-responding depression (NRD)] and n=50 normal controls (NC) underwent clinical measures and a magnetic resonance imaging scan, and the VMHC values were calculated. Receiver operating characteristic (ROC) curve analysis was applied to determine the capability of altered VMHC to distinguish NRD. The NRD showed significantly decreased VMHC in bilateral precuneus (PCU) and inferior temporal gyrus (ITG), and increased VMHC in middle frontal gyrus (MFG) and caudate nucleus as compared to RD. When compared with NC, the NRD exhibited reduced VMHC in bilateral cerebellum anterior lobe, thalamus and postcentral gyrus. Moreover, VHMC in medial frontal gyrus, postcentral gyrus and precentral gyrus were significantly decreased in RD. Correlation analysis showed that reduced VMHC in PCU was negatively correlated with the baseline HAMD score of the NRD group. The ROC curve indicated that the combined changes of the three regional VMHC (PCU, ITG and MFG) could effectively identify NRD. The current study suggests that interhemispheric asynchrony may represents a novel neural trait underlying the prediction of early therapeutic outcome in MDD.

1. Introduction

Major depressive disorder (MDD) is a disease mainly characterized by depressed mood, loss of interest, feelings of worthlessness, and a high risk of suicide (Rubin, 2014). Clinical investigations reveal that only 22–40% of MDD patients benefit from treatment with antidepressants (Anthes, 2014). Due to its significantly adverse impact on public health, the pathophysiology of depression and mechanisms of antidepressant drugs have received attention in depression research. In clinical practice, clinicians need more than 6–8 weeks to judge treatment outcomes. It is crucial to identify pre-treatment predictors of early response in order to avoid long waiting periods, to determine whether to change treatment strategy, and to reduce medical burden. Accumulating evidence (Chi et al., 2015; Gorwood et al., 2015) indicates that early improvement of symptoms after 2-weeks of antidepressant medication (ADM) could predict later outcomes of patients with MDD. However, neuroimaging markers to predict early response are still lacking.

Many neurobiological studies regarding the pathogenesis of MDD have been conducted. Evidence from structural imaging and lesion research indicate that brain circuits, including the frontal lobe, limbic system, thalamus and amygdala mediate emotional behavior (Barthas et al., 2015; Belden et al., 2015; Canu et al., 2015; Hagan et al., 2015). MDD is characterized by dysfunction in the large-scale networks that undermine the emotional processing to external stress (Kaiser et al., 2015; Zhang et al., 2011). Emerging results from resting-state functional magnetic resonance imaging (rs-fMRI) demonstrate disrupted spontaneous activity and impaired functional connectivity in the default mode network (DMN), particularly involving the prefrontal cortex and anterior cingulate cortex (Bebko et al., 2015; Genzel et al., 2015; Liu et al., 2015). Imbalanced activity in these DMN regions disturbs emotion regulation and strengthens the processing of maladaptive rumination in MDD (Hamilton et al., 2015), which is also associated

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with medication responses to ADM (Williams et al., 2015).

Depression is also considered as a "disconnection syndrome" featuring disrupted integrity in the corpus callosum (Chen et al., 2016) and the uncoupling of activity in reward-related regions and positive emotion (Greening et al., 2014; Liao et al., 2013). Recently, several studies indicated that imbalanced interhemispheric functional coordination could shed light on the pathophysiology of MDD (Zuo et al., 2010). An electroencephalographic study detected that the alpha wave is asymmetric between the left and right frontal lobe in MDD (Jesulola et al., 2015). Depressed patients show stronger amygdalar interhemispheric connectivity than healthy controls (Irwin et al., 2004). Utilizing the approach of voxel-mirrored homotopic connectivity (VMHC) focusing on measuring the synchrony of spontaneous activities between anatomically symmetrical brain regions (Salvador et al., 2005), researchers have identified many regions with abnormal VMHC associated with clinical features and treatment response in MDD (Lai and Wu, 2014; Su et al., 2016; Wang et al., 2013; Wei et al., 2014). Those results indicate that the imbalanced neural activities within symmetrical brain regions might explain the "disconnection syndrome" and dysfunctional emotion processing of MDD, especially for DMN related regions. Exploring the early predictors of homotopic connectivity may help clinicians choose effective treatment types for patients and provide an option for personalizing therapy. However, to our knowledge, there are no studies exploring the potential relationship between impaired interhemispheric homotopic functional connectivity (FC) and early antidepressant response in MDD.

The purpose of the present study is to investigate the implicit alteration of interhemispheric FC in healthy controls and in MDD with different treatment responses. Based on the results of previous studies, we aimed to determine if focal disruption of VMHC in the prefrontal cortex, thalamus or other related regions exert an adverse impact on short-term antidepressant response. We hypothesized that individuals with lower VMHC would exhibit greater depression severity or poorer response to treatment.

2. Methods

2.1. Participants

All participants were recruited from the Affiliated Zhongda Hospital of Southeast University, China. All subjects were interviewed in a semi-structured interview included in the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P), Clinician Version, and the diagnoses were determined by a consensus of at least two trained and senior psychiatrists (Y Yuan and Z Hou). All participants also underwent diagnostic evaluations including clinical interview, review of medical history and demographic inventory. The participants met the following inclusion criteria: (1) they met the major depressive disorder in DSM-IV criteria at the time point of enrollment; (2) they were in their first depressive episode and the age of onset was over 18 years; (3) 24 items Hamilton Depression Rating Scale (HAMD) were greater than 20; (4) absence of another major psychiatric illness, including substance abuse or dependence; (5) absence of primary neurological illness, including dementia or stroke; (6) absence of medical illness impairing cognitive function; (7) no history of receiving electroconvulsive therapy; (8) no gross structural abnormalities on T1-weight images, and no gross white matter changes such as infarction or other vascular lesions T2-weighted MRI; (9) have no psychotic symptoms (i.e. hallucination/bizarre delusions/thought broadcasting). All subjects were all unequivocally and naturally right-handed. The Southeast University Research Ethics Committee approved the study and written informed consent was obtained from all participants. The MRI scans were processed before the patients get start to receive ADM. During the 2 weeks follow-up period, 5 patients refused to participate in the study. After the removed of head motion (i.e., exceeding 3 mm in transition or 3° in rotation) or poor quality of image (i.e., ghost intensity), 82 MDD patients and 50 normal controls (NC) completed the procedures of this study. The treatment for the MDD group was as follows: 49 patients used selective serotonin reuptake inhibitor (SSRIs), and 26 patients used serotonin-norepinephrine reuptake inhibitor (SNRIs), 7 patients received a algorithm of antidepressants combinations (SSRIs, SNRIs or mirtazapine). According to the reduction rate (RR) of HAMD [defined as $RR = (HAMD_{baseline} - HAMD_{two\text{-}week})/HAMD_{baseline}$], the patients were grouped into non-responding depression (NRD, n=40) ($RR \leq 50\%$) and treatment-responsive depression group (RD, n=42) ($RR > 50\%$).

2.2. Image acquisition

All subjects underwent the MRI scans at the Affiliated Zhongda Hospital of Southeast University. The subjects were scanned using a Siemens 3.0 Tesla scanner with a homogeneous birdcage head coil. Subjects lay supine with the head snugly fixed by a belt and foam pads to minimize head motion. A gradient-recalled echo-planar imaging (GRE-EPI) pulse sequence was set up to acquire resting-state images. The acquisition parameters of rs-fMRI were as follows: repetition time=2000 ms; echo time=25 ms; flip angle=90°; acquisition matrix=64 × 64; field of view=240 × 240 mm^2; thickness=3.0 mm; gap=0 mm; 36 axial slices, and 3.75 × 3.75 mm^2 in-plane resolution parallel to the anterior commissure-posterior commissure line. High-resolution T1-weighted axial images covering the whole brain were acquired utilizing a 3-dimensional inversion recovery prepared fast spoiled gradient echo (SPGR) sequence presented as follows: repetition time= 1900 ms; echo time=2.48 ms; flip angle=9°; acquisition matrix= 256 × 192; field of view=250 mm × 250 mm; thickness=1.0 mm; gap=0 mm. Those above acquisition sequences generated 240 volumes in 8 min and 176 volumes in 4.3 min, respectively. All subjects were instructed to keep their eyes closed and to relax, to remain awake and to not think anything specific during scanning.

2.3. Functional image preprocessing

Functional images were preprocessed utilizing the Data Processing Assistant for Resting-State Function (DPARSF 2.3 Advanced edition) MRI toolkit (Chao-Gan and Yu-Feng, 2010), which synthesizes procedures based on the Resting-State Functional MRI toolkit (REST, http://www.restfmri.net) (Song et al., 2011), and statistical parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first ten time points were discounted in order to ensure stable-state longitudinal magnetization and adaptation to inherent scanner noise. The remaining 230 rs-fMRI images were sequentially performed according following steps: (1) Slice timed with the 35th slice as reference slice; corrected for temporal differences and head motion correction (participants with head motion of more than 1.5 mm of maximum displacement in any direction (x, y, or z) or 1.5 degrees of angular motion were excluded from the present study); (2) Coregistered T1 to functional image and then reoriented; (3) For spatial normalization, T1-weighted anatomic images were segmented into white matter, gray matter and cerebrospinal fluid, and then normalized to the Montreal Neurological Institute space by using a 12-parameter nonlinear transformation. The above transformation parameters were applied to the functional images and then the functional images with isotropic voxels of 3 mm resampled; (3) spatial smoothing undertaken with a 6 mm full-width at half-