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Research report

Unidirectionally affected causal connectivity of cortico-limbic-cerebellar circuit by structural deficits in drug-naive major depressive disorder

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ABSTRACT

Background: Structural deficits and resting-state functional connectivity (FC) alterations in the cortico-limbic-cerebellar circuit have been implicated in the neurobiology of major depressive disorder (MDD). This study was conducted to examine the causal connectivity biased by structural deficits in MDD patients.

Methods: Resting-state functional magnetic resonance imaging data were acquired from 44 drug-naive MDD patients and 44 healthy controls. Granger causality analysis (GCA) was used to analyze the functional data.

Results: We previously observed two brain regions, the left angular gyrus (AG) and the right inferior temporal gyrus (ITG), with reduced gray matter volume (GMV), which were selected as seeds. Compared with healthy controls, the patients showed inhibitory effect from the left AG to the left superior temporal gyrus (STG) and the left inferior frontal gyrus (IFG, opercular part), and from the right ITG to bilateral cerebellum 6. In contrast, the right ITG exhibited excitatory effect to the right insula. However, no abnormal feedback effect was observed in patients. There was no significant correlation between abnormal causal effect and clinical variables, such as HRSD scores, illness duration, and episode number.

Conclusions: Brain regions within the cortico-limbic-cerebellar circuit showed unidirectionally affected causal connectivities driven by structural deficits in MDD. The findings suggest that the causal topology of the cortico-limbic-cerebellar circuit may be disrupted unidirectionally by structural deficits in MDD.

1. Introduction

Increasing evidence exhibits that the disturbances in major depressive disorder (MDD) are unlikely to be the results of a single region with abnormal function and/or structure, and MDD could be considered as a disorder with distributed brain networks (Damasio, 1997). Several networks have been proposed to elucidate the neurobiology of MDD. For example, Mayberg (2003) emphasized the role of a network with dorsal and ventral components in MDD. Meanwhile, some researchers conceptualized MDD as a disorder with abnormal cortico-limbic-cerebellar circuit, including fronto-limbic network (Drevets et al., 2008; Pizzagalli, 2011). Other researchers observed that patients with MDD have cortico-subcortical alterations including limbic-cortical-striatal-pallidal-thalamic networks (Drevets et al., 2008; Marchand, 2010; Sheline, 2000). Recently, increasing attention has been paid to the abnormalities of the default-mode network (DMN) in MDD (Graham et al., 2013; Guo et al., 2014c). The DMN, including medial prefrontal cortex (MPFC), posterior cingulate cortex/precuneus (PCC/PCu), and lateral parietal cortex (Raichle et al., 2001), is associated with self-referential and introspective mental activity (Raichle and Snyder, 2007), which is active at rest and is deactivated during goal-oriented activity (Garrity et al., 2007).

It remains unclear whether or not functional abnormalities are related to anatomical deficits in MDD for the reason that few studies have examined functional and anatomical abnormalities in the same sample (Guo et al., 2014b). We recently made such a try and found a dissociation pattern of brain functional and

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anatomical deficits existing in MDD (Guo et al., 2014b). Using the combination of the voxel-based morphometry (VBM) and functional connectivity (FC) methods, Ma et al. (2012) observed that gray matter volume (GMV) reduction disrupted FC to distributed regions of the cortico-limbic-cerebellar circuit in patients with treatment-resistant depression and treatment-sensitive depression. However, one question remains to be settled is that the inferences about directed and weighted (i.e., excitatory or inhibitory) connectivities of the cortico-limbic-cerebellar circuit biased by anatomical deficits are unknown in MDD. It is clearly important to understand cortical hierarchies and distributed process, which usually acted as forward and backward connectivities (Bastos-Leite et al., 2014).

Cortico-limbic circuit is the key circuit in Mayberg's classic neurobiological model (Drevets, 2001; Mayberg, 2003; Seminowicz et al., 2004), which considers MDD as cortico-limbic circuit dysfunction in seven key brain regions: MPFC, lateral prefrontal cortex, orbitofrontal cortex, subgenual anterior cingulate cortex (ACC), rostral ACC, hippocampus and anterior thalamus (Seminowicz et al., 2004). In this cortico-limbic circuit, depressed mood is associated with overactivity in limbic regions which is not fully controlled by prefrontal cortex (Mayberg et al., 1999). The subgenual and rostral ACC are thought to act as an important mediatory role in this circuit (Disner et al., 2011; Seminowicz et al., 2004). In addition, other brain regions such as temporal (Lorenzetti et al., 2009), parietal (Graham et al., 2013; Mayberg, 1997) insular cortex (Mayberg, 1997; Sliz and Hayley, 2012), and the cerebellum (Alalade et al., 2011; Krienen and Buckner, 2009) are suggested to be included in this circuit, called the "cortico-limbic-cerebellar circuit".

A confluence of evidence indicates that MDD has both structural and functional alterations of the cortico-limbic-cerebellar circuit, leading to a failure in the coordinated interaction between brain regions of this circuit. For example, structural magnetic resonance imaging (MRI) studies using the region-of-interest (ROI) method have reported GMV reduction in the cortico-limbic-cerebellar circuit, such as the orbitofrontal cortex, ACC, and hippocampus in patients with MDD (Campbell et al., 2004; Hamilton et al., 2008; Koolschijn et al., 2009; Videbech and Ravnkilde, 2004). However, the ROI method is critical for the preselected seeds. Information from other brain regions is neglected by this method. Recently, VBM, an automated and unbiased whole-brain method, is employed to analyze the structural MRI data (Ashburner and Friston, 2000). Using the VBM method, several investigations have reported that patients with MDD have GMV abnormalities in many regions of the cortico-limbic-cerebellar circuit, like the hippocampus (Arnone et al., 2013; Wagner et al., 2008; Zou et al., 2010), ACC (Salvadore et al., 2011; Tang et al., 2007; Wagner et al., 2008), frontal regions (Salvadore et al., 2011; Scheuerecker et al., 2010; Wagner et al., 2008), temporal lobe (Lorenzetti et al., 2009), and cerebellum (Frodl et al., 2008; Liu et al., 2012; Peng et al., 2011; Pillay et al., 1997). Functional findings in MDD also include abnormalities of the cortico-limbic-cerebellar circuit, such as decreased frontal lobe function and increased limbic system activity (Chen et al., 2012; Wang et al., 2012; Liu et al., 2013). Abnormal cerebellar activity and connectivity are observed in MDD by using task-related or resting-state functional MRI (fMRI) (Frodl et al., 2010; Guo et al., 2013). However, these findings are inconsistent in detail. The inconsistency of findings may be partly interpreted by the heterogeneity of samples, such as medication use, depression severity and illness duration. For example, structural deficits seem to decrease progressively over illness duration (Bora et al., 2012) and antidepressants could reverse gray matter atrophy in both adult MDD patients (Kong et al., 2014; Smith et al., 2013) and geriatric MDD patients (Lavretsky et al., 2005). Hence, it is of particular importance to perform a study in drug-naive MDD patients with a short duration of the current episode to limit the possible effect from drug use and long duration of the current episode.

In the present study, we employed brain regions with reduced GMV revealed by the VBM method as seeds, which are reported in our previous study (Guo et al., 2014b). Then, a Granger causality analysis (GCA) method was performed to detect abnormal causality connectivity between seeds and other brain regions. Using a preselected seed of ventral ACC, Hamilton et al. (2011) observed both increased excitatory effect and inhibitory effect in MDD by the GCA method, giving supporting information of the utilization of the GCA method in MDD. The aim of the present study was to determine abnormal causal connectivity biased by structural deficits in MDD. Based on the above-mentioned studies, the cortico-limbic-cerebellar circuit was expected to be involved. We also examined the correlations of abnormal causal connectivity and clinical variables (i.e., illness duration, episode number, and depression severity).

2. Methods

2.1. Participants

Forty-four right-handed, drug-naive MDD patients were recruited from the Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China, and 44 right-handed healthy controls were recruited from the community. Depression diagnosis was made according to the criteria for a current episode of unipolar major depression based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (First et al., 1997). The Structured Clinical Interview of the DSM-IV was applied to confirm the depression diagnosis. The depression severity was assessed by Hamilton Rating Scale for Depression (HRSD, 17 items) (Hamilton, 1967), and all patients had a score of at least 18. Potential subjects were excluded if they had other Axis I disorders, such as schizophrenia, bipolar disorder, substance-induced mood disorder, substance abuse or dependence, acute physical illness, and a history of head injury resulting in loss of consciousness. Healthy controls had no personal history of psychiatric disorders and no psychiatric disorders in their first-degree relatives. The study was approved by the ethics committee of the First Affiliated Hospital, Guangxi Medical University, China, and all participants offered a written informed consent.

2.2. Image acquisition

A Siemens 3T scanner was used to acquire images. Participants were directed to lie still with their eyes closed and remain awake. Participants were fitted with soft earplugs and foam pads to minimize scanner noise and head motion. A gradient-echo echo-planar imaging (EPI) sequence was applied to obtain resting-state functional images with the following parameters: repetition time/echo time=2000 ms/30 ms, 30 slices, 64×64 matrix, 90° flip angle, 24 cm field of view, 4 mm slice thickness, 0.4 mm gap, and 250 volumes (500 s).

2.3. Data preprocessing

Functional data were preprocessed using Data Processing Assistant for Resting-State fMRI (Yan and Zang, 2010) in Matlab. We corrected the images for slice timing and head motion. No participant had maximal translation or maximal rotation exceeding ± 2 mm or $\pm 2^\circ$. Then, the images were normalized to the standard Montreal Neurological Institute (MNI) EPI template in SPM8 and resampled to $3 \times 3 \times 3$ mm^3. The obtained images were smoothed with an 8 mm FWHM Gaussian kernel, bandpass filtered (0.01–0.08 Hz), and linearly detrended. We removed several spurious covariates along with their