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Abnormal resting-state effective connectivity in large-scale networks among obsessive-compulsive disorder

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Abstract

Background. Obsessive-compulsive disorder (OCD) is a chronic mental illness characterized by abnormal functional connectivity among distributed brain regions. Previous studies have primarily focused on undirected functional connectivity and rarely reported from network perspective.

Methods. To better understand between or within-network connectivities of OCD, effective connectivity (EC) of a large-scale network is assessed by spectral dynamic causal modeling with eight key regions of interests from default mode (DMN), salience (SN), frontoparietal (FPN) and cerebellum networks, based on large sample size including 100 OCD patients and 120 healthy controls (HCs). Parametric empirical Bayes (PEB) framework was used to identify the difference between the two groups. We further analyzed the relationship between connections and Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

Results. OCD and HCs shared some similarities of inter- and intra-network patterns in the resting state. Relative to HCs, patients showed increased ECs from left anterior insula (LAI) to medial prefrontal cortex, right anterior insula (RAI) to left dorsolateral prefrontal cortex (L-DLPFC), right dorsolateral prefrontal cortex (R-DLPFC) to cerebellum anterior lobe (CA), CA to posterior cingulate cortex (PCC) and to anterior cingulate cortex (ACC). Moreover, weaker from LAI to L-DLPFC, RAI to ACC, and the self-connection of R-DLPFC. Connections from ACC to CA and from L-DLPFC to PCC were positively correlated with compulsion and obsession scores ($r = 0.209$, $p = 0.037$; $r = 0.199$, $p = 0.047$, uncorrected).

Conclusions. Our study revealed dysregulation among DMN, SN, FPN, and cerebellum in OCD, emphasizing the role of these four networks in achieving top-down control for goal-directed behavior. There existed a top-down disruption among these networks, constituting the pathophysiological and clinical basis.

Introduction

Obsessive-compulsive disorder (OCD), featured as unwanted and distressing thoughts (obsessions) and repetitive behaviors (compulsions) the individual feels driven to perform (Goodman, Storch, & Sheth, 2021), is a chronic and time-consuming psychiatric condition with a prevalence of 1–2% (Fernandez de la Cruz, Isomura, Lichtenstein, Ruck, & Mataix-Cols, 2022). Conventionally, it was generally accepted that cortico-striato-thalamo-cortical (CSTC) played a vital role in the pathophysiology in OCD, and the structural, functional, and metabolic brain disruptions of this loop have been studied through neuroimaging (Zhao et al., 2021*a*). However, more recent evidence showed that the changes of brain imaging were not just limited to this model and many other networks have been reported to be abnormal (Stein et al., 2019). It is proposed that default mode (DMN), salience (SN), frontoparietal (FPN), and cerebellum networks have a functional dysregulation in OCD (Sha et al., 2020; Thirioux et al., 2022) (Table 1).

Resting-state functional magnetic imaging (fMRI) has been widely used to characterize cerebral functional organization in health and illness. Previous study has identified that patients had increased functional connectivity (FC) between posterior cingulate cortex (PCC) and visual cortices and frontostriatal regions (Ravindran et al., 2020). Another found

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Table 1. Montreal Neurological Institute coordinates used as region of interest in DMN, SN, FPN, and cerebellum

Region	MNI coordinate		
	x	*y*	*z*
DMN			
MPFC	1	55	−3
PCC	1	−61	38
SN			
LAI	−44	13	1
RAI	47	14	0
ACC	0	22	35
FPN			
L-DLPFC	−43	33	28
R-DLPFC	41	38	30
Cerebellum			
CA	0	−63	−30

DMN, default mode network; SN, salience network; FPN, frontoparietal network; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; LAI, left anterior insula; RAI, right anterior insula; ACC, anterior cingulate cortex; L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, right dorsolateral prefrontal cortex; CA, cerebellum anterior lobe.

reduced strength of default network FC with the PCC was exhibited in OCD (Peng et al., 2014). Moreover, compared with healthy controls (HCs), there was reduced inverse connectivity between the medial prefrontal cortex (MPFC) and anterior insula (AI), regions within the DMN and SN (Posner et al., 2017); stronger basolateral amygdala connectivity was observed in insula (Cao et al., 2022*b*). The other key node of SN–anterior cingulate cortex (ACC) was also found to have aberrant FC (Zhao et al., 2021*b*) due to its role in cognitive control and emotion regulation. Abnormality of FPN was also reported; a traditional independent component analysis showed alterations in bilateral FPN networks (Gürsel, Avram, Sorg, Brandl, & Koch, 2018). In addition, there is recent convincing evidence confirming the role of the cerebellum in OCD, and many studies have showed weakened connectivity among the left Crus II, lobule VIII (Zhang et al., 2019), increased from ventromedial prefrontal cortex to cerebellum (Apergis-Schoute et al., 2018). Besides the inconsistent results of each research because of methodological difference, neuroimaging techniques, and variation in medication status, they mainly concentrated on undirected rather than causal interactions within these regions, therefore unable to draw a more robust conclusion.

Spectral dynamic causal modeling (spDCM), a new effective connectivity (EC) method, could discover the complex within and between intrinsic connectivity networks relationships and the causal influence that one node exerts over another (Hidalgo-Lopez, Zeidman, Harris, Razi, & Pletzer, 2021). What's more, it can not only evaluate DCM parameters more accurately, but can identify increased or decreased extrinsic and intrinsic connections between different groups through parametric empirical Bayes (PEB) analysis (Lumaca, Dietz, Hansen, Quiroga-Martinez, & Vuust, 2021). A study on internet gaming disorder (IGD) explicated that IGD patients showed an enhanced inhibitory effect of the putamen on the right nucleus accumbens (Nacc) and an enhanced self-inhibition effect of the Nacc (Wang, Zheng, Zhou, Jiang, & Dong, 2021). Depression was associated with weaker excitatory connectivity within the DMN, and between the DMN and SN (Li et al., 2020). Surprisingly, prior research also found that decreased ECs examined by DCM between the bilateral amygdala and insula as well as between the inferior frontal junction and intraparietal sulcus were related to the symptom changes, thus predicting the treatment effects (Fonzo et al., 2021). But to the best of our knowledge, we found there were few corresponding studies considering the causal connectivity of intra- and inter-networks among DMN, SN, FN, and cerebellum of OCD.

In this study, we aimed to investigate the abnormal EC within and between DMN, SN, FPN, and cerebellum networks in the neuropathological mechanisms in OCD using spDCM. Due to the nodes selection limitation, we only selected the major nodes of each network: PCC and MPFC in DMN, bilateral AI and ACC in SN, bilateral dorsolateral prefrontal cortex (DLPFC) in FPN and cerebellum anterior lobe (CA) in cerebellum based on previous research (Sparacia et al., 2020; Tomiyama et al., 2022*a*). Additionally, correlation analysis was also performed in patients to predict the clinical symptoms of each subject. We assumed that the disrupted directed communication among the four networks could be the potential biomarker for OCD patients. Specifically, we hypothesized that patients may display imbalanced interaction with AI, DLPFC, cerebellum, and PCC, and other abnormal connections could be found between two separate networks and within one network.

Methods and materials

Participants

This study randomly recruited 100 drug-naïve patients with first-episode OCD patients as well as 120 age- and sex-matched normal controls. Patients were diagnosed through OCD criteria based on the Structured Clinical Interview of the DSM-IV, Patient Edition, by trained physicians in outpatient services of the Department of Psychiatry. All subjects provided written informed consent. The study was approved by the research ethical committee of the First Affiliated Hospital of Zhengzhou University. Symptom severity of patients was evaluated with Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Patients were included in the group comparison after meeting the following inclusion criteria: (1) one chief physician and one well-trained psychiatrist diagnosed according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID); (2) a total score on the Y-BOCS greater than or equal to 16; (3) age ranging from 12 to 45 years; (4) first onset without taking any medicine or other treatment; (5) primary school education or above. All patients were Han Chinese and right-handed. In addition, the exclusion criteria were following: (1) a history of serious illness, alcoholism, or drug abuse; (2) suffering from other psychological diseases such as depression, autism in addition to OCD; (3) contraindications for MRI scanning; and (4) other conditions, for example, pregnant or lactating women. The course of illness and the evaluation of Y-BOCS were obtained from clinical consultations and examinations. The 20-item Self-Rating Depression Scale (SDS) and the 20-item Self-Rating Anxiety Scale (SAS) were used to assess depressive and anxiety symptoms. Healthy individuals (57 males and 63 females) group-matched for age and gender were recruited through advertisements and met the same criteria as the patients; none of them or their first-degree

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relatives reported a history of serious neuropsychiatric disorder. All of them were Han Chinese and right-handed.

Data acquisition and preprocessing

Whole-brain functional MRI images were acquired using a 3.0 Tesla MR scanner (Discovery MR750, General Electric, Milwaukee, WI, USA) with an eight-channel receiver array head coil. All subjects were instructed to close their eyes but not to sleep during the whole scan, without thinking about anything in particular. In total, 180 contiguous volumes were obtained by the gradient-echo-planar imaging-based BOLD technique. The scanning parameters were used in the resting-state functional scans: repetition time = 2000 ms; echo time = 30 ms; number of slices = 32; thickness = 4 mm; resolution matrix = 64 × 64; flip angle = 90°; field of view = 220 × 220 mm^2; and slice gap = 0.5 mm. The fMRI data were preprocessed by the Data Processing Assistant for Resting-State fMRI Analysis Toolkit (DPARSF). The first five volumes were removed, then slice-timing correction and realignment. Subjects were excluded by head motion of >2.5 mm in maximum displacement or >2.5° rotation in angular motion. No subjects were excluded in this step. The images were then spatially normalized to the standard echo planar imaging (EPI) template and resampled into 3 × 3 × 3 mm^3. Functional images were spatially smoothed with a Gaussian kernel of full-width at half-maximum of 6 mm. Finally, detrending was used to reduce low-frequency drift. We applied a third-order spline to replace the outliners with the optimal estimate fit and to clean the time course portions. Outliners were detected on the basis of the median absolute deviation, as implemented in 3dDespike.

Regions of interest

Based on previous studies (Ravichandran et al., 2021; Sparacia et al., 2020; Tomiyama et al., 2022*a*), following seeds – MPFC, PCC, bilateral AI, ACC, bilateral DLPFC, and CA were selected as regions of interest (ROIs) (Fig. 1). These regions were acquired as spheres with a radius of 6 mm centered as the Montreal Neurological Institute (MNI) coordinate reported before defined by the CONN toolbox and were considered as the hubs of DMN, SN, FPN, and cerebellum networks, commonly used in recent neuroimaging literature (Koh et al., 2020).

Spectral dynamic causal modeling

spDCM, processed in SPM12, was used to specify EC analysis. A general liner model constructed in SPM included cosine basis functions from 1/128 to 0.1 Hz as effects of interest and the mean-time course from white matter (WM) and cerebrospinal fluid (CSF), as well as the motion parameters as multiple nuisance regressors (Fridgeirsson et al., 2020). The time series of activity for all ROIs was adjusted for the confounding corrections. The full model was constructed with the eight ROIs as key nodes without any external stimuli, which resulted in 64 connections, including the self-connections.

After the full DCM for each subject was inverted, specified, and estimated, PEB was employed to evaluate how individual connections relate to groups or condition means. Such parametric random-effects modeling could use the full posterior density over the parameters from each subject's DCM to inform the group-level difference. To know how the connectivity of OCD patients differs from HCs, we then used Bayesian model reduction (BMR) to remove redundant ECs and search over PEB models with different combinations of connections and group differences (Zhou et al., 2018). BMR compares the full model with 256 models where one or more connections by a greedy search, which have the least evidence, are pruned out and thus switched off, whereas the parameters with the most evidence are kept stable (Bencivenga, Sulpizio, Tullo, & Galati, 2021). Group-level analyses are performed using Bayesian posterior inference, which doesn't need to adjust the p value because of the independent prior distributions for the activations over voxels (Friston & Penny, 2003). The Bayesian posterior probability (Bayesian-PP) is an indicator of the confidence in whether the mean of an EC within a group is different from zero or the confidence in the degree of linear relationship between variables. The higher Bayesian-PP indicated the greater confidence. Here, the results were considered reliable if Bayesian-PP > 0.95 (Ma et al., 2021).

Correlation analysis

To examine the correlations between EC and patients' symptomology score, Pearson or Spearman correlation coefficients were tentatively computed to test the relationship between connection strengths and Y-BOCS obsession, compulsion, and total scores, besides anxiety and depression score (uncorrected).

Results

Demographical and clinical data

There was no significant difference in terms of age and gender between the two groups, but patients had shorter educational level than HCs. The clinical data including the Y-BOCS total scores, obsession and compulsion scores, and anxiety and depression scores were all shown in Table 2.

Similarity and differences of resting-state effective connectivity

Figure 2 showed the common EC of the brain networks in OCD patients and HCs group (free energy threshold, Bayesian-PP > 0.95). Our main interest regarded differences between groups, so we will only make some observations about this result. There was a significant main effect among the regions of DMN, SN, FPN, and cerebellum, indicating that these networks were all engaged at the resting state. Specifically, most regions displayed a negative self-connection while another three areas including right anterior insula (RAI), right DLPFC (R-DLPFC), and CA showed positive self-connections. The connections from PCC and CA to other regions were generally inhibitory except from PCC to MPFC, ACC, and R-DLPFC, and from CA to RAI, R-DLPFC, and its self-connection. Moreover, the R-DLPFC exhibited extensive connection with other brain regions; outgoing and entering connections were mostly excitatory. Interestingly, the connections entering left anterior insula (LAI) were mainly negative, while entering RAI generally positive and PCC included both excitatory as well as inhibitory influences.

Different effective connections between the two groups are shown in Fig. 3 (free energy threshold, 95%). Among the 64 ECs, five ECs in OCD consisting of LAI to MPFC, RAI to left DLPFC (L-DLPFC), R-DLPFC to CA, CA to PCC and to ACC were greater than HCs and another three ECs including LAI to L-DLPFC, RAI to ACC, and the self-connection of R-DLPFC were decreased (Table 3).

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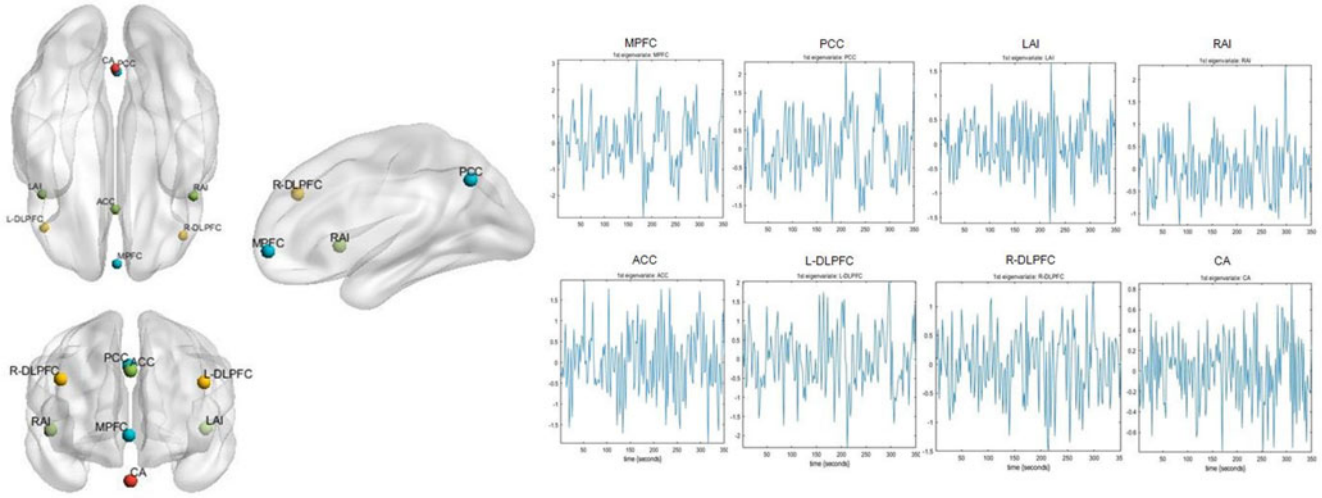

Figure. 1. Locations of eight nodes are marked with light blue indicating DMN, green indicating SN, yellow indicating FPN, and red indicating cerebellum. The right panel shows time series extraction of each node. DMN, default mode network; SN, salience network; FPN, frontoparietal network; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; LAI, left anterior insula; RAI, right anterior insula; ACC, anterior cingulate cortex; L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, right dorsolateral prefrontal cortex; CA, cerebellum anterior lobe.

Correlation analysis

Using patients' specific estimates of EC, we calculated the correlation between the strength of all the connections and Y-BOCS scores. Significant correlation between Y-BOCS scores and strength of connections with differences in OCD patients was observed ($p < 0.05$, uncorrected). To be detailed, The EC from ACC to CA was positively correlated with the compulsion scores of Y-BOCS, and the connectivity from L-DLPFC to PCC was also positively correlated with the obsession scores of Y-BOCS (Fig. 4).

Discussion

OCD is a dysconnectivity disorder with a large consensus in literatures. Indeed, a CSTC model of OCD has been the prevailing model regarding the neural and pathophysiological underpinnings (Pauls, Abramovitch, Rauch, & Geller, 2014). Its essential role in mediating objective measures of loss of inhibitory control and cognitive inflexibility constitutes candidate latent phenotypes for OCD. Moreover, strongly associated genes, HTR2A and NRXNI, encode the synapse cell-adhesion protein, a component of cortico-striatal neural pathway, in which an imbalance between reciprocal pathways has been shown in OCD (Robbins, Vaghi, & Banca, 2019). The interactions with glutamatergic and dopamine neurons originating in the primary synaptopathy are the reason of macroscopic changes in brain imaging and connections (Stein et al., 2019). The specific dysconnections in our results are significant in terms of genetics and neuropathology, contributing to our understanding of the symptoms and treatments of OCD.

This study revealed effective alterations of brain networks in OCD by means of spDCM. Such an approach could define causal effects by analyzing whether the preceding neural activity in one seed region predicts activity in another subsequent region, providing information about directed or causal interactions underlying the observed correlations (Wei, Wu, Bi, & Baeken, 2021), compared with the traditional resting-state FC. Several common

Table 2. Demographic and clinical characteristics of participants

	OCD (*n*=100)	HCs (*n*=120)	*p*
Age, mean (s.d.) [range], y	23.15 (9.26) [12–49]	22.17 (5.89) [13–43]	0.34[a]
Gender (male/female)	52/48	57/63	0.51[b]
Educational level, mean (s.d.), y	11.97 (2.96)	14.35 (3.79)	<0.01[a]
Duration of illness, mean (s.d.), m	45.65 (55.33)	–	
Y-BOCS, mean (s.d.)			
Total scores	22.04 (6.93)	–	
Obsessions	11.73 (3.56)	–	
Compulsions	10.30 (4.28)	–	
Anxiety	23.39 (12.31)	–	
Depression	32.67 (15.11)	–	

OCD, obsessive-compulsive disorder; HC, healthy controls; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
[a]Two-tailed two-sample *t* test.
[b]χ^2 *t* test.

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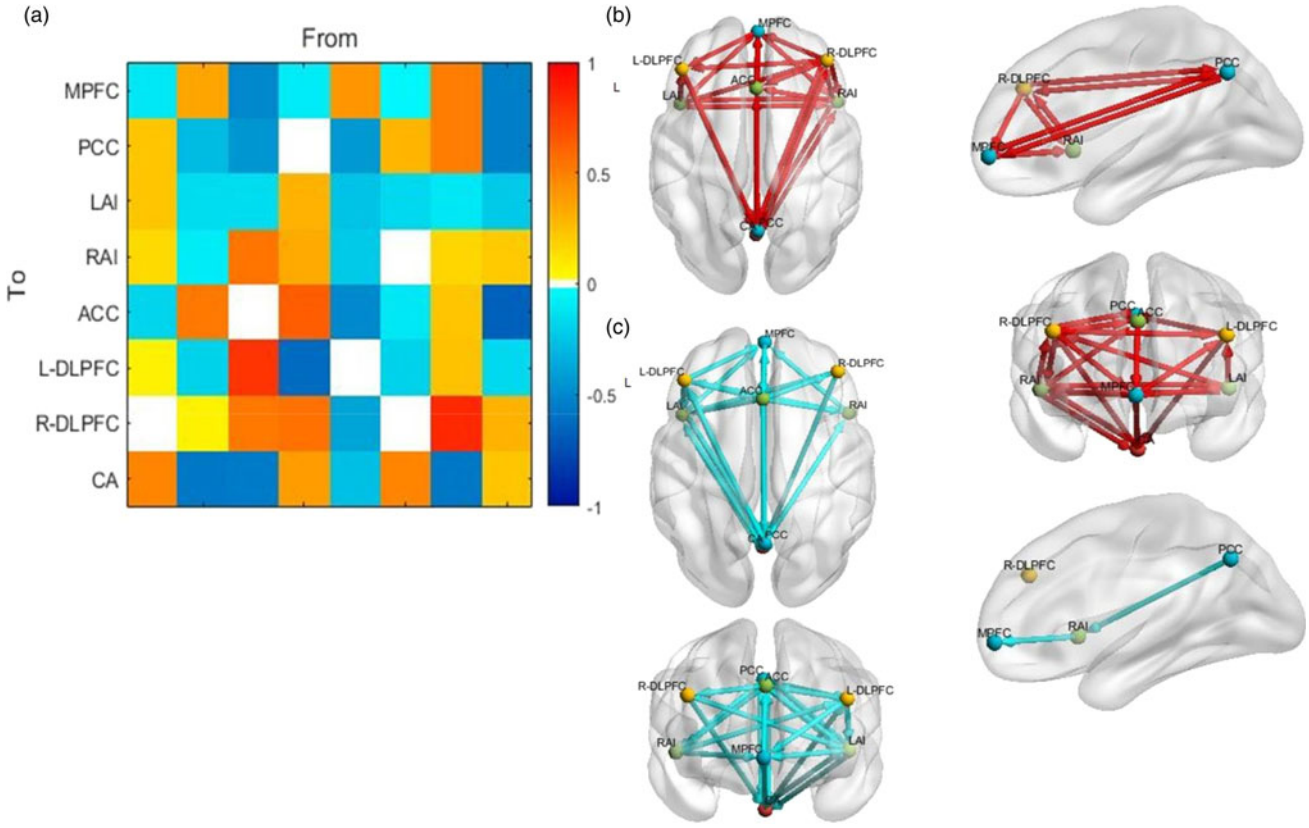

Figure. 2. Mean values in effective connectivity for OCD patients and healthy controls. (a) Communalities in effective connectivity in the patients and HCs. (b) Inhibitory extrinsic connections (blue arrow). (c) Excitatory extrinsic connections (red arrow). L, left.

dynamic functional interaction patterns were shared in both OCD patients and HCs. Additionally, group difference showed that patients exhibited greater connections from LAI to MPFC, RAI to L-DLPFC, R-DLPFC to CA, CA to PCC and to ACC and had decreased from LAI to L-DLPFC, RAI to ACC, and the self-connection of R-DLPFC. Our findings suggested that the functional interactions of the four networks including the cerebellum were altered in OCD and HCs, revealing the potential neurobiological mechanisms of OCD.

Firstly, we observed that DMN, SN, FPN, and cerebellum networks shared some common interaction patterns across HCs and OCD patients. The intrinsic large-scale networks have proved to be significant for understanding the alterations of brain imaging in OCD, as the disease is considered to be far more complicated than just regional brain aberrance with high heterogeneity and multiple characteristics. It has been widely accepted that DMN, SN, FPN, and cerebellum are involved in pathophysiological mechanism of OCD (Gürsel et al., 2018). DMN is a well-described brain system which is reduced in activity when attention is focused on the external environment (Yan, Shan, Li, Liu, & Guo, 2022), but becomes more active when individuals sustained internal mentation processes related to self-referential processing, imagery, auto-biographical memory, and forming one's reliefs (Stern et al., 2022). The SN is a crucial brain network involved in detecting, processing, and switching between the internal attention and external stimuli (Gursel et al., 2020), moreover, the error signal from it is vital for behavioral correction during errors associated with broad inhibitory control tasks (Tomiyama et al., 2022*b*). FPN is an important structure within the dorsal cognitive circuit related to attentional control and subserving attentional gating, shifting, and information retaining to perform adaptive control tasks (Tikoo et al., 2020). Cerebellum has been found to be reciprocally connected with CSTC circuits and implicated in ruminative and obsessive behaviors (Liu et al., 2021). In the current study, we found the Y-BOCS symptoms in OCD were correlated with certain connections in OCD patients. The suppression of cerebellum by ACC was associated with the severity of compulsion symptom, while the excitation of PCC by L-DLPFC was associated with the obsession subscale. Our findings demonstrated that the dynamic functional interactions of the four networks were impaired in OCD.

Additionally, because the self-connections in DCM are always inhibitory, the result of increased self-connections in RAI, R-DLPFC, and cerebellum is more self-inhibited (Li et al., 2020; Zeidman et al., 2019). The connections to the LAI were found to be generally inhibitory, suggesting that other regions in these four networks had suppressive influence on LAI during resting state, which was consistent with the reduced availability of the serotonin transporter 5-HTT (Biria, Cantonas, & Banca, 2021). The connections entering to the cerebellum are both excitatory and inhibitory, indicating that there may exist antagonism within networks. Furthermore, we also identified that DMN was involved in self-awareness and internal processing state by interacting with cerebellum, DLPFC, and ACC.

Secondly, our analysis indicated increased EC in SN–FPN–cerebellum–DMN circuit including RAI, DLPFC, cerebellum, and PCC in OCD patients. Previous research has reported that SN, especially RAI, played a hub role in dynamic cognitive control

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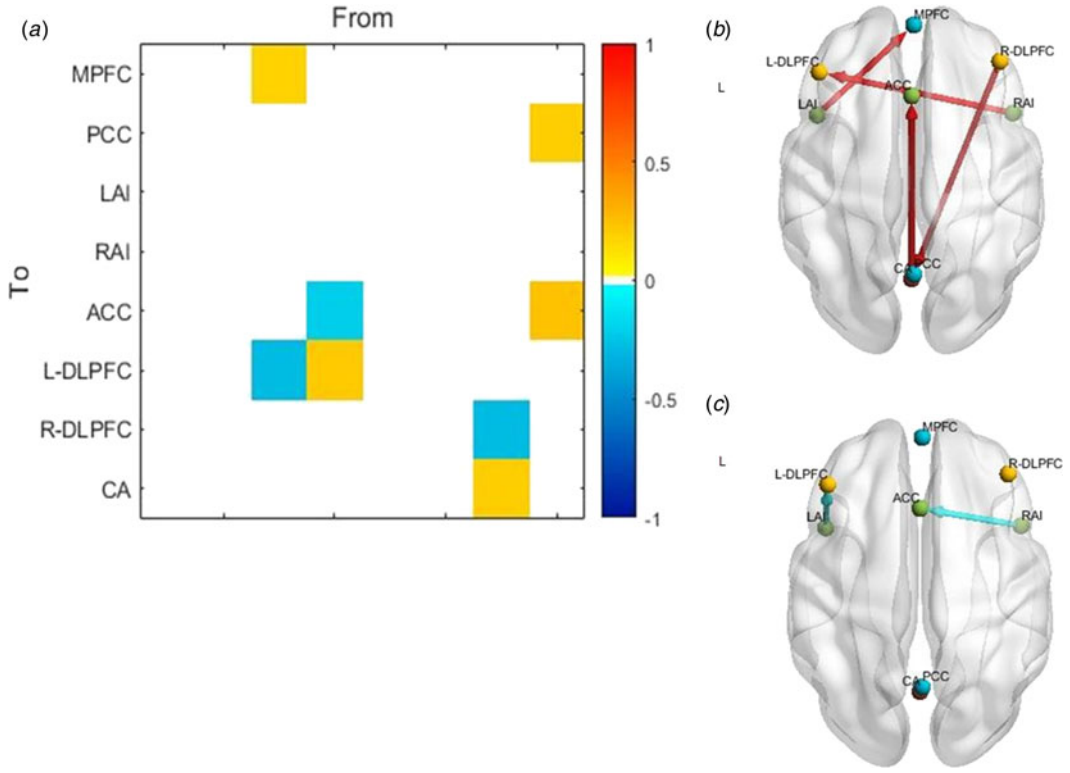

Figure. 3. Group difference between OCD patients and HCs. (a) Differences in EC of patients and HCs. (b) Decreased connections in patients (blue arrow). (c) Increased connections in patients (red arrow).

through engaging the executive control (task-positive) and disengaging the DMN networks (Eng et al., 2022), and it was vital in the detection of external or internal saliency, feeling of uncertainty, conflict monitoring, modulating behavior, human awareness, and insight (Shan et al., 2022). DLPFC was associated with executive cognitive tasks, like cognitive and behavioral programmed modification, and a task-based investigation showed that patients had hyperactivation of DLPFC at the working memory performance, which is related with enhanced task performance (Khedr, Elbeh, Saber, Abdelrady, & Abdelwarith, 2022). It projected to locus coeruleus, raphe, and midbrain dopamine (DA) neurons (Cools & Arnsten, 2022). Enhanced connection from RAI to DLPFC could promote OCD symptoms, such as compulsive avoidance, causing patients relying excessively on the habitual learning system (Gillan et al., 2011). Such abnormal learning pattern could make patients more easily subjected to depression and anxiety, and repetitive transcranial magnetic stimulation (rTMS) targeting DLPFC has been found to be impactable in the treatment of anxiety and Y-BOCS symptom (Liang et al., 2021). Greater connectivity to DLPFC also identified patients had slow response to loss of reward (Kodama, Hikosaka, Honda, Kojima, & Watanabe, 2014). Cerebellum has been ascribed to a role in movement coordination, sensorimotor, cognitive, and affective processing, with extensive FC among cortical regions and activity during cognitive tasks (Chambers et al., 2022). Altered amygdalostriatal transition area-cerebellum resting-state functional connectivity (RSFC) was negatively correlated with the obsession scores in the late-onset OCD patients (Cao et al., 2022*a*). Therefore, the stronger EC from DLPFC to cerebellum may result in disrupted emotional regulation, and activation of negative reinforcement, besides, it perhaps make patients develop more habits to release obsessive thoughts (Cai et al., 2021), resulting in unnecessary behaviors. What's more, PCC is a central region of DMN, involved in regulating arousal and attention and controls the balance between internally and externally focused thoughts (Chen et al., 2019), which is the main pathophysiology of OCD. Increased connectivity circuit (RAI, DLPFC, cerebellum, and PCC) exhibited patients paid more unnecessary attention on introspective and reflective self-awareness processes, and aberrance of episodic memory retrieval and mental imagery (Fransson, 2005).

Furthermore, compared with HCs, significant alterations of LAI–L-DLPFC, RAI–ACC, CA–ACC, and self-connection of R-DLPFC were observed, also indicating abnormality among SN, FPN, and cerebellum. Insula and ACC are important components of SN. ACC is also a key node within CSTC circuitry,

Table 3. EC difference between OCD and HCs

Group	Connectivity	EC (Hz)	Bayesian-PP
OCD > HCs	LAI → MPFC	0.177	1.00
	RAI → L-DLPFC	0.217	1.00
	R-DLPFC → CA	0.201	1.00
	CA → PCC	0.193	1.00
	CA → ACC	0.238	1.00
OCD < HCs	LAI → L-DLPFC	−0.276	1.00
	RAI → ACC	−0.215	1.00
	R-DLPFC → R-DLPFC	−0.291	1.00

EC, effective connectivity; PP, posterior probability.

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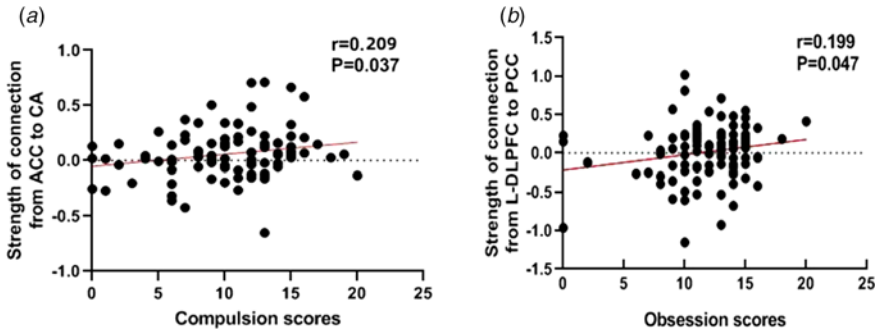

Figure. 4. The correlation analysis between the network connections and Y-BOCS scores in OCD patients. (a) The strength from ACC to CA was positively correlated with compulsion scores. (b) The strength from L-DLPFC to PCC was also positively correlated with obsession scores (uncorrected).

involved in error monitoring and response selection, besides it is crucial in supporting behavioral flexibility in dynamically changing environments (Long et al., 2021; Zhao et al., 2021*b*). Decreased and increased connection from RAI and CA to ACC implicated OCD had aberrant error monitoring and inappropriate response to external surroundings, causing cognitive and behavioral disorder. This finding also demonstrated an asymmetric change in ACC, which may be considered as a slight compensation with each other. In our study, both increased and decreased connectivity to L-DLPFC, a key region in top-down emotion regulation from bilateral AI perhaps because of the imbalance of FPN, so did the decreased self-connection of R-DLPFC reveal. Moreover, prior study has found that FC between insula and DLPFC was depression and social interaction anxiety scores (Zhao et al., 2022), highlighting its role in depression and anxiety in OCD. Finally, a greater LAI–MPFC connectivity was found in patients. MPFC innervates numerous brain regions and is considered to be important in high-level control of the expression of emotions (Lin et al., 2022), moreover, it acts as a pivotal region of DMN, showing the disrupted hyperactivation of this network, leading to different symptoms of OCD.

There are some limitations in our current study. First of all, although this research would provide new insights of alterations in causal connections among four networks within OCD patients, we solely selected the key nodes of each network based on a meta-analysis of OCD (Gürsel et al., 2018) due to the computational limits; other remaining regions consisting of these networks and other disease-related networks should be further included. Then, all patients were all drug naïve which was unable to investigate medication effects. Further efforts, such as intervention studies with comparisons before and after medication, are required to draw valid conclusions on the impact of the EC. Last but not least, as a cross-sectional study, the connections changed with disease progression which cannot be thoroughly reflected by the limited nodes.

Conclusion

In summary, this is the first study to reveal neural interactions among DMN, SN, FPN, and cerebellum in OCD patients, emphasizing the role of these four networks mentioned above in achieving top-down control for goal-directed behavior. More significantly, the connection loop within RAI–DLPFC–cerebellum–PCC could suggest that networks did not exist in isolation, but intertwined with each other, thus constituting the pathophysiological and clinical basis of the disorder together.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001228.

Competing interest. None.

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