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Alteration of spontaneous neuronal activity within the salience network in partially remitted depression

Chun-Hong Liu[a,b], Xin Ma[a,b,*], Lu-Ping Song[c,**], Li-Rong Tang[a,b], Bin Jing[d], Yu Zhang[a,b], Feng Li[a,b], Zhen Zhou[d], Jin Fan[e], Chuan-Yue Wang[a,b]

[a]Beijing Key Laboratory of Mental Disorders, Department of Psychiatry, Beijing Anding Hospital, Capital Medical University, Beijing 100088, China
[b]Laboratory of Brain Disorders, Beijing Institute for Brain Disorders, Capital Medical University, Beijing 100069, China
[c]Rehabilitation College of Capital Medical University, China Rehabilitation Research Center, Beijing 100068, China
[d]School of Biomedical Engineering, Capital Medical University, Beijing 100069, China
[e]Department of Psychology, Queens College, The City University of New York, Queens, New York 11367, USA

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ABSTRACT

Of major depression patients, 29–66% show only partial remission on a single antidepressant trial. Such patients are characterized by residual depressive symptoms such as anhedonia, psychic anxiety, sleep disturbance, and cognitive dysfunction. Despite having a tremendous impact on outcomes such as future relapse, morbidity, and mortality, the neural mechanisms of partially remitted depression remain unclear. Using the amplitude of low-frequency fluctuations (ALFF) approach, we investigated the intrinsic neural oscillation alterations during resting state in partially remitted depression. A total of 23 partially remitted depression patients and 68 healthy controls underwent magnetic resonance imaging for functional imaging. We compared ALFF differences between groups as well as correlations between clinical measurements and ALFF in the brain regions showing significant group differences. Compared with healthy controls, partially remitted depression patients showed increased ALFF in the left ventral anterior insula, bilateral posterior insula, and bilateral supramarginal gyrus, and decreased ALFF in the left calcarine gyrus. A trend positive correlation between the number of depressive episodes and ALFF values was found in the right posterior insula in the partially remitted depression group. In addition, the ALFF in the right supramarginal gyrus were negatively correlated with Hamilton Depression Rating Scale scores. Consistent with the emerging theory of the role of the salience network in sensing the changes of homeostasis that contributes to

*Corresponding author at: Beijing Anding Hospital, Capital Medical University, No. 5, An kang Lane, De wai Avenue, Xi Cheng District, Beijing 100088, China. Fax: +86 10 58303078.
**Corresponding author at: Rehabilitation College of Capital Medical University, and China Rehabilitation Research Center, No. 10, North Road, Feng tai District, Beijing 100068, China. Fax: +86 10 87569436.
E-mail addresses: maxinanding@vip.163.com (X. Ma), songluping882002@aliyun.com (L.-P. Song).

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partially remitted depression, the current findings suggest that the increased intrinsic neural oscillation of the insula is related to the refractoriness to treatment and may be an imaging marker for predicting future depression recurrence.

1. Introduction

Partially remitted depression is characterized by the common presence of residual depressive symptoms such as low mood, psychic anxiety, sleep disturbance, somnolence/fatigue, diminished interest, and cognitive dysfunction (McClintock et al., 2011). Of major depression patients, 29–66% do not recover fully on a single antidepressant trial (Fava et al., 1996; Kennedy and Giacobbe, 2007). Within the four-phase Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study for evaluating various levels of treatment, the remission rates are 37%, 31%, 14%, and 13% from the first to fourth phases, respectively (Rush, 2007). Even worse, lack of complete remission from an acute episode of depression has been associated with a higher relapse rate, more severe depressive episodes, poor prognosis, and risk of suicide events (Fava, 2006; Judd et al., 1997; Judd et al., 2000; Lee et al., 2013). Despite having a tremendous impact on outcomes such as future relapse, morbidity, and mortality, the neural underpinnings of partial remission in depression remain poorly understood at present. A better understanding of the neural correlates of partially remitted depression may inform future treatment choices and ultimately improve prognosis.

Functional magnetic resonance imaging (fMRI) of depressed patients under resting conditions (i.e., without a task) has characterized as impaired interactions within cortico-limbic circuits (Fitzgerald et al., 2008; Wang et al., 2012), particularly in the dorsal and lateral cortical circuits related to cognitive processes, and the ventral limbic brain areas associated with affective appraisal processes and emotional expression (for a review, see Phillips et al., 2003a). Taylor and Liberzon (2007) proposed a hyper-ventral and hypo-dorsal model of cognitive emotional interaction with the pattern reversed after full remission. Recently, the triple network model has become intriguing because the salience network, i.e., the insular cortex, has been speculated to be responsible for the switch between internal (reflected by default mode network (DMN) activity) and external (reflected by central executive network activity) attention (Menon, 2011; Orliac et al., 2013). Although each of these models has its distinct theory regarding the interaction between cortical and limbic regions, the regions involved in these models are largely overlapped. Because the insular cortex, a core region in the salience network, has been regarded as an indicator of treatment response during resting state in depression (Horn et al., 2010), we hypothesized that altered intrinsic insular activity might be related to partial remission of depression.

Given that a substantial proportion of major depressive disorder (MDD) patients are partial responders, it is surprising that so few studies have investigated the neural correlates of partially remitted depression. The only fMRI study that has compared depression with partial remission had a small sample size and studied only older adults (Lee et al., 2013). This study revealed that geriatric depressive patients showed enhanced activity in the left middle frontal gyrus and left parietal gyrus, and reduced activity at several temporal gyri and left amygdala during an n-back working memory task. Although working memory tasks have been widely employed to investigate the neural characteristics of depression, it is hard to implement and accomplish these tasks for patients. In contrast to traditional cognitive tasks (e.g., motor, visual, sensory, and memory tasks), resting-state fMRI allows researchers to investigate spontaneous fluctuations in brain activity without using externally controlled task paradigms (Raichle et al., 2001).

Recent years have witnessed an increase in the number of resting-state fMRI studies, and there are many strategies used to analyze resting-state fMRI data, including functional connectivity, regional homogeneity (ReHo), amplitude of low-frequency fluctuation (ALFF), and fractional amplitude of low-frequency fluctuation (fALFF). ALFF measures the local features of amplitude or strength of the spontaneous low-frequency oscillations (Yang et al., 2007; Zang et al., 2007; Zou et al., 2008) and has successfully been applied to detect alterations in various mental disorders (e.g., Hoptman et al., 2010; Liu et al., 2012). We hypothesized that the altered activity during resting states within cortico-limbic circuits, particularly in the insular cortex with partially remitted depression, might contribute to inadequate treatment responses. We also conjectured that such an abnormality is a state marker. Additionally, we conducted a correlation analysis between the severity of depression and observed fALFF measurements.

2. Results

2.1. Demographic information and standardized test

The demographic and clinical data are shown in Table 1. There were no significant differences in participant age (t (1, 90) = −0.73, p=0.47), years of education (t (1, 90) = −0.99, p=0.32), sex (x^2 (1)=0.82, p=0.37) between the partially remitted depression group and the healthy control group. The HAMD total scores, illness duration (years), and number of depressive episodes for the partially remitted depression group were 10.87±2.62, 6.87±7.78, and 2.43±1.88, respectively. There were no significant differences in the mean head motion parameters, including three rotations (pitch, roll, yaw) and three translation parameters (X, Y, Z) between groups (Figs. 1 and 2). The mean displacement=square root ($x^2+y^2+z^2$) was calculated for every subject in both groups, which is thought to be the central metric of head motion (van Dijk et al., 2012). Then, a two-sample t-test was used to compare the mean motion between groups, and there were no significant differences between the two groups in mean displacement (t (1, 90)=0.41, p=0.43) (Table 1). Table 2 shows the detailed data on number of depressive episodes,