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Abnormal resting-state cerebellar–cerebral functional connectivity in treatment-resistant depression and treatment sensitive depression

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ABSTRACT

Background: Previous studies have commonly shown that patients with treatment-resistant depression (TRD) and treatment-sensitive depression (TSD) demonstrate a different cerebellar activity. No study has yet explored resting-state cerebellar–cerebral functional connectivity (FC) in these two groups. Here, seed-based FC approach was employed to test the hypothesis that patients with TRD and TSD had a different cerebellar–cerebral FC. The identified FC might be used to differentiate TRD from TSD.
Methods: Twenty-three patients with TRD, 22 patients with TSD, and 19 healthy subjects (HS) matched with age, gender, and education level participated in the scans. Seed-based connectivity analyses were performed by using cerebellar seeds.
Results: Relative to HS, both patient groups showed significantly decreased cerebellar–cerebral FC with the prefrontal cortex (PFC) (superior, middle, and inferior frontal gyrus) and default mode network (DMN) [superior, middle, and inferior temporal gyrus, precuneus (PCu), and inferior parietal lobule (IPL)], and increased FC with visual recognition network (lingual gyrus, middle occipital gyrus, and fusiform) and parahippocampal gyrus. However, the TRD group exhibited a more decreased FC than the TSD group, mainly in connected regions within DMN [PCu, angular gyrus (AG) and IPL]. Further receiver operating characteristic curves (ROC) analyses showed that cerebellar-DMN couplings could be applied as markers to differentiate the two subtypes with relatively high sensitivity and specificity.
Conclusions: Both patient groups demonstrate similar pattern of abnormal cerebellar–cerebral FC. Decreased FC between the cerebellum and regions within DMN might be used to separate the two patient groups.

1. Introduction

The cerebellum is traditionally regarded as a region which simply subserves motor coordination. This view has been challenged recently. An ample amount of convergent, multimodal data has been gathered to build a strong case for the involvement of the cerebellum in emotion and cognition (Schmahmann, 2010; Stoodley, 2012). Several studies have substantiated an altered neural response in the cerebellum, such as reduced cerebellar volume (Frodl et al., 2008; Peng et al., 2011), and increased cerebellar–vermal blood flow in major depressive disorder (MDD) (Dolan et al., 1992). The cerebellar cognitive–affective syndrome is also observed in patients with cerebellar damage (Parvizi et al., 2001; Schmahmann and

Abbreviations: TRD, treatment-resistant depression; TSD, treatment-sensitive depression; FC, functional connectivity; PFC, prefrontal cortex; MFG, middle frontal gyrus; SMA, supplementary motor area; ITG, inferior temporal gyrus; IPL, inferior parietal lobule; MDD, major depressive disorder; DMN, default mode network; HRSD, Hamilton Rating Scale for Depression; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitor; SNRIs, serotonin-norepinephrine reuptake inhibitor; MNI, Montreal Neurological Institute; ROI, regions of interest; ANOVA, analysis of variance; ROC, receiver operating characteristic curves; HS, healthy subjects; PCu, precuneus; AG, angular gyrus; FD, framewise displacement; GSReg, global signal regression.

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Sherman, 1998). However, the mechanism of the cerebellum affecting mood and cognitive processing remains equivocal.

Anatomically, the cerebellum reciprocally connects with brain regions, such as reticular nuclei, hypothalamus, ventral tegmental area, periaqueductal gray, hippocampus, and amygdala (Haines et al., 1984). The prefrontal cortex (PFC) and anterior cingulate are connected to the cerebellum via the pons or thalamus (Vilensky and van Hoesen, 1981). Responses in brain regions, such as the orbitofrontal cortex, anterior cingulate, amygdala, and hippocampus are evoked by electrical stimulation of the cerebellum in animals (Heath et al., 1978). These connections are supposed to be the neural substrates for the cerebellar–cerebral functional connectivity (FC).

Recent resting-state FC based on intrinsic activity fluctuations provides a potentially powerful approach for mapping cerebellar–cerebral circuit (Krienen and Buckner, 2009). The cerebellum is identified as "belonging" to the dorsal executive, salience, default-mode, and sensorimotor networks by using independent component analysis (Habas et al., 2009). Meanwhile, the cerebellum is confirmed to participate in networks important to cognition including a specific fronto-cerebellar circuit that interacts with the default mode network (DMN) by using seeds from four fronto-cerebellar circuits in frontal cortex (Krienen and Buckner, 2009). Moreover, using seed-based connectivity analysis, Alalade et al. (2011) suggest that cerebellum-vmPFC coupling is linked with cognitive function whereas cerebellum-posterior cingulate cortex coupling is related to emotion processing in geriatric depression. These FC studies between the cerebellum and cerebrum indicate that the cerebellum contributes to parallel associative cerebro-cerebellar networks involved in cognition and emotion (Schmahmann, 2004). However, some researchers fail to observe significant cognitive impairment in cerebellar lesion patients (Haarmeier and Thier, 2007). Therefore, cerebellar involvement in cognition remains to be debated.

Clinically, treatment-resistant depression (TRD) and treatment-sensitive depression (TSD) respond to antidepressants differently (Petersen et al., 2001). This clinical phenomenon indicates that the two subtypes of depression may differ at the neural level. For example, in a seed-based FC study, refractory depression is associated with disrupted FC mainly in thalamo-cortical circuits, while nonrefractory depression is related to more distributed decreased FC in the limbic-striatal-pallidal-thalamic circuits (Lui et al., 2011). We recently detected regional differences between the two subtypes, and the activity of the cerebellum could be used to separate the two subtypes (Guo et al., 2012a, 2012b; Liu et al., 2012a). Evidence of cerebellar involvement in depression-related alterations has been accumulated (Liu et al., 2012b). To date, resting-state cerebellar–cerebral FC has not been systematically explored in patients with TRD and patients with TSD, partly due to the general lack of attention to the cerebellum.

In the present study, the intrinsic cerebellar–cerebral FC related to the executive, default-mode, affective-limbic, and motor networks were investigated in patients with TRD and TSD and healthy subjects (HS), by using seeds in the cerebellum which were suggested by previous studies (Alalade et al., 2011; Krienen and Buckner, 2009). We hypothesized that the patients with TRD would exhibit decreased cerebellar–cerebral FC in distributed networks, especially in cerebellar-PFC coupling, and that the patients with TSD would exhibit similarly decreased but less notable cerebellar–cerebral FC. We also hypothesized that the cerebellar–cerebral FC with significant differences between the patient groups could be utilized to differentiate the two subtypes.

2. Methods

2.1. Subjects

The subjects involved in the present study were from our previous study (Guo et al., 2012a). Twenty-four right-handed patients with TRD were recruited from the Mental Health Institute of the Second Xiangya Hospital, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, China. Depressive attack was diagnosed with the Structured Clinical Interview according to the DSM-IV criteria (First et al., 1997). Exclusion criteria were any history of neurological diseases, other medical illnesses, or other psychiatric disorders such as schizophrenia, bipolar disorders or substance-induced mood disorder, and those with comorbidities such as anxiety disorders, alcohol or drug dependence, or severe Axis II personality disorders or mental retardation. Patients younger than 18 years or older than 50 years were also excluded. The depression severity was rated by using the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). To be eligible for the study, patients should have a HRSD total score of $\geq$18. Treatment resistance was termed as non-responsiveness to at least two adequate trials with different classes of antidepressants with adequate dosage, minimal 6 week duration of each trial, and acceptable compliance (Furtado et al., 2008; Guo et al., 2011). The non-response was defined as a reduction of $<$50% in HRSD scores after the treatment with a minimum dose of 150 mg/day of imipramine equivalents for 6 weeks (Nierenberg and Amsterdam, 1990). All patients with TRD were in treatment-resistant state. They had taken at least two classes of antidepressants before participating in the study. Among these patients, 16 patients suffered their first episode, 4 patients were at their second episode and 3 patients were at their third episode.

Thirty-one right-handed, first-episode, and treatment-naive patients were recruited from the same hospital. Inclusion and exclusion criteria were similar to those of the TRD group. An additional inclusion criterion was that the current illness duration was less than six months. After MR imaging, all patients took antidepressants at a minimum dose of 150 mg/day of imipramine equivalents (Iidaka et al., 1997) for 6 weeks. The drugs included one of the three typical classes of antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitor (SSRIs) and serotonin–norepinephrine reuptake inhibitor (SNRIs). The treatment response was defined as more than a 50% reduction in the HRSD scores after treatment (Furtado et al., 2008; Guo et al., 2011).

Twenty right-handed HS 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 met the criteria of a DMS-IV Axis I or II disorder. In addition, 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. They were well matched with the patients in age, gender and education level.

The study was approved by the local Ethics Committee. All participants were informed about the procedures and signed a written informed consent form.

2.2. Scan acquisition

Scanning was performed on a 1.5 T GE scanner (General Electric, Fairfield, Connecticut, USA) equipped with high-speed gradients just at the recruitment day. A prototype quadrature birdcage head coil fitted with foam pads was applied to minimize head motion. The participants were instructed to lie motionless, keep their eyes closed and not think of anything in particular.

Functional images were obtained by using an echo-planar imaging sequence with the following parameters: TR/TE = 2000/40 ms, 20 slices, 64 × 64 matrix, 90° flip angle, 24 cm FOV, 5 mm section thickness and 1 mm gap. For each participant, the scans lasted for 6 min and 180 volumes were acquired.

2.3. Data processing

Data preprocessing was performed using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes were discarded for scanner to reach steady state and allowing