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Research article

Intrinsic functional connectivity alteration of dorsal and rostral anterior cingulate cortex in obsessive-compulsive disorder: A resting fMRI study

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HIGHLIGHTS

- OCD showed decreased functional connectivity between rACC and DLPFC.
- OCD displayed increased functional connectivity between dACC and caudate.
- Functional connectivity of dACC-caudate in OCD was positively correlated with clinical scores.

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ABSTRACT

Cortico–striato–thalamo–cortical (CSTC) circuit has been implicated in OCD pathophysiology by converging neuroimaging findings. The anterior cingulate cortex (ACC), as an important part within CSTC circuit, plays a critical role in OCD etiology. The ACC can be divided into dorsal and rostral parts anatomically, which are involved in cognitive process and emotional function, respectively. However, the diverse function of intrinsic signals from dorsal and rostral ACC regions remains unclear in OCD study. In this work, we applied resting-state functional magnetic resonance imaging (rs-fMRI) technology to investigate and differentiate the functional connectivity (FC) characteristics between dACC and rACC in unmedicated OCD patients. Also, the correlation between the altered FC and clinical symptom severity was analyzed. Decreased FC of rACC-DLPFC and increased FC between dACC and caudate were found. Moreover, the altered dACC-caudate FC was positively correlated with total Y-BOCS and compulsion score in OCD patients. Our findings implied the crossed function of dorsal and rostral circuits in the pathophysiologic mechanism of OCD. The dorsal cingulate-striatum functional pathway served as a potential biomarker for OCD symptomatology and merits further investigations.

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by unwanted obsessions and intrusive compulsions. As a common neuropsychiatric disorder, OCD has a lifetime prevalence rate of 2% to 3% and badly influences patients' social function [1–3]. Cortico–striato–thalamo–cortical (CSTC) circuit has been implicated in OCD pathophysiology by converging findings from a number of neuroimaging studies [4–7]. The anterior cingulate cortex (ACC), as an important part within CSTC circuit, is involved in mood regulation, executive function, error detection, conflict monitoring and movement plan [8]. Meta–analysis of OCD examined the white matter (WM) integrity using diffusion tensor imaging (DTI) technology and showed that the altered WM microstructure was located mainly in ACC and orbital frontal cortex (OFC)regions [9]. Altered functional connectivity (FC) was shown between ACC and other cortical regions in OCD patients [10], suggesting the critical role of ACC in OCD etiology.

The ACC is composed of a number of subregions with different functional significance, within which the dorsal and rostral components are most relevant in OCD pathophysiology. The dACC is involved in cognitive process for making reward-based decisions,

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while the rACC is more related to emotional function [11]. The necessity to differentiate divisions of ACC was demonstrated in task-related functional imaging studies. It was shown that the Emotional Counting Stroop task activated the affective division (rostral division), while the Cognitive Stroop task activated the cognitive division (dorsal division) of ACC [8,12]. Using functional magnetic resonance imaging (fMRI) technology, Fitzerald et al. [13] found that dACC was activated in error commission and rACC showed an increased activation during error-related process in OCD patients. However, the diverse function of intrinsic signals from ACC dorsal and rostral subregions remains unclear in OCD study. Also, previous study reported that different (ventral and dorsal) loops with different functions in OCD [14].

Resting-state fMRI (rs-fMRI) technology measures spontaneous changes in blood-oxygen-level dependent (BOLD) signal, and is increasingly applied to study brain intrinsic signals in psychiatric disorders. Hou et al. [15] applied amplitude of low-frequency fluctuation (ALFF) analysis in rs-fMRI data of OCD patients and reported increased ALFF in ACC and orbito frontal cortex (OFC) areas. Li et al. [16] used regional homogeneity (ReHo) method to analyze the brain intra-regional synchronized activity in OCD patients, showing significantly reduced ReHo in the ventral ACC area.

In this study, we aimed at investigate and differentiate the FC characteristics between dACC and rACC regions in unmedicated OCD patients using rs-fMRI technology. We performed seed-based analysis to examine the intrinsic FC originating from these two regions with the whole brain. Moreover, we show the clinical relevance between the altered FC and clinical symptom severity measures (e.g. the scores of Y-BOCS, HAMA and HAMD). The goal of this work is to differentiate dorsal and rostral ACC pathways in the aspect of intrinsic brain connectivity to provide additional insights in OCD's pathophysiology.

2. Material and methods

2.1. Participants

Twenty-three patients with OCD (15male and 8female) were recruited from Shanghai Mental Health Center, and twenty-three age, gender and education-matched healthy controls were recruited through local advertisement. All subjects were 18–54 years old, right-handed, and at junior high school or higher education level. The OCD patients were not taking psychotropic drugs for at least eight weeks. All patients were diagnosed by a trained psychiatrist according to DSM-IV diagnostic criteria and screened by Mini-International Neuropsychiatric Interview (MINI 5.0) to exclude other psychiatric disorders. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was utilized to assess the symptom severity for patients and the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) were applied to measure the anxiety and depression symptomology for all the subjects. (Table 1).

The exclusion criteria included: 1) diagnosis of pulmonary, cardiac, hepatic, neurological diseases, endocrine systems or metabolic disorders; 2) current or past DSM-IV axis I psychiatric disorders except for OCD; 3) serious negative ideas and suicide tendency; 4) implanted mental like pacemakers incompatible with MRI device. All the participants were given the written informed consent approved by Shanghai Mental Health Center Ethics Committee prior to the MRI scan.

2.2. MRI data acquisition and preprocessing

The resting-state fMRI images were collected on a 3.0-Tesla Sigma MR scanner (Sigma Horizon LX; General Electric Healthcare, Milwaukee, Wisconsin) by a professional radiologist at Shanghai Ruijin Hospital. During MRI scanning, sponge block was filled around the head and head coil to minimize the head motion. The T1 scans were taken and used to exclude significant structural abnormality. Subsequent fMRI data were acquired using gradient-echo echo-planar imaging (EPI) sequence with the following parameters: Time of Repetition (TR) = 2100 ms; Time of Echo (TE) = 30 ms; Flip Angle (FA) = 90°; Field of View (FOV) = 24 cm; data matrix = 64 × 64; slice number = 33; thickness = 4.0 mm; interslice gap = 0.6 mm; voxel size = 3.75 × 3.75 × 4.6 mm^3; and total volumes = 200. The subjects were required to lie still with their eyes closed and remain awake. The fMRI scan took about seven minutes for each participant.

The resting-state fMRI image preprocessing was conducted using Data Processing Assistant for Resting-State fMRI (DPARSF) program, which is based on Statistical Parametric Mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST1.8, http://www.restfmri.net).The first 10 vols were discarded to allow the signal equilibrium and the subjects' adaptation to scanning noise. The remaining 190 vols were corrected for the signal acquisition time of different slices. For individual participant, head-motion correction was performed by aligning each time series to the first volume using a least-square minimization method and a six-parameter (three for translation and three for rotation) linear spatial transformation. Five patients were excluded for excessive head movement, which are over 2 mm of translation and 2°of angular rotation in any direction. Subsequently, the functional images were spatially normalized to the stereotactic space of Montreal Neurological Institute (MNI) using the standard EPI template, and each voxel was resampled to isotropic 3*3*3 mm^3. The data were spatially smoothed using a Gaussian kernel of 4 mm full width at half-maximum (FWHM). The linear trends were further removed and a temporal band-pass filter (0.01–0.08 Hz) was applied to reduce the influence of very low frequency drift and high frequency physiological noise. The estimated six head motion parameters, global mean signal, white matter signal and cerebrospinal fluid signal, were regressed out through linear regression.

2.3. Seed-based brain functional connectivity analysis

The regions of interest (ROIs) were generated from Brodmann template by selecting the rostral and dorsal subregions of anterior cingulate cortex (Fig. 1). The rACC (often referred as 'pregenual' or 'perigenual' in the literature) is located anterior to the genu, and includes Brodmann area (BA) 32 and inferior parts of BA24 [17]. The dACC area includes caudal area of BA 24and BA 32, as well as cingulate motor area [18]. Functional connectivity analysis is widely used in resting state fMRI [4,10,19]. In this study, seed-

Table 1
Demographic and clinical information of OCD and controls.

Characteristics	OCD (n = 23)	Control (n = 23)	p-value[a]
Age (years)	32.09 ± 10.55	31.39 ± 10.04	0.82
Gender	15male, 8female	15male, 8female	–
Educational status (years)	13.87 ± 2.65	14.22 ± 2.65	0.67
Age of onset	24.80 ± 10.68(20)	–	–
Duration of illness (years)	6.85 ± 4.66(19)	–	–
YBOCS-total	21.48 ± 5.63	–	–
YBOCS-obsessions	11.30 ± 2.57	–	–
YBOCS-compulsions	10.17 ± 3.78	–	–
HAMD	11.00 ± 7.91***(22)	1.95 ± 3.47***(22)	<0.001
HAMA	9.47 ± 8.07***(19)	0.95 ± 2.37***(19)	<0.001

Data are presented as mean ± S.D.
OCD: obsessive compulsive disorder; YBOCS: Yale-Brown Obsessive Compulsive Scale; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale.
[a] Independent samples *t*-test.
*** $p < 0.001$, statistically significant.