



Disrupted reward and cognitive control networks contribute to anhedonia in depression

Liang Gong^a, Cancan He^a, Haisan Zhang^b, Hongxing Zhang^{b,**}, Zhijun Zhang^{a,c}, Chunming Xie^{a,c,*}

^a Department of Neurology, Affiliated ZhongDa Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, 210009, China

^b Department of Psychiatry, Henan Mental Hospital, The Second Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan, 453002, China

^c Neuropsychiatric Institute, Affiliated ZhongDa Hospital, Southeast University, Nanjing, Jiangsu, 210009, China

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ABSTRACT

Neuroimaging studies have identified that anhedonia, a core feature of major depressive disorder (MDD), is associated with dysfunction in reward and cognitive control processing. However, it is still not clear how the reward network (β -network) and the cognitive control network (δ -network) are linked to biased anhedonia in MDD patients. Sixty-eight MDD patients and 64 cognitively normal (CN) subjects underwent a resting-state functional magnetic resonance imaging scan. A 2*2 ANCOVA analysis was used to explore the differences in the nucleus accumbens-based, voxelwise functional connectivity (FC) between the groups. Then, the β - and δ -networks were constructed, and the FC intensities were compared within and between the β - and δ -networks across all subjects. Multiple linear regression analyses were also employed to investigate the relationships between the neural features of the β - and δ -networks and anhedonia in MDD patients. Compared to the CN subjects, the MDD patients showed synergistic functional decoupling in both the β - and δ -networks, as well as decreased FC intensities in the intra- and inter- β - and δ -networks. In addition, the FC in both the β - and δ -networks was significantly correlated with anhedonia severity in the MDD patients. Importantly, the integrated neural features of the β - and δ -networks could more precisely predict anhedonic symptoms. These findings initially demonstrated that the imbalance between β - and δ -network activity successfully predicted anhedonia severity and suggested that the neural features of both the β - and δ -networks could represent a fundamental mechanism that underlies anhedonia in MDD patients.

1. Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder and is a seriously hazardous disease to human health and mental wellness (Marcus et al., 2012). Anhedonia, which refers to the loss of pleasure and/or decreased reactivity to reward stimuli, has been considered one of the key features of MDD that even frequently persists after treatment (Berlin et al., 1998; Pechtel et al., 2013). Recent studies have shown that anhedonia may represent a negative prognostic predictor for suicide and treatment response (McMakin et al., 2012; Spijker et al., 2010). Thus, elucidating the core neural signatures and processes of anhedonia is necessary for a more complete understanding and effective development of treatment of MDD (Der-Avakian and Markou, 2012). Traditionally, anhedonia has been viewed as a deficit in pleasure experience; recent evidence also suggested that the disrupted systems

implicated in reward and motivation are a core feature of anhedonia (Del Arco and Mora, 2008). In the immediate reward state, depression patients showed significantly weaker responses to gains in the nucleus accumbens (NAc) and in the caudate regions, and these blunted activity levels in the reward circuits were associated with worse treatment responses (Admon et al., 2015; Pizzagalli et al., 2009). In the positive emotion-maintaining and regulation states, individuals with depression were also found to display failures in NAc activity and disrupted connectivity in the fronto-striatal network over time (Heller et al., 2009). Therefore, these pieces of evidence suggested that the dysfunction in the reward circuit would lead to the symptom of anhedonia in MDD patients.

According to McClure et al.'s dual-process theory of reward, there are two separate neural networks in the reward process of the human brain: the brain regions in the reward network (β -network) for primary

* Corresponding author. Department of Neurology, Affiliated ZhongDa Hospital, School of Medicine, Southeast University, No.87 DingJiaQiao Road, Nanjing, 210009, PR China. Tel.: 0086 25 83262241; fax: 0086 25 83285132.

** Corresponding author. Department of Psychiatry, Henan Provincial Mental Hospital, No. 338 JianShe Road, Xinxiang, Henan, 453002, China. Tel.: 0086 25 83262241; fax: 0086 25 83285132.

E-mail addresses: ZHX166666@163.com (H. Zhang), chmxie@163.com (C. Xie).

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rewards and the brain regions in the cognitive control network (δ -network) for secondary rewards (McClure et al., 2004, 2007). Furthermore, the balanced activity between the β - and δ -networks is crucial for self-control, reward motivation, emotion regulation, and adaption (Barkley, 2001; Heatherton, 2011; Heatherton and Wagner, 2011; Hu et al., 2015). Our previously published data from heroin-addicted patients, which examined the neural correlates of addictive behavior also supported competitive processes between the β - and δ -networks (Xie et al., 2014). Interestingly, neuropsychological studies have shown that MDD involves broad impairments in executive function that can mainly be attributed to δ -network processing (Alvarez and Emory, 2006; Reineberg et al., 2015; Snyder, 2013). Recent evidence also suggested that the reduced cognitive control might be attributable to one of the important factors in depression, which has been consistently linked with the onset and maintenance of depression (Disner et al., 2011; Ebmeier et al., 2006). A meta-analysis of resting-state functional magnetic resonance imaging (R-fMRI) studies also revealed the reduced connectivity within the cognitive control circuit and imbalanced connectivity between the control system and emotion processing in MDD (Kaiser et al., 2015). These converging results strongly suggested that the dysfunctional cognitive control network might also contribute to the core neuropathological mechanism in MDD. Although dysregulated β - and δ -networks have been identified in individuals with depression, the controlling mechanisms of these networks that underlie anhedonia in MDD are poorly understood.

In the current study, we aimed to investigate the neural characteristics of intrinsic functional connectivity (FC) in the β - and δ -networks, the controlling mechanisms of the δ -network on β -network, and their associations with anhedonic symptoms in MDD patients by using R-fMRI data. We first hypothesized that MDD patients represented a disrupted balance between the β - and δ -networks compared with CN subjects. We further hypothesized that the impaired FC features in these networks would predict the anhedonic symptoms in MDD patients.

2. Materials and methods

2.1. Participants

A total of 140 participants (67 CN and 73 MDD) were enrolled in the current study. All CN subjects were recruited through community health screening and media advertisements. MDD patients were recruited from the population of outpatients and inpatients (No difference of the clinical traits was found between inpatient and outpatient groups, see Table S1) at the Department of Psychiatry of the Affiliated ZhongDa Hospital of Southeast University. All subjects were Chinese Han and right-handed. Each neuropsychiatric examination was performed by two experienced psychiatrists (Z.J. Zhang and C. Xie), and consensus diagnoses were reached. The inclusion criteria for the MDD group were as follows: 1) met the diagnostic criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V); 2) scores on the 17-item Hamilton Depression Rating Scale (HAMD) equal or above 17; 3) naïve to antidepressant medications or had undergone a washout period of at least five half-lives of previously prescribed medicine; 4) age approximately 18–59 years and an age of onset under 55 years; 5) no history of other major psychiatric or neurological disorders, head injury, or substance abuse; and 6) no contraindications to MRI scanning. This study was approved by the Research Ethical Committee of the Affiliated ZhongDa Hospital of Southeast University, and informed consent forms were signed by all participants. Because of excessive head motion (i.e., translational movement exceeding 1.5 mm or rotational movement exceeding 1.5°) and/or incomplete imaging scans, five MDD and three CN subjects were excluded. Finally, the remaining 68 MDD and 64 CN subjects were entered into the final analyses.

2.2. Behaviors assessment

All subjects underwent clinical and behavioral examinations, including the HAMD for depression severity and the Hamilton Anxiety Rating Scale (HAMA) for anxiety evaluation; anhedonia was evaluated using a 6-point Likert scale of 18 items of the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006). In addition, the 10-item TEPS subscale of Anticipatory (TEPS-A) and the 8-item subscale of Consummatory (TEPS-C) were conducted separately.

2.3. MRI data acquisition

Imaging was performed using a Siemens Verio 3.0 T scanner (Siemens, Erlangen, Germany) with a homogeneous birdcage head coil at the Affiliated ZhongDa Hospital of Southeast University. During the data scans, all subjects were instructed to relax and maintain closed eyes, and stabilizers were used to immobilize the heads of the subjects. The T1 parameters were repetition time (TR) = 1900 ms, echo time (TE) = 2.48 ms, flip angle (FA) = 9°, acquisition matrix = 256 × 256, field of view (FOV) = 240 × 240 mm, thickness = 1.0 mm, gap = 0 mm, number of slices = 176, and number of excitations (NEX) = 1.0. The R-fMRI data were obtained over 8 min with a gradient-recalled echo-planar imaging (GRE-EPI) pulse sequence. The R-fMRI imaging parameters included TR = 2000 ms, TE = 25 ms, FA = 90°, acquisition matrix = 64 × 64, FOV = 240 × 240 mm, thickness = 4.0 mm, gap = 0 mm, NEX = 1.0, and number of slices = 36.

2.4. fMRI data preprocessing

The functional data were preprocessed using the SPM8 toolkit (<http://www.fil.ion.ucl.ac.uk/spm>) and MATLAB version 7.10 (The MathWorks, Inc., Natick, MA, USA). The fMRI images were preprocessed in the following manner: the first ten volumes of the scanning session were discarded due to T1 equilibration effects. The remaining 230 vol were corrected for slice timing, realigned, and were subsequently spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template using the default settings. To further reduce the effects of confounding factors, six motion parameters, the global mean signal, white matter (WM) signal, and cerebrospinal fluid (CSF) signal were removed from the data via linear regression. We also calculated the framewise displacement (FD), which reflects the mismatch of volume-to-volume head position (Power et al., 2012, 2013). There was no significant difference in the FD among the groups ($p > 0.05$), and the mean FD was also applied as a covariate in the imaging analyses. Moreover, a bandpass filter was applied to maintain low-frequency fluctuations within a frequency range of 0.015–0.1 Hz.

2.5. Structural image analysis

To avoid the bias of the functional connectivity strength derived from anatomical variation, gray matter (GM) volume was considered an important covariate in the functional connectivity analysis (Xie et al., 2015). An optimized voxel-based morphometry (VBM) analysis was conducted using SPM8 to calculate the GM volume in all subjects. The T1-weighted images were segmented into GM, white matter, and CSF, and subsequently, the segmented GM was normalized and smoothed with a 6-mm FWHM Gaussian kernel. The GM volume was regressed out as a covariate to control for the effects on the functional connectivity strength.

2.6. Functional connectivity analysis

First, a voxel-wised, whole-brain functional connectivity analysis was conducted using the REST software version 1.8 (www.restfmri.net).

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