Behavioural Brain Research 281 (2015) 339–347

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Abnormal spontaneous neural activity in the anterior insular and anterior cingulate cortices in anxious depression

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HIGHLIGHTS

- To examine adult anxious depression patients using ALFF and fALFF method.
- Increased ventral cingulate activity might be related to neurobiology of anxious depression.
- Increased insular activity might be related to the core symptoms of anxious depression.

ARTICLE INFO

Article history:
Received 16 July 2014
Received in revised form
25 November 2014
Accepted 29 November 2014
Available online 13 December 2014

Keywords:
Anxious depression
Resting-state
Functional magnetic resonance imaging (fMRI)
Fractional amplitude of low-frequency fluctuation (fALFF)
Amplitude of low-frequency fluctuation (ALFF)

ABSTRACT

Objective: Anxious depression is a distinct clinical subtype of major depressive disorder (MDD) characterized by palpitations, somatic complaints, altered interoceptive awareness, high risk of suicide, and poor response to pharmacotherapy. However, the neural mechanisms of anxious depression are still not well understood. In this study we investigated changes in neural oscillation during the resting-state of patients with anxious depression by measuring differences in the amplitude of low-frequency fluctuation (ALFF).

Methods: Resting-state functional magnetic resonance imaging was acquired in 31 patients with anxious depression, 18 patients with remitted depression, as well as 68 gender- and age-matched healthy participants. We compared the differences both in the ALFF and fractional ALFF (fALFF) among the three groups. We also examined the correlation between the ALFF/fALFF and the severity of anxiety as well as depression.

Results: Anxious depression patients showed increased ALFF/fALFF in the right dorsal anterior insular cortex and decreased ALFF/fALFF in the bilateral lingual gyrus relative to remitted depression patients and healthy controls. The increased ALFF in the dorsal anterior insula was also positively correlated with stronger anxiety in the anxious depression group. Anxious depression patients also displayed increased fALFF in the right ventral anterior cingulate cortex (ACC) compared to remitted depression patients and healthy controls.

Conclusions: Our results suggest that alterations of the cortico-limbic networks, including the right dorsal anterior insula and right ventral ACC, may play a critical role in the physiopathology of anxious depression.

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http://dx.doi.org/10.1016/j.bbr.2014.11.047
0166-4328/

1. Introduction

Anxious depression is a common clinical subtype of major depressive disorder (MDD) characterized by dysphoric mood, disturbed sleep, somatic complaints, altered interoceptive awareness, and increased morbidity [1–3]. Compared with depression without anxiety, anxious depression has a greater severity of depressive illness, longer illness chronicity, and a higher risk of disability and suicidal tendency [4–6]. Anxious depression is also more likely to exhibit somatic symptoms, to take twice as long to recover from a depressive episode, and to have lower remission rates [7]. Despite the poor clinical outcomes and increasing social and economic burdens of anxious depression [8], little attention has been paid to the neurobiology of the disorder. There is a compelling need to investigate the underlying neural mechanisms of anxious depression to develop a better target for treatment.

The existing psychological models of anxious depression (such as the valence-arousal and approach-withdrawal models) are focused on anxiety-related hyperarousal. However, limited neuroimaging studies in literature have found widespread structural and functional changes in anxious depression within the cortico-limbic circuits including the anterior cingulate cortex (ACC), prefrontal cortex, middle temporal gyrus, and insula [2], which are largely overlapped with the regions involved in major depression. It is unclear about which structural or functional changes observed in the literature are specifically related to anxious depression and which to depression in general. The only functional MRI study that has compared depression with high versus low anxiety had a small sample size and studied only older adults [9]. This study revealed that elderly depressed subjects with high anxiety showed stronger functional connectivity in the posterior regions of the default mode network (e.g., the precuneus), and lower functional connectivity in the anterior regions of the default mode network (e.g., the rostral ACC, medial prefrontal cortex and orbitofrontal cortex) compared with low anxiety depressed subjects during resting-state using posterior cingulate cortex from automated anatomical labeling template as seed point. Although functional connectivity can disclose network changes related to anxious depression, it does not address which changes and regions are related to primary deficits in the disorder. Given the autonomic nervous deficits associated with anxious depression and the insula's role in interception [10], activity change in the insula might be associated with the anxiety-related symptoms of anxious depression [11,12]. To test this hypothesis, we examined the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) during resting-state which allowed us to compute the strength of neural oscillation in each voxel instead of connectivities between regions.

The ALFF and fALFF are thought that can reflect the strength of intrinsic spontaneous neuronal activity [13,14]. ALFF measures the regional intensity of spontaneous fluctuations by integrated the square root of power spectrum in a low-frequency range [15] and fALFF is the ratio between the low frequency band and the entire detectable frequency range in a given signal without filtering [14]. ALFF reflects the absolute strength or intensity within a specific low frequency range, whereas fALFF represents the relative contribution of the low frequency band to the whole detectable frequency range in a given signal [16]. Abnormal ALFF and fALFF measurements have been found in a number of psychiatric disorders including Alzheimer's disease [17] and major depression [16,18]. Therefore, in this study, we used ALFF and fALFF to reveal neural alteration related to the pathology of anxious depression. In addition, in order to compare the changes in the ALFF and fALFF of anxious depression patients with those of healthy controls, we also included remitted depression patients to investigate the anxiety depression state effect. We also examined whether anxiety severity was specifically correlated with the changes in the ALFF and fALFF measurements. Our hypothesis was that anxious depression patients might have an altered ALFF or fALFF in the insula and cortico-limbic circuits.

2. Materials and methods

2.1. Participants

This study was approved by the Institution of Review Boards of Beijing Anding Hospital, Capital Medical University and State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University. Participants included 31 patients diagnosed with anxious depression, 18 patients diagnosed with remitted depression and 69 healthy controls. All participants were right-handed, determined by the Edinburgh Inventory of handedness [19]. The criteria of selection for patients were as follows (also described in [18]): (1) between the ages of 18 and 60 years and has the ability to give voluntary informed consent; (2) meets the Structured Clinical Interview DSM-IV Axis I Disorders (SCID) diagnostic criteria for MDD; (3) no other psychiatric illnesses (e.g., schizophrenia, obsessive–compulsive disorder, and no alcohol or substance abuse or dependence) and no neurological illnesses; and (4) able to be scanned by MRI. The Hamilton Depression Rating Scale (HAMD) [20] was used to measure depressive symptoms on the day of scanning. Patients were grouped into anxious depression and remitted depression based on the anxiety/somatization factor score of the Hamilton Rating Scale for Anxiety (HAMA) and the HAMD. Anxious depression was defined as a total HAMA score of 15 or higher and a total HAMD score of 17 or higher, whereas the remitted depression was defined as a total HAMA score of eight or lower and a total HAMD score of eight or lower [9,21]. The healthy controls were recruited from the local community. The non-patient edition of the Structured Clinical Interview for the DSM-IV [22] was used to screen the healthy controls. Participants were excluded as healthy controls if they reported a history of neurological or neuropsychiatric disorders, or a positive family history of psychiatric disorders.

2.2. Image acquisition

Two hundred and forty contiguous gradient echo planar imaging (EPI) functional volumes were acquired with 33 axial slices, with parameters of repeat time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; matrix size = 64 × 64; thickness/gap = 3.5/0.6 mm; and sequence duration = 480 s for each subject using a Siemens Trio 3.0 T scanner at the National Key Laboratory for Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China. One hundred and twenty-eight (128) slices of structural 3D-T1 weighted images were also acquired sagittally without gaps (TR = 2530 ms; TE = 3.39 ms; slice thickness = 1.33 mm; field of view (FOV) = 256 mm × 256 mm; in-plane resolution = 256 × 256; inversion time (TI) = 1100 ms; voxel dimension = 1 mm × 1 mm × 1.33 mm; and FA = 7°). All participants were instructed to close their eyes and relax but not to fall asleep.

2.3. Data preprocessing

EPI data was first preprocessed using Data Processing Assistant and Resting-State fMRI (DPARSF) [23] based on statistical parametric mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) using MATLAB R2009a (The Mathworks, Natick, MA). The first 10 volumes of functional time points were discarded to reach stability of initial MRI signal and allow the participants to adapt to the MRI acquisition environment. The remaining 230 volumes were slice-timing corrected and head motion corrected. One healthy control was excluded from further analysis due to excessive head motion (head movements exceeded 2 mm in translation or 2° of