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Intrinsic cerebral activity at resting state in adults with major depressive disorder: A meta-analysis

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ABSTRACT

Numerous neuroimaging studies have been undertaken to detect cerebral intrinsic activity in major depressive disorder (MDD) with resting state fMRI (rs-fMRI). However, the inconsistent results have hindered our understanding of the exact neuropathology related to MDD. The current meta-analysis used state-of-the-art conjunction analysis techniques to systematically review and summarize all available neuroimaging studies using rs-fMRI with amplitude of low frequency fluctuation (ALFF) and/or fractional ALFF (fALFF) on MDD patients and further explored the effect of antidepressants on the intrinsic activity of the brain. The anisotropic effect size version of signed differential mapping (AES-SDM) was applied to investigate changes in ALFF/fALFF in depression. We performed a subgroup analysis and group comparison on medicated and drug naïve patients to detect drug effect on MDD patients and conjunction analysis to identify congruent results between the two methods. Meta-regression was used to explore the effects of demographics and clinical characteristics. Adult MDD patients showed a robust increase in intrinsic activity in the resting state in the anterior cingulate cortex (ACC) in both ALFF ($P<0.001$) and fALFF ($P < 0.01$) studies. The subgroup analysis demonstrated that the increased activity in the ACC was prominent in medicated patients only and not seen in drug-naïve MDD patients, while medication-naïve patients showed a specific decreased activity in the cerebellum ($P<0.01$). Group comparison showed that the intrinsic ACC activity is elevated in medicated MDD patients compared with drug naïve MDD patients. Meta-regression analysis demonstrated that the increased ACC activation was positively correlated with illness duration ($P<0.001$). Our findings suggest that increased activity of the ACC is more likely to be associated with antidepressant treatment, while decreased intrinsic activity of the cerebellum might be a specific biomarker for current MDD.

1. Introduction

Major depressive disorder (MDD) is a globally prevalent psychiatric disorder characterized by affective, cognitive, and somatic symptoms (Wolfers et al., 2015). Neuroimaging evidence has suggested that it is a disorder that involves alterations in brain connectivity in multiple neuronal circuits (Gong and He, 2015), with a node occupying a central position in the overall organization of the network (van den Heuvel and Sporns, 2013). Moreover, past studies have also found that the response of the brain to the external world is effectively modulated by intrinsic activity at resting state (Mennes et al., 2011). Thus, apart from the detection of functional connectivity (FC), which reflects simultaneity in cerebral neural activity between the regions, the properties of the intrinsic functional dynamics of the brain in certain regions in resting state are fundamental and worth exploring (Vargas et al., 2013).

Among the various approaches for measuring the temporal dynamics of the resting-state fMRI (rs-fMRI) signal at a given voxel, frequency-based approaches, namely the so-called amplitude of low-frequency fluctuations (ALFF), have the advantage of providing frequency-specific indices of oscillatory phenomena and directly reflecting the intensity of regional spontaneous neural activity (Zang et al., 2007). Fractional ALFF (fALFF) was subsequently developed as an improved approach to detect intrinsic spontaneous brain activity with higher sensitivity and specificity (Zou et al., 2008). This metric measures the relative contribution of the low frequency oscillatory (LFO) amplitude in a specific frequency band to the total frequency band, thus reflecting the relative intensity of LFOs. Previous studies have applied both methods to the same sample group and obtain different results (Cui et al., 2014; Lv et al., 2014), which suggests an inherent difference between these two indices measuring neural activity. In recent years, both parameters have been applied to evaluate the cerebral intrinsic activity in normal subjects in an eyes-open versus an eyes-closed state (Yang et al., 2007) and in

Abbreviations: MDD, major depressive disorder; HC, healthy control; ALFF, amplitude of low frequency fluctuation; fALFF, fractional amplitude of low frequency fluctuation; AES-SDM, anisotropic effect size-signed differential mapping; ACC, anterior cingulate cortex.

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disorders such as schizophrenia (Huang et al., 2010), depression (Sambataro et al., 2014) and ADHD (Fei Li et al., 2014). Previous studies on MDD have demonstrated that local cerebral intrinsic functional abnormalities were found in widespread brain regions, such as the anterior cingulate cortex (W. B. Guo et al., 2012), cerebellum (Liu et al., 2013), superior temporal gyrus (Fan et al., 2013; Guo et al., 2014), precuneus (Jing et al., 2013) and insula (Liu et al., 2014). However, these results are often inconsistent, probably due to the small sample sizes in each study, heterogeneity in subject recruitment and methodological differences in the imaging process.

Meta-analyses are helpful to summarize this vast literature and offer insights that are not apparent from individual studies. A meta-analysis of FC studies found large-scale network dysfunction in the frontal-parietal network and default mode network in MDD (Kaiser et al., 2015). Sarina et al. concluded that there were functional alterations of the "local connectivity" in the medial prefrontal cortex as revealed by regional homogeneity (ReHo) (Iwabuchi et al., 2015). Both studies focused on "connectivity" alterations instead of intrinsic changes. Just one recent published meta-analysis based on all available resting state fMRI data in drug-naïve MDD patients that had included ALFF/fALFF studies. However, combining different parameters blurred the results of the cerebral connectivity and regional intrinsic activity (Zhong et al., 2016). The inclusion of only first episode drug-naïve patients also hinders the further exploration of drug effect on brain activity at resting-state.

In the current study, we conducted a meta-analysis on all available ALFF and fALFF studies carried out on adult MDD populations to detect alterations in the cerebral intrinsic spontaneous activity using the anisotropic effect size-signed differential mapping (AES-SDM) software, which combines several useful features of earlier methods, such as activation likelihood estimation and multilevel kernel density analysis (Radua et al., 2012, 2014). The overlap in the brain intrinsic activity between the ALFF and fALFF was analyzed using a conjunction analysis function in the AES-SDM software. As medication has been proven to affect brain structure (Fu et al., 2015; Kong et al., 2014) and function (Ebert et al., 1991; Gyurak et al., 2015; Yang et al., 2014), we also performed a subgroup analysis and group comparison according to the medication state. Other complementary analyses, such as jack-knife analyses, were conducted to assess the robustness and heterogeneity of the results, and meta-regression analyses were used to look for potential confounding variables and moderators.

2. Materials and methods

2.1. Search and study selection

PubMed, Embase and Web of Science databases were searched up to December 2015 using the following keywords: "depression" or "unipolar disorder" or "depressive disorder;" and "functional magnetic resonance imaging" or "fMRI;" and "amplitude of low frequency fluctuation" or "fractional amplitude of low frequency fluctuation". Additional articles were identified through major reviews and reference lists of eligible articles.

A study was included if it (1) reported comparisons between patients with MDD and healthy controls (HCs), (2) employed fMRI; (3) assessed brain activation using ALFF or fALFF processing, and (4) reported the whole-brain results of activity alterations in standard stereotactic coordinates (Talairach/Tournoux or Montreal Neurological Institute (MNI) space). In cases in which similar studies met the aforementioned inclusion criteria but had overlapping data, the study with the largest sample size was selected. For studies containing multiple independent patient samples, the appropriate coordinates were included as separate studies.

Studies were excluded if (1) participants were in an age range of <18 or >60 years, (2) the data were unavailable (e.g., missing neuroanatomical coordinates) even after the authors were contacted by email or telephone, (3) the data overlapped with those of another included publication, (4) depression was secondary to a somatic condition such as temporal lobe epilepsy or multiple sclerosis and was investigated solely as a comorbid psychiatric condition or as postpartum depression, and (5) a region-of-interest approach was used.

2.2. Voxel-wise meta-analysis

The meta-analysis was conducted using AES-SDM, version 4.31 (http://www.sdmproject.com/software), a voxel-based meta-analytic approach that uses the reported peak coordinates to recreate maps of the effect size of the differences in BOLD response between patients and controls. For peak coordinates, the recreation is based on first converting the peak t value to Hedges' effect size and then applying a non-normalized Gaussian kernel to the voxels close to the peak. In AES-SDM, both positive and negative differences are reconstructed in the same map, which prevents a particular voxel from appearing to be significant in opposite directions. Importantly, negative studies were also included in the meta-analysis.

2.3. Subgroup analysis

We performed 2 subgroup meta-analyses for ALFF and fALFF studies separately, including studies of patients with antidepressant drugs and studies in which all patients were medication naïve. Strategically, this helped to illuminate the confounders of antidepressant drugs (Bora et al., 2010).

2.4. Group comparison analysis

To directly contrast the brain intrinsic activity of treated and untreated patients, we conducted two meta-analytic group comparisons for ALFF and fALFF studies using AES-SDM, which provided an indication of where the computed effect sizes differed significantly between groups (Radua et al., 2010).

2.5. Reliability analysis

A systematic whole-brain voxel-based jack-knife sensitivity analysis was used to test the reliability of the results. Briefly, jack-knife sensitivity analyses consist of repeating the analysis discarding only one study each time to assess the reproducibility of the results (Gyurak et al., 2015). If a brain region remains significant in all or most of the combinations of studies, it can be concluded that this finding is highly replicable.

2.6. Meta regression analysis

Meta-regression analysis was used to examine the potential confounding effect of relevant variables that were available in the primary studies, such as age, illness duration, gender, severity and the percentage of individuals receiving medication. To minimize the detection of spurious relationships, we decreased the probability threshold to 0.0005 required abnormalities to be detected both in the slope and in one of the extremes of the regressor, and discarded findings in regions other than those detected in the main analyses (Radua and Mataix-Cols, 2009). Peak coordinates were submitted to MRIcron (http://www.nitrc.org/projects/mricron/) which provided templates to visualize the results.

2.7. Conjunction analysis

To localize brain regions with both ALFF and fALFF abnormalities in MDD, between-group contrasts of brain functional activity were summarized in a single meta-analytic map (Radua et al., 2013). The overlap of the ALFF and fALFF P values was computed to identify multimodally affected brain regions. The method implemented in AES-SDM accounts