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Research report

Clinical, cognitive, and functional connectivity correlations of resting-state intrinsic brain activity alterations in unmedicated depression

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ABSTRACT

The pervasive and persistent nature of depressive symptoms has made resting-state functional magnetic resonance imaging (rs-fMRI) an appropriate approach for understanding the underlying mechanisms of major depressive disorder. The majority of rs-fMRI research has focused on depression-related alterations in the interregional coordination of brain baseline low frequency oscillations (LFOs). However, alteration of the regional amplitude of LFOs in depression, particularly its clinical, cognitive and network implications, has not been examined comprehensively yet. rs-fMRI amplitudes of low-frequency fluctuation (ALFF/fALFF) mediated by two LFO bands of 0.01–0.08 Hz (LF-ALFF/fALFF) and 0.1–0.25 Hz (HF-ALFF/fALFF) were measured in unmedicated subjects with major depressive disorder ($n=20$) and a healthy control group ($n=25$). A novel method of "ALFF-based functional connectivity" analysis was developed to test regional/network interaction abnormalities in depression. Our results revealed abnormal alterations in ALFF for both lower and higher frequency bands of LFOs in regions that participate in affective networks, corticostriatal circuits and motor/somatosensory networks. A strong positive correlation was detected between depressive symptom severity and fALFF in the anterior cingulate cortex. Functional connectivity of the thalamus and postcentral area with altered ALFF were found to be decreased with other interacting regions of their involved networks. Major depressive disorder relates to the alterations of regional properties of intrinsic neural activity with meaningful clinical and cognitive correlations. This study also proposes an integrating regional/network dysfunction in MDD.

1. Introduction

Major Depressive Disorder (MDD) has been reported as the leading cause of disability in the United States and the second cause of disability worldwide (Ferrari et al., 2013). Despite the availability of different treatment options, the remission rate from MDD is estimated not to be more than 50%, even after one year of treatment (Whiteford et al., 2013). Better understanding of the underlying mechanisms of MDD and development of more effective treatment options are critical for reducing the huge burden of this mental illness for affected patients, their families and society in general.

Neuroimaging has been one of the principal research modalities for investigating the neuropathology of depression. Structural brain imaging studies in MDD have pointed to cortico-striato-limbic neurocircuitries as the anatomical substrates of depression (Ballmaier et al., 2008; Bora et al., 2012; Koolschijn et al., 2009; Kumar et al., 2014; Liao et al., 2013; Sheline, 2003; Tadayonnejad and Ajilore, 2014). Another major line of research in the neuroimaging of depression uses functional magnetic resonance imaging (fMRI) to explore abnormal alterations of brain function in depressed subjects. In those studies, abnormal activity in terms of the blood-oxygen-level dependent (BOLD) signal is examined in patients with MDD during the performance of a cognitive, emotional or reward processing task (Diener et al., 2012; Hamilton et al., 2012; Hasler et al., 2009; Heller et al., 2009; Pizzagalli, 2011).

Recent advances in fMRI have led to the development of resting-state fMRI (rs-fMRI) (Biswal et al., 1995; Fox and Raichle, 2007). In rs-fMRI, brain baseline fluctuations in the BOLD signal are measured when a subject with open or closed eyes is not doing anything in the scanner. Considering the pervasive nature of several depressive symptoms like depressed mood, negative rumination or lack of motivation, rs-fMRI actually might be even a better approach for investigating the abnormal neural mechanisms of depression.

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In rs-fMRI, two measures are used commonly to examine the network-related and regional characteristics of low frequency oscillations (LFOs): Functional Connectivity (FC) and Amplitude of Low-Frequency Fluctuation (ALFF). In FC analysis, the temporal correlation (synchronicity) of resting-state BOLD signals of spatially distributed brain areas is calculated as a measure of brain region resting-state functional interaction (Fox and Greicius, 2010; Fox et al., 2005). In ALFF analysis, the baseline intensity or the amplitude of LFOs is quantified as a regional characteristic of resting-state intrinsic neural activity (Zang et al., 2007; Zou et al., 2008; Zuo et al., 2010). Although FC or ALFF analysis have commonly focused on the 0.01 to 0.08 Hz frequency range, some reports have suggested the involvement of higher frequencies range in LFOs characteristics under normal physiological conditions in regions like brain stem, basal ganglia, or amygdala (Salvador et al., 2008; Zuo et al., 2010), during pathological conditions such as pain (Baliki et al., 2011) or after noninvasive cortical stimulation (Chen et al., 2013).

Alterations in ALFF values in depression have been the subject of a few recent rs-fMRI studies. Those studies mainly focused on the pattern of ALFF changes in depression and reported MDD-related ALFF alterations in several brain areas like the frontal cortex, parietal cortex, temporal cortex, limbic system, visual network and cerebellum (Guo et al., 2013; Liu et al., 2014; Wang et al., 2012; Zhang et al., 2014). Clinical and cognitive correlations of ALFF alterations in MDD have not been examined comprehensively. The possible contribution of higher frequency ALFF (0.1–0.25 Hz) changes has also not been tested yet. Furthermore, it has not been investigated that how regions with ALFF changes in depression behave differently in their interactions with other elements of involved networks.

In this study, we aimed to test three hypotheses. First, MDD is related to alterations in ALFF calculated for traditional lower frequency (0.01–0.08 Hz) as well as untested higher frequency (0.1–0.25 Hz) ranges in areas that belong to cortico-striato-limbic circuits. Second, changes in ALFF values in MDD are correlated with depression symptoms severity and cognitive performance. Third, FC between regions with ALFF alterations and other nodes in the related networks are altered in depression.

2. Methods

2.1. Participants

For this study, we recruited 45 subjects. Of these, 20 were unmedicated subjects with unipolar major depression (MDD) and 25 were nondepressed comparison subjects (HC). All study subjects were recruited from the local community through advertisements in flyers, newspapers, and radio. The inclusion criteria for all subjects were 30 years of age and older, antidepressant-naive or free of antidepressant use for at least two weeks and no history of unstable cardiac or neurological diseases. The exclusion criteria included schizophrenia, bipolar or any psychotic disorders; history of anxiety disorder outside of major depressive episodes; history of head trauma or loss of consciousness; history of substance abuse; contraindications to MRI such as metal implants; and Mini Mental Status Exam (MMSE) score $\leq$ 24. This study was approved by the University of Illinois-Chicago Institutional Review Board, and written informed consent was obtained from each participant.

All eligible subjects were assessed by a trained research assistant with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (First et al., 2012). The severity of depression was quantified by a board-certified/board-eligible psychiatrist (AK or OA) using the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). At the time of enrollment, depressed subjects met *DSM-IV* criteria for MDD and required a score of 15 or greater on the HAM-D. Subjects were also administered the Center for Epidemiological Studies-Depression (CES-D) scale as an independent measure of depression severity (Yesavage et al., 1982). The CES-D was used for correlation analyses as the HAM-D was the measure used in the determination of subject eligibility for depression.

2.2. Neuropsychological battery

All subjects underwent a comprehensive neuropsychological battery covering domains of attention/information processing (AIP: Stroop Word Score, Stroop Color Score, Trail Making Test Part A, WAIS-III Digit Symbol Coding), learning and memory (LM: California Verbal Learning Test (CVLT), Wechsler's Memory Scale 3rd Edition Logical Memory and Visual Reproduction), and executive function (EF: Category Switching Accuracy, Trail Making Test Part B, Digit Span Backwards, Stroop Interference Score, Self-Ordered Pointing Task) (Delis et al., 2011; Golden et al., 1978; Wechsler, 1997; Woods et al., 2006). Individual test scores for each domain were averaged and converted to *z*-scores. Cronbach's alpha calculated for each domain was 0.87 for AIP, 0.84 for LM, and 0.77 for EF, demonstrating high internal consistencies for each domain.

2.3. MRI acquisition

Brain MRI data were acquired on a Philips Achieva 3.0 T scanner (Philips Medical Systems, Best, The Netherlands) using an 8-channel SENSE (Sensitivity Encoding) head coil. Participants were positioned comfortably on the scanner bed and fitted with soft ear plugs; foam pads were used to minimize head movement. Participants were instructed to remain still throughout the scan. High-resolution three-dimensional T_1-weighted images were acquired with an MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) sequence (field of view (FOV)=240 mm; 134 contiguous axial slices; TR/TE=8.4/3.9 ms; flip angle=8°; voxel size=1.1 × 1.1 × 1.1 mm^3). rs-fMRI data were acquired with the following parameters: Single-shot gradient-echo EPI sequence, TR/TE=2000/30 ms, Flip angle=80 degree, EPI factor=47, FOV=23 × 23 × 15 cm^3, in-plane resolution=3 × 3 mm^2, slice thickness/gap=5/0 mm, slice number=30, SENSE reduction factor=1.8, NEX=200, total scan time=6:52′. Subjects were instructed to keep their eyes close and "not think of anything in particular."

2.4. fMRI data preprocessing

All preprocessing were conducted using statistical parametric mapping software (SPM8, http//www.fil.ion.uvl.ac.uk/spm). The first 10 volumes of the functional images were discarded for obtaining signal equilibrium and allowing participants adaptation to scanning noise. The artifact detection tool (ART: http://www.nitrc.org/projects/artifact_detect) was used to measure motion artifacts in all subjects. None of the subjects used in this study had more than 2 mm maximum displacement in *x*, *y* or *z* axis or 2° angular motion during fMRI scanning. Furthermore, there was no significant difference in composite motion between groups (HC: 0.24 ± 0.12; MDD: 0.24 ± 0.11; p = 0.98). Raw EPI images were subsequently realigned, coregistered, normalized, and smoothed with a smoothing kernel of 8 mm before analyses. Confound effects from motion artifact, white matter, and CSF were regressed out of the signal. Finally, BOLD signal data were passed through two band-pass filters (lower frequency band: 0.01 to 0.08 Hz and higher frequency band: 0.1 to 0.25 Hz) for further ALFF and FC analyses.