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Resting-State Functional Connectivity Alterations in Drug-Naive Adolescents with Obsessive-Compulsive Disorder

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ABSTRACT

Objective: It is known that there are alterations in functional brain networks in pediatric obsessive-compulsive disorder (OCD) and new studies are needed to identify and conceptualize these alterations. This study aimed to investigate resting-state functional connectivity (Rs-FC) changes in adolescents with OCD.

Materials and Methods: We compared FC alterations in 15 drug-naive adolescents with OCD and 15 healthy controls (HC). Rs-FC networks were obtained with independent component analysis and logistic regression was used to identify the components that displayed significant group differentiation.

Results: Data were decomposed into 30 independent components, and 4 components corresponding to functional networks showed a significant difference between the 2 groups (sensitivity and specificity value was 86.7%): Posterior cingulate cortex (PCC), cerebellum, right frontoparietal network (R-FPN), and anterior DMN (aDMN). The expression scores of the PCC, cerebellum, and R-FPN were significantly lower in OCD, while the expression score of the aDMN was significantly higher in OCD as compared with HC. In addition, OCD patients demonstrated a significant anti-correlation between the R-FPN and lateral sensorimotor network, and a positive correlation between the PCC and parahippocampal gyri.

Conclusion: These findings indicate that alterations in FC networks incumbent on high mental processes are involved in the pathophysiology of OCD in adolescents.

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KEYWORDS: Default mode network (DMN), functional connectivity, Independent component analysis (ICA), pediatric, resting-state networks (RSN)

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder characterized by recurrent intrusive thoughts and repetitive, stereotyped, or ritualized behaviors apparently designed to neutralize the anxiety associated with obsessions.[1] The prognostic importance of OCD in children and adolescents is remarkable since the age of onset and duration of the disease were found to be the baseline predictors of disease resistance.[2] Studying OCD in early ages might further provide valuable information about the neural pinnings of the disorder. Among these, differences in neural circuitry associated with cognitive processes such as executive functions and memory are of particular importance as there are age-related progressive changes in various cortical and subcortical brain areas. A crucial part of these changes is the progressive age-related neurocognitive differentiation of cognitive control which is not limited to the frontal lobes but extends to its connections to the basal ganglia and to parietal and temporal association areas, as reported in both adolescents and adults.[3]

Functional connectivity (FC) is defined as the temporal dependency between the temporal activities of spatially remote anatomical areas to reveal the level of possible functional communication between different parts of the brain.[4] The studies of resting-state functional connectivity (rs-FC) have identified a number of well-defined intrinsic connectivity networks (ICNs), such as the default mode network (DMN), salience network (SN), and the executive control network (ECN) that includes both left and right frontoparietal networks (FPN). While a wide set of studies on rs-FC patterns of large healthy volunteer groups have revealed consistent and replicable patterns of these neurocognitive networks,[5] Marusak et al.[6] (2017) have emphasized the age-related temporal variability of FC of core neurocognitive networks in 146 healthy children and adolescents plausibly corresponding to the

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developmental level of cognitive functions and their neural underpinnings.[6] Hence, age-dependent changes in FC are important in evaluating cognitive functions and their neural bases along the developmental stages including adolescence, which is a critical stage in the development of behavioral and cognitive flexibility, and rs-FC changes in adolescence due to OCD may be expected to differ from those in adult patients.

Functional connectivity studies in OCD generally implicated seed-based analysis which primarily focused on specific seeds and their connectivity with other regions. A meta-analysis of 18 seed-based voxel-wise rs-fMRI studies found that a common pattern of hypoconnectivity among ECN, DMN, and SN, as well as general dysconnectivity between ECN and the main structures of the cortico-striato-thalamo-cortical (CSTC) loops in OCD compared to healthy controls. In this work, aberrant connectivity of ECN has been also emphasized as being the core feature for OCD pathophysiology.[7] On the basis of these findings, Gürsel and coworkers (2019) discuss the 2 hypothesized models about the network dynamics in OCD.[8] While the first of these models is based on unspecific connectivity aberrations in the frontostriatal circuitry, the recently suggested "triple-network" model emphasizes the aberrant intrinsic FC patterns within and between the DMN, also known as the task negative network, ECN, referred to the task-positive network and the SN as core features of psychiatric disorders.[8]

While seed-based FC studies are strong in testing hypotheses about specific neuroanatomical structures, a second group of widely used FC analyses is based on the independent component analysis (ICA), which is a completely data-driven exploratory approach based on the decomposition of the temporospatial rs-fMRI data into statistically independent components, whereby mostly the independence in the spatial domain is used as the pre-requisite of the decomposition. Thus far, relatively fewer studies assessed FC using the ICA method in OCD.[9-12] Gruner and colleagues (2014) reported higher expression of the middle frontal/dorsal cingulate and anterior/posterior cingulate networks in a pediatric OCD population compared with healthy controls.[9] Another study on a small group of child and adolescent patients with OCD found increased FC in the right auditory network and decreased FC in the right part of the cingulate network.[10] Moreira et al.[12] (2019) examined FC in adults and reported that patients displayed reduced FC in visual and sensorimotor networks and additionally decreased FC between sensory networks and increased FC between default-mode and cerebellar networks.[12] In another study, Cheng et al.[11] (2013) found that drug-naive adult OCD patients showed significantly increased intrinsic connectivity in the anterior (ACC) and the middle (MCC) cingulate cortex but decreased connectivity within the PCC compared to the controls.[11] As seen in these studies, the results across the age ranges of the patients show certain variability related to the difference between their developmental stages.

Although significant neuropsychological deficits are suggested as potential endophenotype markers in adults with OCD, a meta-analysis reported that studies investigating youth with OCD have not shown significant neuropsychological deficits, and further research was recommended.[13] We hypothesize that the functional connectivities within the neurocognitive network regions that extend beyond the cortico-striato-thalamo-cortical circuits are altered in drug-naive adolescents with OCD.

METHODS

Considering the variability of the results plausibly due to the different methods, different developmental stages of the OCD patients, and due to less strictly controlled comorbid conditions and medication status of the patients, the current study aims to repeat rs-FC analyses on an adolescent group with OCD by a robust analysis method and by controlling the comorbidities and medication status of the patients in a strict manner. We employed the objective, data-driven group ICA method on balanced groups of newly diagnosed drug-naive patients ($N=15$) and healthy controls (HC) ($N=15$). Furthermore, instead of voxelwise comparison, we compared the obtained independent components by computing the expression scores, which represent the expression level of each network in each subject in a multivariate manner, covering the whole extent of the network as in study of Gruner and coworkers.[9]

Participants and Clinical Assessment

A group of 15 (10 female) OCD patients were recruited from the Child and Adolescent Psychiatry Clinic at Istanbul Medical Faculty of Istanbul University. All 15 patients met the DSM-5 criteria for OCD and were drug-naive. The exclusion criteria for the OCD group were any psychiatric disorder comorbidity and history of major medical or neurological problems. The diagnosis of OCD and comorbidity for each patient was established by a child psychiatrist independently according to the Schedule for Affective Disorders and Schizophrenia for School-Age-Children, Present and Lifetime Version (K-SADS-PL).[14] The severity of OCD symptoms was assessed using the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS).[15] Patients having a CY-BOCS total score of $\geq$16 were included in the study.

A total of 15 healthy voluntary controls (10 female) were recruited from the general community. They were required to be free of any significant current or past psychiatric diagnosis as confirmed by an interview using the K-SADS-PL. Additional exclusion criteria for all participants were having a history of drug or alcohol abuse, craniocerebral trauma, serious physical illness, pregnancy, left-handedness, and contraindications to MRI. Handedness was assessed using

the Edinburgh Handedness Inventory.[16] This study was approved by the Ethics Committee of Istanbul Medical Faculty of Istanbul University (08.09.2016/329061), and written informed consent was obtained from 1 parent or legal guardian for each participant. All of the subjects signed the consent forms before their participation.

MRI Data Acquisition

Structural and echo-planar imaging (EPI) images were acquired on a Philips 3 Tesla magnetic resonance imaging system equipped with a SENSE-32 channel head coil (Philips Achieva, Best, The Netherlands). High resolution T1-weighted structural 3D images were collected with 250 × 250 mm field of view (FOV), 160 slices, 1 mm slice thickness, 0 mm gap. Rs-fMRI data were obtained using an EPI sequence with the repetition time [TR] = 2 s, echo time [TE] = 30 ms, flip angle = 90°, FOV = 224 mm × 240 mm, acquisition matrix size = 112 × 117, voxel size = 2 × 2 × 4 mm^3 in-plane resolution. Following 10 dummy volumes, 214 volumes each containing 36 axial slices covering the whole brain, were obtained with a total scan time of 451 s. All participants were instructed simply to rest with their eyes closed, not to think of anything in particular, and not to fall asleep during the scan.

fMRI Data Preprocessing

The MRI data preprocessing was performed using the SPM8 (Statistical Parametric Mapping software, www.fil.ion.ucl.ac.uk). For each participant, functional images were first realigned to the first volume. None of the participants was excluded due to excessive head movement (the exclusion threshold in any single scan was set to 3 mm in *x*, *y*, or *z* directions and to 3° rotations in each axis). After coregistration to the mean functional image, the anatomic image was segmented and normalized to the Montreal Neurological Institute (MNI) standard space. Then, the realigned functional images were spatially normalized using the resulting transformation matrix and resampled to 2 mm^3 voxels. Lastly, the functional images were spatially smoothed by convolution with an isotropic Gaussian kernel (full width half maximum = 8 mm). Additionally, we applied several extra steps to account for head motion. First, the mean frame-wise displacement (FD) of functional images was calculated.[17] Afterwards, mean FD, mean global signal (GS) change, and mean motion were compared between the OCD group and HC with 2-samples *t*-tests. There were no significant differences in mean FD ($t(18.66) = 1.65$, $P = .116$), mean GS change ($t(28) = 0.265$, $P = .793$), and mean motion ($t(18.48) = 1.542$, $P = .140$).

Functional Connectivity Analysis

The rs-fMRI data were decomposed into intrinsic connectivity networks (ICNs) by using the infomax algorithm implemented in the Group ICA Toolbox (GIFT)[18] (http://icatb.sourceforge.net/). The number of independent components (IC) was estimated based on the minimum description length (MDL) criterion[19] and it was set as 30.

ICASSO method with 10 runs was implemented to stabilize the results of the ICA algorithm. The 30 ICs and their frequency spectra were visually inspected to define the artifactitious components and those ICs corresponding to the well-known ICNs in the literature[20] were used for further analyses. Spatiotemporal (dual) regression was implemented to obtain the ICs at the single-subject level. The expression level of each IC in each subject was computed by calculating the inner product of subjects' ICs with the group-level ICs.[9] By this way, scalar values have been obtained that represent the expression of each IC in each subject both in terms of its spatial pattern and intensity.

As the reconstruction process also provides the time course of each IC in each subject, the inter-network temporal correlations were obtained by computing the Pearson correlation coefficients between the time series of the component pairs, *z*-transformed, and subjected to *t*-statistics for testing the significant differences of the inter-network connectivities between both groups.

Statistical Analyses

To test whether the expression scores of the ICNs in any combination may classify the subjects correctly into groups, the forward stepwise conditional binary logistic regression analysis in SPSS software (21.0., IBM, Armonk, NY, USA) has been run on all 13 ICs expression scores. The resulting set of ICs was further analyzed with regard to their functional connectivities with the remaining 12 ICs by comparing the z-transformed Pearson correlation coefficients between each pair of ICs by means of a *t*-test between the HC and OCD groups. The multiple comparisons for all pairs of internetwork correlations were corrected by Bonferroni correction ($P < .001$).

RESULTS

The subjects' demographic and clinical characteristics are summarized in Table 1. No significant difference was found between OCD and HC groups in terms of age, gender, and education levels. No significant relationship was found between altered connectivity patterns of the brain networks and clinical variables (i.e., CY-BOCS) in the OCD group.

fMRI Findings

After manual removal of the ICs that corresponded to typical artifacts with their spatial and spectral patterns, 13 out of the 30 ICs have been evaluated to represent ICN components that have been replicated many times in the literature. These ICs were medial and lateral parts of the somatomotor network (medial SMN and lateral SMN), medial and lateral parts of the visual network (medial VN

Table 1. Demographical and Clinical Characteristics of the Sample

	OCD ($N=15$) Mean ± SD	HC ($N=15$) Mean ± SD	t	P Value
Age (years)	15.27 (±1.49)	15.4 (±1.35)	0.257	.799
Education (years)	9.07 (±1.79)	9.8 (±1.21)	1.315	.199
Gender (female, %)	10 (66.67%)	10 (66.67%)		
CY-BOCS-OS	15.2 (±2.1)			
CY-BOCS-CS	14.8 (±2.3)			
CY-BOCS-Total	30.13 (±4.27)			
Duration of symptoms (months)	13 (±9)			

CY-BOCS-OS: CY-BOCS obsession score; CY-BOCS-CS: CY-BOCS compulsion score; SD: standard deviation.

and lateral VN), cerebellum, right, and left frontoparietal networks (R-FPN and L-FPN) of the ECN, dorsal attention network (DAN), salience network (SN), and 4 subcomponents of the DMN (anterior DMN [aDMN], posterior cingulate cortex [PCC], precuneus [PC], and parahippocampal gyri [PHG]). The logistic regression analysis performed on the subject-level expression scores of the ICNs, computed by the inner product of the group ICN map with the individual map, revealed that the combination of the PCC (part of posterior DMN), cerebellum, R-FPN, and aDMN was successful in discriminating the OCD group from HC ($x^2=19.88$, $df=4$, $P < .001$) with an overall accuracy of 86.7% (both sensitivity and specificity values of 86.7%) with the final model Nagelkerke $R^2=0.646$. The group averages of these networks for both groups are displayed in Figure 1. While the expression scores of the PCC, cerebellum, and R-FPN were lower in OCD, the expression score of the aDMN was significantly higher in the OCD group as compared with the HC group. The mean and range of the effect sizes (odds ratios) for the corresponding networks were PCC: 0.023 (0.001-0.548, $P=.02$), cerebellum: 0.025 (0.001-0.561, $P=.02$), R-FPN: 0.001 (2×10^{-6}-0.95, $P=.048$), aDMN: 8.171 (0.831-80.375, $P=.072$).

We also investigated any significant changes in pairwise inter-network correlations between each of the above 4 networks and each of the remaining 12 networks. After Bonferroni correction with the factor $4 \times 12=48$ ($P=.001$), 2 inter-network connectivities displayed significant differences between the OCD and HC groups. While a significant anti-correlation appeared between the R-FPN and lateral SMN, a positive correlation was introduced between the PCC and PHG in the OCD group ($P < .001$) (Figure 2).

DISCUSSION

In this study, we aimed to investigate the brain's functional connectivity changes in drug-naive adolescents experiencing a first episode of OCD by investigating the

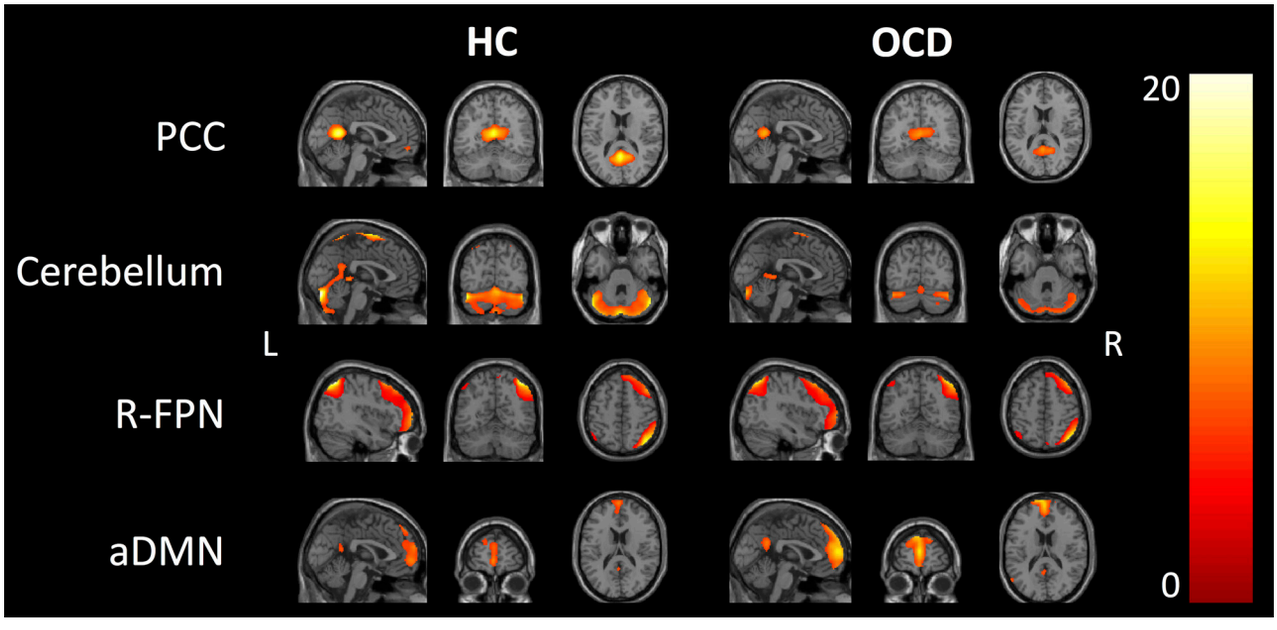

Figure 1. Four ICNs that successfully discriminate the OCD group from HCs. PCC, posterior cingulate cortex; R-FPN, right frontoparietal network; aDMN, anterior DMN; HC, healthy controls; OCD, obsessive-compulsive disorder.

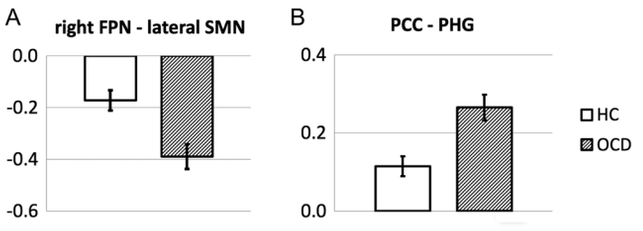

Figure 2. Significant (Bonferroni corrected) inter-network connectivities between (A) the right frontoparietal (R-FPN) and lateral somatomotor networks (lateral SMN) and (B) posterior cingulate cortex (PCC) and parahippocampal gyri (PHG). Error bars depict the standard error of the mean.

intrinsic connectivity networks obtained using independent component analysis on the resting-state fMRI data. In addition to this, the pediatric and drug-naive nature of our cohort allowed us to minimize confounding factors such as age, disease duration, and chronic pharmacological treatment. Logistic regression applied on the expression levels of the ICNs revealed 4 network components that were successful in discriminating the OCD group from HC.

Expression scores were significantly lower in OCD in 3 ICNs comprising the PCC, cerebellum, and R-FPN compared to healthy controls showing that decreased intrinsic connectivity in these networks increases significantly the probability of a subject belonging to the OCD group. On the other hand, the expression score of the aDMN was significantly higher in the OCD group pointing to the increased intrinsic connectivity of the anterior part of the DMN in contrast to the posterior PCC component in OCD patients as compared with the HC group.

Moreover, we investigated the inter-network correlations, and our findings revealed that patients with OCD exhibited a significant (Bonferroni corrected) anti-correlation between the R-FPN and lateral SMN and a positive correlation between the PCC and PHG compared to HC.

Previous studies have reported correlations between abnormal FC and clinical variables.[21,22] However, no relationships were found between brain network connectivity and clinical variables in the OCD group in the current study, which indicated that abnormal FC values might be trait changes independent of clinical variables for patients with OCD.

DMN Connectivity Alterations in Adolescents with OCD

The most outstanding results of the present study were the altered FC observed in DMN subcomponents aDMN and PCC. DMN is related to the internally oriented mental processes including autobiographical memory, thinking about one's future, self-referential, and affective decision-making.[23] Furthermore, recent imaging studies showed that there is functional differentiation within the subsystems of the DMN, while the anterior nodes of DMN (ACC and medial prefrontal cortex) are more engaged in processing of self-referential and emotional states, the posterior nodes of the DMN (PCC and precuneus) are more involved in episodic memory and perceptual processing.[24,25] Moreover, PCC regulates arousal state and the breadth of attention and controls the balance between internally and externally focused thoughts.[26]

Our results dissociate the DMN connectivities into 2 distinct patterns, where the PCC (posterior part of DMN) showed hypoconnectivity, whereas aDMN displayed hyperconnectivity. Decreased intrinsic connectivity of PCC in pediatric OCD corroborate the findings of the numerous previous studies[27-29] and might be functionally related to the episodic memory deficits in OCD,[30] while patients with OCD fail to adjust the level of arousal and attention on external events and show decreased sensitivity to external events, so that they focus mostly to their own intrusive thoughts thereby leading to the maintenance of repetitive symptoms Additionally, hyperconnectivity of aDMN in OCD could be related to the overactive internal rumination in OCD, which is similar to the results of a study in adult patients with OCD showing an increased intra-network FC in the right anterior superior frontal gyrus within the aDMN in OCD.[31]

Furthermore, we also found a positive correlation increase between intrinsic FC of the PHG with PCC in OCD. The parahippocampal gyri, a part of the medial temporal lobe (MTL), interacts with widespread cortical regions to support the memory processes such as encoding and retrieval and also shows strong FC with the PCC in the lack of explicit task demands.[32] In line with our hypothesis, these correlation increases observed in pediatric OCD might be related to previously reported important cognitive impairments in memory processes and goal-directed learning.[33]

Briefly, we found altered DMN connectivity in adolescent patients with OCD showing that hyperactivity of the aDMN and hypoactivity of the PCC may reflect the pathophysiology of OCD related to the high error detection but low self-control because of the overactive internal rumination in the rest condition.[34]

R-FPN Connectivity Alterations in Adolescents with OCD

Recent meta-analyses have noted that alterations in FPN network are the most commonly reported fMRI findings in OCD pathophysiology.[7,35] The FPN as an attention network plays a role in goal-directed behavior and is highly integrated with other brain networks.[36,37] Therefore, alterations in FPN can be linked to excessive monitoring of thoughts in OCD, which could explain some of the symptoms.[35]

We found a hypoconnectivity of R-FPN in drug-naive patients which is in line with the findings of a meta-analysis of rs-fMRI studies in OCD by Gürsel and colleagues.[7] In this meta-analysis, specifically reduced intrinsic FC within and among the DMN, FPN, and SN and as well as general altered connectivity between FPN and DMN were reported.

Moreover, another study reported reduced prefrontal connectivity associated with increased illness severity.[22] In contrast to this, some previous studies reported stronger FPN connectivity in OCD[21] and another study found no group differences in the Rs-FC of cognitive control networks between OCD patients and controls.[38] Inconsistencies between results may be associated with patient characteristics (such as medication status or comorbidity or age) and methodological differences but both studies showed alterations in FPN.

Additionally, the anti-correlation between the R-FPN and lateral SMN in patients with OCD is another finding in our study. The hypoconnectivity within the R-FPN and the anti-correlation between frontoparietal regions and somatomotor network might be related to dysfunctional inhibitory control which could contribute to compulsive behaviors.[39]

Cerebellum Hypoconnectivity in Adolescents with OCD

The cerebellar network is 1 of the ICNs that demonstrates decreased expression scores in OCD patients compared to the HC in our study. The cerebellum plays a role in cognitive processing and emotional control besides its role in motor coordination.[40] The role of the cerebellum in the pathophysiology of OCD has recently been discussed by Xu and colleagues[41] and decreased cerebello-cerebral FCs in OCD including executive, default-mode, affective-limbic, and sensorimotor networks were reported. A comparative meta-analysis of 30 voxel-based morphometry examining the grey matter differences between youth and adult OCD patients revealed greater gray matter volume in the dorsal part of the left cerebellum in medicated OCD adults, whereas there were no significant differences between youth and unmedicated adults with OCD.[42] Researchers suggested that medical treatment might contribute to this cerebellar expansion that is only found in medicated OCD adults. Therefore, the decrease in FC in the cerebellum might contribute to the impairment in cognitive and affective processes in OCD patients and could regulate rumination and obsessive behavior.[43]

CONCLUSIONS

In conclusion, the current study revealed 4 ICNs that are maximally discriminating the adolescent with OCD and HC, indicating higher expression scores within aDMN, but lower within PCC, cerebellum, and right FPN in OCD. Additionally, anti-correlation between the right FPN and lateral sensorimotor network as well as a positive correlation between the PCC and parahippocampal gyri were found in patients. These findings reveal the importance of FC changes within and between ICNs involved in the triple network and CSTC model. These findings suggest that ICNs are potential treatment targets in OCD, and therefore future follow-up studies would shed light on the treatment effects on these FC changes. Several limitations should be considered when interpreting the results of the present study. First, this study includes a small sample size. A larger sample size would have increased the statistical power of comparisons. Second, the average duration of symptoms in patients was 13 (±9) months; however, due to the small number of rs-FC studies using the same ICA method in pediatric OCD, we discussed our findings mostly based on the reports on adult studies.

In spite of these limitations, the present study certainly improves our understanding of disease-specific neural connectivity changes by providing a more homogeneous group, since we included only drug-naive patients without comorbidity and by using robust data-driven analysis method in contrast to the common OCD literature involving high rates of comorbid diagnoses and seed-based methods.

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Informed Consent: Informed consent was obtained from either parent or legal guardian of each research participant.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed.; 2013.
2. Micali N, Heyman I, Perez M, et al. Long-term outcomes of obsessive–compulsive disorder: follow-up of 142 children and adolescents. *Br J Psychiatry*. 2010;197(2):128-134. [CrossRef]
3. Rubia K, Smith AB, Woolley J, et al. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. *Hum Brain Mapp*. 2006;27(12):973-993. [CrossRef]
4. Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab*. 1993;13(1):5-14. [CrossRef]
5. Calhoun VD, Miller R, Pearlson G, Adalı T. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. *Neuron*. 2014;84(2):262-274. [CrossRef]
6. Marusak HA, Calhoun VD, Brown S, et al. Dynamic functional connectivity of neurocognitive networks in children. *Hum Brain Mapp*. 2017;38(1):97-108. [CrossRef]
7. Gürsel DA, Avram M, Sorg C, Brandl F, Koch K. Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal

interactions in OCD: a meta-analysis of resting-state functional connectivity. *Neurosci Biobehav Rev*. 2018;87:151-160. [CrossRef]
8. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*. 2011;15(10):483-506. [CrossRef]
9. Gruner P, Vo A, Argyelan M, et al. Independent component analysis of resting state activity in pediatric obsessive-compulsive disorder. *Hum Brain Mapp*. 2014;35(10):5306-5315. [CrossRef]
10. Weber AM, Soreni N, Noseworthy MD. A preliminary study of functional connectivity of medication naive children with obsessive-compulsive disorder. *Progr Neuro-Psychopharmacol Biol Psychiatry*. 2014;53:129-136.
11. Cheng Y, Xu J, Nie B, et al. Abnormal resting-state activities and functional connectivities of the anterior and the posterior cortexes in medication-naive patients with obsessive-compulsive disorder. *PLoS ONE*. 2013;8(6):e67478. [CrossRef]
12. Moreira PS, Marques P, Magalhães R, et al. The resting-brain of obsessive-compulsive disorder. *Psychiatry Res Neuroimaging*. 2019;290:38-41. [CrossRef]
13. Abramovitch A, Abramowitz JS, Mittelman A, et al. Research Review: neuropsychological test performance in pediatric obsessive-compulsive disorder-a meta-analysis. *J Child Psychol Psychiatry Allied Discip*. 2015;56(8):837-847. [CrossRef]
14. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980-988. [CrossRef]
15. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale: I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46(11):1006-1011. [CrossRef]
16. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9(1):97-113. (https://doi.org/10.1016/0028-3932(71)90067-4).
17. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*. 2012;59(3):2142-2154. [CrossRef]
18. Calhoun VD, Liu J, Adali T. A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *Neuroimage*. 2009;45(1)(suppl):S163-S172. [CrossRef]
19. Li YO, Adali T, Calhoun VD. Estimating the number of independent components for functional magnetic resonance imaging data. *Hum Brain Mapp*. 2007;28(11):1251-1266. [CrossRef]
20. Raichle ME. The brain's dark energy. *Sci Am. Scientific American*. 2010;302(3):44-49. [CrossRef]
21. Göttlich M, Krämer UM, Kordon A, Hohagen F, Zurowski B. Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. *Hum Brain Mapp*. 2014;35(11):5617-5632. [CrossRef]
22. Anticevic A, Hu S, Zhang S, et al. Global resting-state fMRI analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biol Psychiatry*. 2014;75(8):595-605.
23. Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW, Schacter DL. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage*. 2010;53(1):303-317. [CrossRef]
24. Xu X, Yuan H, Lei X. Activation and connectivity within the default mode network contribute independently to future-oriented thought. *Sci Rep*. 2016;6:21001. [CrossRef]
25. Coutinho JF, Fernandesl SV, Soares JM, et al. Default mode network dissociation in depressive and anxiety states. *Brain Imaging Behav*. 2016;10(1):147-157. [CrossRef]
26. Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. *J Neurosci*. 2011;31(9):3217-3224. [CrossRef]
27. Fitzgerald KD, Stern ER, Angstadt M, et al. Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. *Biol Psychiatry*. 2010;68(11):1039-1047. [CrossRef]
28. Koch K, Reeß TJ, Rus OG, et al. Increased default mode network connectivity in obsessive-compulsive disorder during reward processing. *Front Psychiatry*. 2018;9:254. [CrossRef]
29. Stern ER, Fitzgerald KD, Welsh RC, Abelson JL, Taylor SF. Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PLoS ONE*. 2012;7(5):e36356. [CrossRef]
30. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain*. 2014;137(1):12-32. [CrossRef]
31. Fan J, Zhong M, Gan J, et al. Altered connectivity within and between the default mode, central executive, and salience networks in obsessive-compulsive disorder. *J Affect Disord*. 2017;223:106-114. [CrossRef]
32. Ward AM, Schultz AP, Huijbers W, et al. The parahippocampal gyrus links the default-mode cortical network with the medial temporal lobe memory system. *Hum Brain Mapp*. 2014;35(3):1061-1073. [CrossRef]
33. Gottwald J, de Wit S, Apergis-Schoute AM, et al. Impaired cognitive plasticity and goal-directed control in adolescent obsessive-compulsive disorder. *Psychol Med*. 2018;48(11):1900-1908. [CrossRef]
34. Gonçalves ÓF, Soares JM, Carvalho S, et al. Patterns of default mode network deactivation in obsessive compulsive disorder. *Sci Rep*. 2017;7:44468. [CrossRef]
35. Gürsel DA, Reinholz L, Bremer B, et al. Frontoparietal and salience network alterations in obsessive-compulsive disorder: insights from independent component and sliding time window analyses. *J Psychiatry Neurosci*. 2020;45(3):214-221. [CrossRef]
36. Marek S, Dosenbach NUF. The frontoparietal network: function, electrophysiology, and importance of individual precision mapping. *Dial Clin Neurosci*. 2018;20(2):133-140. [CrossRef]
37. Eng GK, Sim K, Chen SHA. Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review. *Neurosci Biobehav Rev*. 2015;52:233-257. [CrossRef]

38. de Vries FE, de Wit SJ, van den Heuvel OA, et al. Cognitive control networks in OCD: a resting-state connectivity study in unmedicated patients with obsessive-compulsive disorder and their unaffected relatives. *World J Biol Psychiatry*. 2019;20(3):230-242. [CrossRef]

39. Jang JH, Kim JH, Jung WH, et al. Functional connectivity in fronto-subcortical circuitry during the resting state in obsessive-compulsive disorder. *Neurosci Lett*. 2010;474(3):158-162. [CrossRef]

40. Apps R, Garwicz M. Anatomical and physiological foundations of cerebellar information processing. *Nat Rev Neurosci*. 2005;6(4):297-311. [CrossRef]

41. Xu T, Zhao Q, Wang P, et al. Altered resting-state cerebellar-cerebral functional connectivity in obsessive-compulsive disorder. *Psychol Med*. 2019;49(7):1156-1165. [CrossRef]

42. Hu X, Du M, Chen L, et al. Meta-analytic investigations of common and distinct grey matter alterations in youths and adults with obsessive-compulsive disorder. *Neurosci Biobehav Rev*. 2017;78:91-103. [CrossRef]

43. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum-insights from the clinic. *Cerebellum*. 2007;6(3):254-267. [CrossRef]