Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 13–18

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Is there a cerebellar compensatory effort in first-episode, treatment-naive major depressive disorder at rest?

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ARTICLE INFO

Article history:
Received 5 May 2013
Received in revised form 4 June 2013
Accepted 13 June 2013
Available online 23 June 2013

Keywords:
Cerebellum
Default mode network
Fractional amplitude of low-frequency fluctuations
Functional connectivity
Major depressive disorder

ABSTRACT

Background: This study was undertaken to explore whether there is a cerebellar compensatory response in patients with first-episode, treatment-naive major depressive disorder (MDD). The cerebellar compensatory response is defined as a cerebellar hyperactivity which would be inversely correlated with both the activation of the functionally connected cerebral regions and the depression severity.
Methods: Resting-state functional magnetic resonance imaging (fMRI) data of 24 patients with MDD and 24 healthy subjects were analyzed with the fractional amplitude of low-frequency fluctuations (fALFF) and functional connectivity (FC) methods. The structural images were processed with the voxel-based morphometry (VBM) method.
Results: Compared to healthy controls, depressed patients had significantly increased fALFF in the left Crus I and the left cerebellar lobule VI. FC analysis of these two seeded regions found that depressed patients had increased FC between the left Crus I and the right hippocampus, but had decreased FC between the left Crus I and the left inferior parietal lobule (IPL), and between the left cerebellar lobule VI and bilateral inferior temporal gyrus. No correlation was observed between the abnormal fALFF of the seeds and their connected regions and the depression severity or the executive function. The VBM results did not show significant reduction in gray or white matter volume in any above-mentioned region.
Conclusions: Our findings suggest that increased cerebellar activity at resting state may be a disease state phenomenon but not a compensatory response to the dysfunction of the default mode network (DMN) in MDD.

1. Introduction

The role of the cerebellum in mood and cognitive processing and other nonmotor functions has been established through neurological, anatomical, and neuroimaging studies (Schmahmann, 2004, 2010). Functional connectivity (FC) studies have shown that different parts of the cerebellum were distinctly connected to intrinsic networks related to mood regulation, cognitive processing, executive function, pain modulation, and so on (Habas et al., 2009; Krienen and Buckner, 2009; Moulton et al., 2010; Schmahmann, 2010). In contrast to both increased and decreased FC of the cerebellum with other brain regions at resting state in patients with major depressive disorder (MDD) (Alalade et al., 2011; Liu et al., 2012b), increased activation in the cerebellum was observed during a rewarded sustained attention task in adolescents with treatment-naive, first-episode MDD (Chantiluke et al., 2012). However, using face-matching task paradigm in treatment-free adult patients with MDD, Frodl et al. (2010) found that cerebellar activity had less connectivity with the orbitofrontal cortex compared to healthy controls.

Obviously, the role of the cerebellum in MDD is far from clear. The different findings from different studies could be due to the nature of the illness, such as the duration of illness, the severity of illness, the effect for treatment or study designs such as resting-state versus task-related. Furthermore, the identification of seeds in the cerebellum is critical. Most of the previous studies selected their regions of interest (ROIs) based on experience (Alalade et al., 2011; Liu et al., 2012b; Ma et al., 2013), including our previous study from a 1.5T

Abbreviations: FC, functional connectivity; MDD, major depressive disorder; ROI, region of interest; fALFF, fractional amplitude of low-frequency fluctuations; BOLD, blood oxygen level-dependent; VMHC, voxel-mirrored homotopic connectivity; MPFC, medial prefrontal cortex; PCC/PCu, posterior cingulate cortex/precuneus; DMN, default mode network; VBM, voxel-based morphometry; GM, gray matter; WM, white matter; HRSD, Hamilton Rating Scale for Depression; WCST, Wisconsin Card Sorting Test; EPI, echo-planar imaging; TR/TE, repetition time/echo time; FOV, field of view; MPRAGE, magnetization-prepared rapid gradient echo; TI, inversion time; fMRI, functional magnetic resonance imaging; DPARSF, Data Processing Assistant for Resting-State fMRI; CSF, cerebrospinal fluid; FWHM, full width at half maximum; AAL, Anatomical Automatic Labeling; GRF, Gaussian Random Field; FD, framewise displacement; IPL, inferior parietal lobule; GSReg, global signal regression.

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http://dx.doi.org/10.1016/j.pnpbp.2013.06.009

GE scanner (Guo et al., 2013b). We endorsed these studies for their interesting findings. However, it is unclear whether there is altered activity in these pre-selected ROIs or the connected brain regions. In the present study, the fractional amplitude of low-frequency fluctuations (fALFF) method was applied to identify the cerebellar regions with abnormal fALFF, which could be used as the cerebellar ROIs. fALFF is designed to detect the regional intensity of spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals (Zou et al., 2008). The regional intensity of BOLD signals varies depending on spontaneous fluctuations of blood flow to the region. Therefore, increased fALFF might be an index of neural hyperactivity in a brain region and decreased fALFF would indicate neural hypoactivity (Biswal et al., 1995; Liu et al., 2013; Lui et al., 2009).

Brain hyperactivity has been typically viewed as reflecting either (1) a compensatory reallocation such that there is a tradeoff for the neural system to compensate for neuronal deficits and prevent performance from decreasing (Cabeza et al., 2002; Grady et al., 2005), or (2) a generalized nonfunctional spread of activity, namely dedifferentiation (Logan et al., 2002). In contrast, brain hypoactivity is reported to be specifically associated with depressive symptoms of low functional activities such as anhedonia and psychomotor retardation (Alalade et al., 2011). Meanwhile, evidence has been accumulated that altered cerebellar–cerebral resting-state FCs exist in patients with drug-naive depression (Liu et al., 2012b; Ma et al., 2013), treatment-resistant depression (Guo et al., 2013b), and geriatric depression (Alalade et al., 2011).

Here, we conducted a resting-state fMRI study to examine whether there is a cerebellar compensatory effort in first-episode, treatment-naive MDD. According to a previous study (Chantiluke et al., 2012), if the increased activation in the cerebellum in patients was a compensation for the activation of the connected region, the activation in the two regions would be inversely correlated with each other, and inversely correlated with the depression severity. To test this possibility, we applied the fALFF method to identify the cerebellar regions with abnormal fALFF as seeds at first. Then a FC method was utilized to detect the connected cerebral regions with the cerebellar seeds. Previously, the same dataset was analyzed by a voxel-mirrored homotopic connectivity (VMHC) method (Guo et al., 2013a), and the results showed that the depressed patients had significant lower VMHC in the medial prefrontal cortex (MPFC) and the posterior cingulate cortex/precuneus (PCC/PCu), two core regions within default mode network (DMN). Although examination of the DMN was not the primary focus of that study, the VMHC results, together with previous studies (Grimm et al., 2009; Liu et al., 2012a), indicated that the DMN might play a critical role in the pathophysiology of MDD. Therefore, we expected that the DMN would be particularly affected. To test whether increased activation in the cerebellum in patients was a compensation for their connected cerebral regions, we correlated the brain activation (fALFF) of the cerebellar seeds and their connected regions. The correlations between the brain activation of the above-mentioned regions and the symptom severity or executive function were further examined.

Since reduction in cerebellar volume (Peng et al., 2011) and hippocampal volume (Gonul et al., 2011) was reported in patients with MDD, voxel-based morphometry (VBM) analysis was employed to determine the potential impact of structural changes of gray matter (GM) or white matter (WM) on the FC.

2. Methods

2.1. Subjects

Twenty-five right-handed, first-episode, treatment-naive patients with MDD were recruited from the Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China. These subjects were from our previous study (Guo et al., 2013a). A major depressive episode was ascertained by using the Structured Clinical Interview according to the DSM-IV criteria (First et al., 1997). The severity of depression was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1967). Only patients who were in the first episode with illness duration less than 6 months and naive to any medication with HRSD total score of $\geq$18 were eligible for the study. The executive function was evaluated by using Wisconsin Card Sorting Test (WCST). Patients with the following criteria were excluded: patients with other Axis I disorders such as schizophrenia, bipolar disorder, substance-induced mood disorder, and substance abuse within the six months prior to the study, with severe Axis II personality disorders and mental retardation, and with any history of serious medical or neurological illness or with a history of the loss of consciousness were also excluded.

Twenty-five right-handed healthy subjects matched with the patients age, gender, and the years of education were recruited from the community. They were also interviewed by using the Structured Clinical Interview for DSM-IV, non-patient edition (First et al., 1997). None of them had a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness in their first-degree relatives.

All subjects were given information about the procedures and gave written informed consent. This study was approved by the local Ethics Committee.

2.2. Image acquisition

Subjects were scanned with a Siemens 3T scanner equipped with high-speed gradients at the recruitment day. A prototype quadrature birdcage head coil fitted with foam padding was used to minimize head motion. Participants were informed to remain motionless, keep their eyes closed and do not think anything in particular during the image acquisition. The resting-state functional images were acquired by using an echo-planar imaging (EPI) sequence with the following parameters: repetition time/echo time (TR/TE) = 2000/30 ms, 30 slices, 64 × 64 matrix, 90° flip angle, 24 cm FOV, 4 mm slice thickness, 0.4 mm gap, and 250 volumes (500 s). After the scan, each subject was asked some questions to ensure cooperation.

Three dimensional T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sagittal images were collected by using the following parameters: TR/TE = 2300/2.98 ms, inversion time (TI) = 900 ms, 9° flip angle, 256 × 256 matrix, 176 slices, 1.0 mm slice thickness, no slice gap, and 0.5 × 0.5 × 1 mm^3 voxel size.

2.3. Data preprocessing

Image preprocessing was conducted by using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF) (Yan and Zang, 2010). The fMRI images were corrected for the acquisition delay between slices by shifting the signal measured in each slice relative to the acquisition of the slice acquired in the middle time of each TR. The head motion was corrected by estimating the values for translation (mm) and rotation (degree) for each subject. Only subjects with head motion less than 2 mm in the x, y or z direction and less than 2° rotation about each axis were included. The motion corrected functional volumes were spatially normalized to the standard SPM8 EPI template and resampled to 3 × 3 × 3 mm^3. Then, the processed images were spatially smoothed with an 8 mm full-width at half-maximum Gaussian kernel. Finally, linear trend removal and temporal band-pass filtering (0.01–0.08 Hz) were performed on the time series of each voxel.

The individual T1 weighted MPRAGE images were coregistered to the mean functional images which were produced with a linear transformation after head motion correction (Collignon et al., 1995). Afterwards, the transformed structural images were segmented into GM,