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Disrupted causal connectivity anchored on the anterior cingulate cortex in first-episode medication-naive major depressive disorder

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ABSTRACT

In recent years, major depressive disorder (MDD) has been demonstrated to be associated with abnormalities in neural networks, particularly the prefrontal-limbic network (PLN). However, there are few current studies that have examined information flow in the PLN. In this study, Granger causality analysis (GCA), based on signed regression coefficient, was used to explore changes in causal connectivity in resting-state PLNs of MDD patients. A total of 23 first-episode medication-naïve MDD patients and 20 normal control participants were subjected to resting-state functional magnetic resonance imaging (RS-fMRI) scans. Increased causal effects of the right insular cortex, right putamen and right caudate on the rostral anterior cingulate cortex (rACC) and reduced causal effects of bilateral dorsolateral prefrontal cortex (DLPFC) and left orbitofrontal cortex (OFC) on the rACC were found in MDD patients compared to normal controls. The extensive reduction in the causal effect of the prefrontal cortex (PFC) demonstrates impaired top–down cognitive control in MDD patients. Changes in the causal relationship between the right insula and rACC suggest problems in coordination of the default mode network by the right anterior insular cortex (rAI). These findings provide valuable insight into MDD-related neural network disorders reported in previous RS-fMRI studies and may potentially guide clinical treatment of MDD in the future.

1. Introduction

Depression is a very common mental disorder. The clinical manifestations of depression include not only depressed mood, but also cognitive impairments and patients with depression showing significant suicidal tendencies. The World Health Organization projected that by 2020, major depressive disorder (MDD) would be second only to coronary heart diseases, in terms of disease burden, causing great personal and social problems (Sliz and Hayley, 2011). However, the neurophysiological mechanism(s) of MDD is still not entirely clear (Smith et al., 2009).

The current predominance neural network model believes that MDD is caused by disruptions of the limbic-cortical network. Converging evidence for the hypothesis has been obtained with positron-emission tomography (PET) and fMRI (Mayberg et al., 1999; Siegle et al., 2007). A general reduction in prefrontal cortex (PFC) neural activity accompanied by increased activities of limbic system structures, such as the amygdala and hippocampus (Bennett, 2011; Davidson et al., 2002; Taylor and Liberzon, 2007), are consistently found in MDD patients. The amygdala is the core area of the limbic system and is responsible for processing emotional information and generating emotional reactions, which projects to subcortical and cortical areas (DeRubeis et al., 2008). Changes in amygdala volume and increase in its activity suggest deregulated amygdala activity in MDD patients. The PFC is capable of exerting inhibitory effects on many parts of the limbic system such as the amygdala (Ochsner et al., 2002; Ochsner et al., 2004). The decrease in PFC activity suggests that the deregulated emotional activity may be due to the decreased prefrontal executive control. This strongly suggests that maintaining depressive functioning may result from a combination of enhanced bottom–up emotional reactions and reduced top–down cognitive control (Lu et al., 2012). So Bennett summarized these results and proposed that MDD patients showed significant disorders of the prefrontal-limbic network (PLN) (Bennett, 2011).

MDD is a psychiatric disease at the network level. Investigating and analyzing PLN disorders may be the key to understanding the pathophysiological mechanism of MDD. The anterior cingulate cortex (ACC) is extensively connected to the prefrontal cortex and the limbic system, both structurally and functionally (Bush et al., 2000). The rostral

Abbreviations: MDD, major depressive disorder; PFC, prefrontal cortex; PLN, prefrontal-limbic network; RS-fMRI, resting-state functional magnetic resonance imaging; SEM, structural equation modeling; DCM, dynamic causal modeling; GCA, Granger causality analysis; ACC, anterior cingulate cortex; rACC, rostral anterior cingulate cortex; ROI, region of interest; NC, normal control; HAMD, Hamilton Depression Rating Scale; SCWT, Stroop Color-Word Test; TR, repetition time; TE, echo time; MNI, Montreal Neurological Institute; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; rAI, right anterior insular cortex; ALFF, amplitude of low frequency fluctuation; ReHo, regional homogeneity; rTMS, transcranial magnetic stimulation; DMN, default mode network.

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anterior cingulate cortex (rACC) is the core nexus between the amygdala and the PFC, plays a critical role for the integration of emotional and cognitive functions (Wagner et al., 2006). Some clinical studies on MDD examined whether rACC neural activity was increased or decreased, in order to indirectly determine whether PFC dysfunction or a limbic system abnormality was the dominant factor in PLN dysregulation and then customized individualized treatment plans for patients with MDD, accordingly (DeRubeis et al., 2008). Understanding the processes by which rACC contributes to balance PLN may assist clinicians in their MDD therapeutic work (Stevens et al., 2011).

Some resting-state functional magnetic resonance imaging (RS-fMRI) studies have examined functional connectivity and have analyzed synchronized functional changes between brain regions by calculating time-series correlations in order to explore abnormalities in MDD functional integration (Friston, 1994). Peng et al. found patients with depression showed increased functional connectivity between the ACC and the parahippocampus gyrus (Peng et al., 2012). However, the previous studies on functional connectivity did not take into account the direction of information flow between brain areas, which is crucial for determining the order of causality in interactions between PLN brain regions.

Effective connectivity represents the direct or indirect causal effect of one brain region on another brain region (Deshpande and Hu, 2012; Deshpande et al., 2011a). Structural equation modeling (SEM) and dynamic causal modeling (DCM) were earlier applied in effective connectivity analysis (Schlosser et al., 2008; Seminowicz et al., 2004),since they both are typical model-driven approaches, an a priori model is required to do data analysis and statistical inference. Granger causality analysis (GCA) is a relatively data-driven effective connectivity analytical method. GCA analyzes the direction of information flow between brain areas using time series of information processing and can depict resting-state directional brain networks (Deshpande et al., 2011b; Jiao et al., 2011). RS-fMRI GCA analysis does not require the design of a complicated task, so it is convenient for clinical application. Most previous GCA studies used a residual algorithm based on the F-test (Morgan et al., 2011; Szaflarski et al., 2010). However, only positive effects between brain regions can be evaluated using this method, thus it is not sufficient for reflecting true brain activities. Chen et al. proposed an algorithm based on a regression coefficient, in which a signed regression coefficient is used to assess Granger effects a positive value suggests an excitatory effect, whereas a negative value suggests an inhibitory effect or negative feedback (Chen et al., 2009a). Iwabuchi et al. had carried out coefficient GCA research, in which seed points on the insula have been selected, and found that MDD-affected lobes failed to interact with higher frontal regions, and the effect of sensory regions on the insular cortex was weakened (Iwabuchi et al., 2014).

In the present study, the coefficient GCA method was used to investigate the causal connectivity of rACC with the rest of the brain in MDD patients during resting-state. Only first-episode medication-naive MDD cases were studied in order to avoid the complex effect of treatment factors on resting-state brain functions. The rACC was selected as the seed region since it is an important node in the bottom–up and top–down pathways of the PLN. We anticipated that there would be alterations in the causal connectivity between the rACC and other PLN regions in MDD patients, and we also explored whether an abnormal GCA coefficient was related to the severity of the disease and executive function using the Stroop Color-Word Test (SCWT) within MDD patients.

2. Methods

2.1. Participants

This study included 23 MDD patients and 20 normal control participants. The patients were recruited from the Department of Psychiatry, First Affiliated Hospital of Zhejiang University School of Medicine. The inclusion criteria were as follows: (1) the symptoms complied with the diagnostic criteria for major depression according to the Structured Clinical Interview of the DSM-IV; (2) this was the first episode of major depression experienced by the patients and they had not yet received any treatment; and (3) patients had a score greater than 17 points on the 17-item Hamilton Depression Rating Scale (HAMD).

A total of 20 normal control (NC) participants, matched for age, gender and educational level, were recruited from hospital staff and students of the First Affiliated Hospital of Zhejiang University School of Medicine. The controls were screened using the non-patient version of the Structured Clinical Interview from the DSM-IV to exclude any history of psychiatric or neurological disorder.

The exclusion criteria for all participants were as follows: (1) a history of severe organic brain disease or brain trauma; (2) severe mental retardation; and (3) drug, alcohol or other psychoactive substance abuse.

In addition, patients with depression often suffer from cognitive executive function impairment (Lim et al., 2013). All participants were subjected to a SCWT ≤3 days prior to MR scanning. Since aging may cause a decline in cognitive function (Lockwood et al., 2002), we chose 18–45 year-old patients as subjects. This study was approved by the local Medical Ethics Committee of First Affiliated Hospital of Zhejiang University and written informed consent was obtained from each subject.

2.2. Image acquisition

MRI data were collected in the Department of Psychiatry, First Affiliated Hospital of Zhejiang University School of Medicine using a Philips Achieva 3.0 T scanner. The participants were asked to lie down in the scanner with eyes closed, not to think about anything in particular and not to fall asleep. The echo planar imaging sequence was used for fMRI scanning. The parameters were as follows: repetition time (TR)/echo time (TE): 2000/35 ms, flip angle: 90°, slice thickness/interval: 5.0/1.0 mm. A total of 24-slice transverse scans, aligned parallel to the anterior–posterior commissure, were taken and 200 time points were collected. Next, a gradient-echo sequence was used to obtain high-resolution structural MRI data. The parameters were as follows: TR/TE: 8/4 ms, flip angle: 8°, field of view: 240 mm.

2.3. Data preprocessing

DPARSF (http://www.restfmri.net) (Chao-Gan and Yu-Feng, 2010) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm) toolkits were used for MRI data pre-processing. To take into account the impact from the uniform field effect of the resonance apparatus, as well as participants not adapting to the scanning environment during the initial part of the experiment, data from the first 10 volumes were removed. The subsequent 190 volumes were subjected to slice timing to compensate for the time difference between different slices in each volume. A head movement correction was then done and data with translational displacement over ± 1.5 mm or rotation over $\pm 1.5°$ were removed. Functional data were registered to a high-resolution structural image and subjected to simulation transformation into Montreal Neurological Institute (MNI) space, with a resolution of $3 * 3 * 3$ mm^3. A Gaussian kernel, with a full width at half maximum of 4 mm, was then used to smooth the data, followed by bandpass filtering (0.01–0.08 Hz) to remove low-frequency linear drift and high-frequency noises caused by breathing and heartbeat. Finally, the six head movement parameters, the mean white matter signal and the mean cerebrospinal fluid signal were used as covariates in the regression.

2.4. Granger causality analysis

The basic idea of GCA is as follows. If, when analyzing two discrete time series, X and Y, the values of the past time series X and Y are more accurate than using the values of the past time series X only to predict the value of the current time series X, then the time series X and Y are considered to have a Granger prediction relationship (Chen