Altered Functional Network Architecture in Orbitofronto-Striato-Thalamic Circuit of Unmedicated Patients with Obsessive-Compulsive Disorder

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Abstract: Dysfunction of corticostriatal loops has been proposed to underlie certain cognitive and behavioral problems associated with various neuropsychiatric disorders, such as obsessive-compulsive disorder (OCD) characterized by repetitive, unwanted thoughts, and behaviors. Although functional abnormalities in the loops involving the orbitofronto-striato-thalamic (OFST) circuitry in patients with OCD have been reported, our understanding of a link between disruptions in the architecture of the intrinsic functional network of the OFST circuit and their symptoms remain incomplete. Using resting-state functional MRI in conjunction with unsupervised clustering and multilevel functional connectivity (FC) techniques, FC of the OFST network and its topological organization in 61 OCD patients versus 61 matched controls were characterized. Patients exhibited disruptions in small-world properties of the OFST circuit, which indicates an imbalance between functional integration and segregation. Patients also showed decreased FC between the central orbitofrontal cortex and dorsomedial striatum but increased FC between the medial thalamus and striatal areas. Using one of the largest samples of unmedicated OCD patients to date, our findings provide evidence supporting the OFST dysconnection hypothesis in OCD as a basic pathophysiological mechanism underlying the disorder, showing the disruption of FC between specific cortical, striatal, and thalamic clusters and aberrant topological patterns of the OFST circuit. *Hum Brain Mapp* 38:109–119, 2017. © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

It is well known that corticostriatal loops are organized into a set of discrete circuits functionally segregated (cognitive, affective, and motor processing) by specific compartments of the cortical, striatal, and thalamic areas that belong to them [Alexander et al., 1986]. Dysfunction of the circuits has been proposed to underlie certain cognitive, affective, and behavioral problems associated with various neurological (e.g., Huntington's disease and Parkinson's disease) and neuropsychiatric disorders (e.g., obsessive-compulsive disorder, major depressive disorder, and schizophrenia) [Shepherd, 2013]. Therefore, understanding abnormalities in information processing and topological organization in the circuits can provide new insights into mechanisms underlying such neurological and neuropsychiatric disorders and further provide the advancement of treatment and prevention strategies.

Obsessive-compulsive disorder (OCD) is characterized by complaints of persistent or repetitive thoughts or behaviors. Neuroimaging studies have consistently reported dysfunction in the corticostriatal loops in people with OCD. OCD research has emphasized dysfunction in the orbitofronto-striato-thalamic (OFST) circuit [Menzies et al., 2008]. More specifically, investigations indicate that the altered executive function and reward processing exhibited by OCD patients is linked to disruptions in functional connectivity (FC) within this circuit [Jung et al., 2013; Marsh et al., 2014]. Recent resting-state fMRI (rs-fMRI) studies have provided complementary evidence supporting the aforementioned "dysconnection hypothesis of OCD." For example, OCD patients showed aberrant FC between the ventral striatum and medial prefrontal cortex (mPFC) [Harrison et al., 2009, 2013; Jung et al., 2013]. Additionally, studies using graph theoretical analysis (GTA) to investigate the organization of brain networks, found OCD patients display deficits in global brain connectivity (the average connectivity of a given voxel/region with all other voxels/regions) of the orbitofrontal cortex (OFC) and striatum, as well as abnormal small-world organization, which indicates an imbalance between local specialization and global integration of brain functional activity, of a top-down executive control network, and a whole-brain network [Anticevic et al., 2014; Beucke et al., 2013; Shin et al., 2014; Zhang et al., 2011].

More recent rs-fMRI studies indicate that each of the functional networks has its own unique topological organization, which is often missed by whole-brain network literature [He et al., 2009; Zhang et al., 2011]. It remains unclear whether changes within the topological organization of the OFST circuit underlie some of the clinical

symptomatology typically observed in OCD. Importantly, studies of corticostriatal FC in OCD patients have focused exclusively on the FC of striatal seed regions [Harrison et al., 2009, 2013; Posner et al., 2014], even though each subdivision of other regions within this circuit (i.e., the OFC and thalamus) are equally likely to have specific patterns of connectivity disruptions [Anticevic et al., 2014; Fitzgerald et al., 2011]. Of further relevance, these studies of corticostriatal FC typically include a large proportion of patients with comorbid mental health problems, such as depression, and who were exposed to stable medication regimes at the time of study [Fitzgerald et al., 2011; Harrison et al., 2013]—both of which may influence patterns of brain connectivity. Therefore, the current understanding of the role of the OFST network in OCD remains incomplete.

To more conclusively test the "dysconnection hypothesis of OCD," we investigated whether there are disturbances in topological organization and/or FC between pairs of brain regions within the OFST circuit in OCD. The current study extends upon previous literature in a few key ways. First, we obtained one of the largest samples of unmedicated OCD patients, which were characterized by markedly fewer comorbid mental health symptoms compared with previous studies. Second, we utilized nodes (or seeds) defined by FC-based parcellation (see our previous study [Jung et al., 2014] for details), which allowed for the examination of FC patterns within functionally distinct corticostriatal loops characterized by functionally homogeneous nodes [Jung et al., 2014; Kahnt et al., 2012; Park et al., 2013]. Ultimately, these analyses provide greater precision to our understanding of altered FC in the neural architecture of OCD patients. On the basis of previous work, we predicted that patients would demonstrate disrupted topological organization and altered FC in circuits embedded within the prevailing OFST circuit model of OCD, which includes the lateral OFC, ventral striatum, and medial thalamus.

MATERIALS AND METHODS

Participants

Seventy-eight drug-free patients with OCD were recruited from the outpatient clinic at Seoul National University Hospital. All patients were evaluated by certified psychiatrists using the Structured Clinical Interview for DSM-IV-TR and fulfilled criteria for OCD. Of the 78 patients initially evaluated, 15 were excluded due to lifetime or current axis I psychiatric comorbidities. Patients were administered the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and Hamilton depression (HAMD) and

TABLE I. Demographic and clinical characteristics of controls and patients

Variable	Controls (<i>n</i> = 61)	Patients (<i>n</i> = 61)	<i>P</i> -value
Age (years)	25.639 (6.499)	26.082 (7.203)	0.722 ^b
Gender (male/female)	36/25	41/20	0.349 ^c
Handedness (right/left)	58/3	55/6	0.308 ^c
Full scale IQ ^a	114.721 (12.103)	110.623 (11.164)	0.054 ^b
Education (years)	14.426 (1.821)	14.262 (2.449)	0.676 ^b
Age of onset (years)	–	18.951 (6.960)	
Duration of illness (years)	–	7.475 (5.857)	
Y-BOCS-Obsessions	–	14.377 (3.333)	
Y-BOCS-Compulsions	–	12.115 (4.910)	
Y-BOCS-Total	–	26.492 (7.263)	
Hamilton depression scale	–	9.934 (6.077)	
Hamilton anxiety scale	–	9.426 (6.040)	

The Hamilton Depression Scale and the Hamilton Anxiety Scale were used to measure the severity of depression and anxiety, respectively, and the severity of OCD symptoms was measured using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Data are given as mean (SD).

^aEstimated by Korean-Wechsler Adult Intelligence Scale.

^bIndependent sample *t*-test.

^c χ^2 test.

Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

anxiety (HAMA) rating scales to measure the severity of their obsessive-compulsive symptomatology and the extent of their accompanying depressive mood and anxiety. We also recruited 65 healthy controls that were matched for age, gender, and IQ. For both patients and controls, additional exclusion criteria were a lifetime history of head injury, a seizure disorder, or mental retardation. After preprocessing the rs-fMRI data, two patients and four controls were also excluded due to excessive head motions. The final sample consisted of 61 patients and 61 matched controls. At the time of the study, 25 patients were drug-naïve, 36 had been medication-free for at least 1 month (range, 1–72 months). All medication-free patients had prior exposure to selective serotonin reuptake inhibitors (fluoxetine equivalent dose, range 20–80 mg/day). Seven of these patients were concomitantly medicated with benzodiazepines (*n* = 4) or atypical antipsychotics (*n* = 3). Fifty-six patients were free of axis I or axis II psychiatric comorbidities, and five had the following axis II psychiatric comorbid disorders: obsessive-compulsive personality disorder (*n* = 2), schizotypal personality disorder (*n* = 1), impulse control disorder not otherwise specified (NOS; *n* = 1), and anxiety disorder NOS (*n* = 1). The demographic and clinical data of the subjects are provided in Table I. This study was approved by the Institutional Review Board of Seoul National University Hospital and all participants signed an informed consent form prior to their participation.

Data Acquisition and Preprocessing

All images were acquired using a 3T Trio MRI scanner (Siemens, Erlangen, Germany). All subjects were asked to

abstain from smoking, caffeine and other stimulants from midnight the night before his/her scan. During rs-fMRI scan, each subject was asked to relax with his/her eyes closed while a 6 min and 53 s rs-fMRI scan was acquired (echo time = 30 ms, repetition time = 3,500 ms, flip angle = 90°, 35 slices, and voxel size = 1.9 × 1.9 × 3.5 mm). To ensure that subjects did not fall asleep, they were reminded to stay awake through microphone immediate before the rs-fMRI acquisition. After scanning, a simple questionnaire was administered to confirm they had not fallen asleep. High-resolution T1-weighted magnetization-prepared rapid-gradient echo anatomical images were also obtained with the following characteristics: echo time = 1.89 ms, repetition time = 1,670 ms, flip angle = 9°, 208 slices, and voxel size = 1.0 × 0.98 × 0.98 mm.

After discarding the first four scans, SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) was used to correct the rs-fMRI data for slice-timing and the images were realigned to the first scan via rigid-body alignment. Next, the images were spatially normalized to the Montreal Neurological Institute (MNI) template using a nonlinear warping algorithm, resampled to 3 × 3 × 3 mm (3 mm set) and 4 × 4 × 4 mm (4 mm set), which was used only for functional parcellation analysis), and spatially smoothed with a 6 mm full-width half-maximum Gaussian kernel. All subjects included in the present study exhibited (i) spatial movement less than 1.5 mm and rotation movement less than 1.5° in any direction and (ii) volume-level mean frame-wise displacement less than 0.30 mm (0.124 ± 0.051 for controls and 0.114 ± 0.051 for patients). There were no significant group differences in the head motion parameters. The CONN toolbox [Whitfield-Gabrieli and Nieto-Castanon, 2012; <http://www.nitrc.org/projects/conn/>]

was used for despiking, regression of nuisance signals (six head-motion and their first derivatives, five principal components obtained from the white matter and the cerebrospinal fluid masks using a component-based noise correction method [CompCor] and a linear detrending term), and band-pass filtering (0.009–0.1 Hz). A detailed description of the image analyses is provided as Supporting Information.

Functional Parcellation

We utilized the Automated Anatomical Labeling (AAL) atlas to define the regions-of-interest (ROI; OFC, striatum, and thalamus) and the rest of the brain as previously described [Jung et al., 2013; Kahnt et al., 2012]. For each participant, Pearson correlations were calculated between each voxel in a given ROI (from the 3 mm set) and all other voxels throughout the rest of the brain (using the 4 mm set) using time series information extracted from rs-fMRI. Then the individual correlation matrices were Fisher's z -transformed, averaged across all subjects, and used for the agglomerative hierarchical cluster analysis to parcellate each ROI based on FC profiles. The optimal number of clusters was determined by Mojena's stopping rule [Mojena, 1977]. The segmented clusters from each ROI (five for the OFC, seven for the striatum, and five for the thalamus) were used for all subsequent analyses. Thus, data was represented as a 17×17 connectivity matrix for each subject, where each row/column represented a given cluster (subdivision) from a given ROI. Each subject's connectivity matrix was populated with the Pearson correlation coefficient between time series extracted from each cluster and these values were used for the GTA and network-based statistic (NBS) analyses. The GTA was performed using the GRETNA toolbox [Wang et al., 2015; <http://www.nitrc.org/projects/gretna/>].

Graph Theoretical Analysis

Single-subject connectivity matrices were binarized by applying a sparsity threshold that was equivalent to the ratio between the number of edges and all possible edges for each group. To characterize the global and regional network measures, the clustering coefficient (C_p), characteristic path length (L_p), and the betweenness centrality (BC) were computed. The values of the C_p and L_p were normalized by comparing random networks ($\gamma = C_p^{\text{real}} / C_p^{\text{rand}}$ and $\lambda = L_p^{\text{real}} / L_p^{\text{rand}}$) and their ratio was defined as the small-worldness value ($\sigma = \gamma / \lambda$). The BC was normalized as $b_i = BC_i / \langle BC \rangle$, where $\langle BC \rangle$ denotes the average betweenness of the network. The normalized BC values were averaged across the range of sparsity and then regions with a high b_i value (>1.5) were identified as hubs [Seo et al., 2013]. Given the absence of a gold standard for selecting a single threshold, the above network properties were computed over a wide range ($0.16 \leq S \leq 0.30$) because

this range was the small-world regime identified in both groups ($\gamma > 1$ and $\lambda \approx 1$). For further statistical comparisons, the area under the curve (AUC) for each network metric was calculated.

Inter-Regional Connectivity Analysis

The NBS was applied to localize specific pairs of brain regions in which FC was altered in OCD patients [Zalesky et al., 2010]. The NBS controls the family-wise error rate (FWE-corrected $P < 0.05$) in mass-univariate testing of a ROI-to-ROI connectivity matrix based on the principle underpinning traditional cluster-based thresholding of statistical parametric maps. For the NBS analysis, the significant nonzero connections ($P < 0.05$, uncorrected) on Fisher's z -transformed correlation matrices were detected for each group by performing multiple one-sample t -tests and the nonzero connections were combined within either the patients or controls as a connection mask. Then the NBS approach was conducted within the mask.

Next, a seed-to-voxel approach was taken to further delineate the FC of clusters showing group differences in the GTA and NBS analysis. To do so, a multiple regression analysis implemented in SPM8 was performed for each ROI of each subject, which included the average time series from each cluster as regressors [Di Martino et al., 2008; Kahnt et al., 2012]. As mentioned above, we focused on the FC of clusters showing group differences from the GTA and NBS, although the seed-to-voxel FC results for all subdivisions of each ROI are provided for reference (see Supporting Information Figures).

Statistical Analysis

To analyze between-group comparisons for network parameters from the GTA and for inter-regional FC from the NBS, nonparametric permutation tests with 10,000 repetitions were performed for two alternative hypotheses: patients $>$ controls and patients $<$ controls. Prior to the permutation tests, multiple linear regression analyses were conducted to remove the confounding effects of age, gender, and IQ from each network metric and each of the regional pairings. Group differences in global network metrics (i.e., γ , λ , and σ) are reported at a stringent threshold (false discovery rate [FDR]-corrected $P < 0.05$; Benjamini and Hochberg, 1995] for comparisons of AUC values of network metrics and at a less stringent threshold ($P < 0.05$, uncorrected) for comparisons of network metrics at each sparsity threshold to determine possible group differences because of the exploratory nature of this analysis with mass univariate t -tests. For normalized BC comparisons, we used $P < 0.05$ uncorrected. However, this value corresponds to the significance level corrected for multiple comparisons using a false-positive adjustment of $P < 1/N$, where N is the number of nodes (in our case, N is 17). Although this correction method is not as conservative as

a Bonferroni or FDR correction, it has been used in many studies, particularly for comparisons of regional network metrics [Alexander-Bloch et al., 2010; Lynall et al., 2010].

To investigate group differences in the z -value maps of seed-to-voxel FC, two-sample t -tests were performed. These analyses were restricted to the voxels showing significant positive correlation maps for either the patients or controls using a binary mask from the combined sets of results from the one-sample t -tests of two groups. The results of all t -tests were thresholded at a whole-brain clusterwise-corrected significance of $P < 0.05$, determined using AlphaSim, based on previous rs-fMRI studies [Fornito et al., 2013].

Once significant group differences were found, we further assessed the relationships between brain measures and OCD symptom severity. Owing to the exploratory nature of these correlation analyses, we applied a statistical significance level of $P < 0.05$, uncorrected.

RESULTS

Functional Subdivisions

Figure 1A and Supporting Information Figure S1 show the segmented patterns for each ROI. These segmented patterns were consistent with those of previous rs-fMRI studies that employed similar clustering methods [Jung et al., 2013; Kahnt et al., 2012; Zhang et al., 2008] and cytoarchitecture patterns [Ongür et al., 2003].

Changes in Network Properties

The OFST network of both groups demonstrated small-world network architecture over a preselected sparsity range ($0.16 \leq S \leq 0.30$). However, the values of normalized clustering coefficient γ , normalized characteristic path length λ , and small-worldness σ in the patients were smaller than those of controls over multiple sparsity levels ($P < 0.05$ uncorrected; Fig. 1B). Further statistical comparisons of the patients using the AUC revealed a significant decrease in λ (Unadjusted [FDR-adjusted] $P = 0.016$ [0.047]), a trend toward a decrease in γ ($P = 0.067$ [0.100]), and no difference in σ ($P = 0.185$ [0.185]).

Several brain regions in the OFST network of each group were identified as hubs: striatum Cluster 2 and thalamus Cluster 4 for the patients and striatum Clusters 3 and 5 for the control subjects (Table II). Compared with the controls, there were significant increases in the b_i values of the patients in striatum Cluster 2 and OFC Cluster 3, whereas the b_i value of striatum Cluster 3 exhibited a significant decrease (all $P < 0.05$ uncorrected). However, these group differences disappeared when applying more stringent P -value threshold (i.e., FDR-corrected $P < 0.05$).

Changes in Inter-Regional Connectivity

NBS analyses revealed that the patients exhibited decreased connectivity between OFC Cluster 1 and striatum Cluster 6 and between the striatum clusters relative to the controls. In contrast, the patients showed increased connectivity between striatum Clusters 1, 2, and 5 and thalamus Clusters 4 and 5 (Fig. 1C).

The seed-to-voxel FC maps for each cluster for the OFC, striatum, and thalamus were functionally segmented into cognitive, affective, and motor functions (Supporting Information Figs. S2–S4). For example, among diverse cortico-striatal loops [Lawrence et al., 1998], the FC maps to dorsal caudate (striatum Cluster 2) and to ventral striatum (striatum Cluster 5) corresponded with the spatial loop and the affective loop, respectively. Between-group comparisons (Fig. 2) revealed a reduction in FC between the central OFC (Cluster 1) and dorsomedial striatum as well as an increased FC between the medial thalamus (Cluster 5) and several striatal areas. The patients exhibited increased FC between the ventral striatum (Clusters 3 and 5) and the medial PFC but reduced FC between the dorsal caudate (Cluster 2) and parietal cortex. The patients also exhibited increased and decreased FC between the dorsal caudate (Cluster 2) and the dorsolateral PFC (DLPFC) and medial PFC, respectively, and increased and decreased FC between the ventral putamen (Cluster 3) and the inferior and middle frontal cortices and parietal cortex, respectively. We also provide between-group comparison maps for other clusters as Supplements (Supporting Information Figs. S5–S7).

Brain-Behavior Associations

Significant correlations between total Y-BOCS scores and λ were observed at 0.17, 0.18, and 0.19 sparsity (r -/ P -value = $-0.276/0.036$, $-0.296/0.024$, and $-0.306/0.020$, respectively). However, these associations disappeared after correction for multiple comparisons.

DISCUSSION

This study is one of the largest investigations of FC so far to use unmedicated OCD patients who experience limited other mental health problems. Additionally, this is the first study to utilize multiple complementary measures of functional network topology and inter-regional connectivity in an rs-fMRI investigation to comprehensively characterize disruptions in FC architecture within the OFST circuit of OCD. Consistent with previous findings on medicated patients [Harrison et al., 2009, 2013], our results confirmed the OFST dysconnectivity hypothesis. That is, OCD is associated with functional network alterations between the frontal cortex and striatum, with increased FC between ventral striatum and mPFC and decreased FC between the central OFC and dorsomedial striatum. More

Figure 1.

Results of connectivity-based parcellation and network analysis. This figure shows results of connectivity-based parcellation for each region and of group differences in small-world network properties and inter-regional connectivity. (A) The 3D rendering and axial view of functionally segmented clusters for each of the orbitofrontal cortex, striatum, and thalamus. (B) Results of graph theoretical analysis including normalized clustering coefficient (γ), normalized characteristic path length (λ), and small-worldness (σ). The x-axis is the sparsity threshold. * indicates

significant group differences at $P < 0.05$ uncorrected. The q -value is an FDR-adjusted P -value. (C) Results of the network-based-statistic. Red indicates group differences in functional connection between clusters of orbitofrontal and of striatal areas; blue in connection between those of striatal areas; and green in connection between those of striatal and of thalamic areas. OFC, orbitofrontal cortex; ST, striatum; THAL, thalamus; c, Cluster. [Color figure can be viewed at wileyonlinelibrary.com.]

TABLE II. Hubs in the orbitofronto-striato-thalamic network of controls and patients

Area ^a	Normalized betweenness centrality ^b		Unadjusted <i>P</i> -value	FDR-adjusted <i>P</i> -value
	Controls (<i>n</i> = 61)	Patients (<i>n</i> = 61)		
Striatum Cluster 3	1.580	1.237	0.021 ^c	0.179
Striatum Cluster 5	1.529	1.464	0.460	0.460
Thalamus Cluster 2	1.292	1.088	0.176	0.414
Thalamus Cluster 4	1.280	1.545	0.104	0.295
Striatum Cluster 2	1.208	1.663	0.009 ^c	0.153
Orbitofrontal cortex Cluster 2	1.164	1.154	0.377	0.414
Striatum Cluster 6	1.136	0.867	0.103	0.295
Orbitofrontal cortex Cluster 1	1.017	0.932	0.307	0.414
Striatum Cluster 1	0.958	0.823	0.299	0.414
Orbitofrontal cortex Cluster 4	0.885	0.996	0.277	0.414
Thalamus Cluster 5	0.842	1.160	0.053	0.225
Striatum Cluster 4	0.837	0.788	0.390	0.414
Thalamus Cluster 3	0.824	0.724	0.292	0.414
Orbitofrontal cortex Cluster 5	0.798	0.711	0.377	0.414
Striatum Cluster 7	0.669	0.718	0.340	0.414
Orbitofrontal cortex Cluster 3	0.510	0.724	0.047 ^c	0.225
Thalamus Cluster 1	0.472	0.407	0.319	0.414

^aRegions are listed in descending order of normalized betweenness centrality in controls.

^b**Bold** indicates the hub regions ($b_i > 1.5$) for each group.

^cRegions showing significant differences between controls and patients ($P < 0.05$).

specifically, our results extended prior findings by showing altered FC between the medial thalamus and striatum as well as altered OFST network organization including disruptions in small-world parameters and betweenness centrality in the lateral OFC and ventral striatum.

Altered Network Properties in the OFST Network of OCD

Despite the common small-world topology, the patients exhibited a decrease in the values of global network measures over multiple sparsity levels compared with the controls. In addition, the normalized characteristic path length of the patients was negatively correlated with symptom severity. These findings suggest loss of optimal balance between functional integration and segregation in the OFST network of OCD patients according to their symptom severity. Although it is inconsistent, previous OCD studies reported abnormalities in the small-world network characteristics, showing an increased clustering coefficient in the top-down control network of patients [72% medicated; Zhang et al., 2011] and decrease in clustering coefficient and small-worldness in the whole-brain network of unmedicated patients [Shin et al., 2014]. As such, these discrepant findings may reflect the effects of medication, which were well controlled in the current study.

We also identified hubs in the OFST network. Hubs are crucial for efficient communication in a complex network [Bassett and Bullmore, 2006]. Two hubs for each group were identified in this study: the ventral striatal areas (striatum

Clusters 3 and 5) for the controls and the dorsal caudate (striatum Cluster 2) and anterior thalamus (thalamus Cluster 4) for the patients. These hubs are considered to be the major sites that receive input from the cerebral cortex and the basal ganglia system [Alexander et al., 1986]. The betweenness centrality of the patients significantly increased in dorsal caudate (striatum Cluster 2) and lateral OFC (OFC Cluster 3) but significantly decreased in ventral putamen (striatum Cluster 3) at $P < 0.05$ uncorrected. Interestingly, these regions exhibiting group differences were compatible with the regions belonging to the lateral OFC circuit that was proposed by Alexander et al. [1986]. The lateral OFC circuit is strongly linked to OCD [McClure, 2012; Menzies et al., 2008]. Although there was not a direct match between the present parcellation and the previously defined cytoarchitectonic divisions of the OFC, the lateral OFC was labeled as areas 47/12 in the system of Ongür et al. [2003]. The lateral OFC modulates the influence of emotional information on emotion regulation, judgment, and decision-making via the inhibition or interference of unwanted stimuli [Hooker and Knight, 2006].

Altered Functional Connectivity in the OFST Network of OCD

NBS analyses revealed two aberrant FC components in the OFST network of patients. The first component exhibited decreased connectivity and was composed of several striatal clusters and central OFC (OFC Cluster 1), which is mapped onto area 13l (the central part of the OFC) in the system of Ongür et al. [2003]. The second component

Figure 2.

Results of seed-to-voxel functional connectivity. This figure shows within-group and between-group comparison results of seed-to-voxel functional connectivity with clusters showing group differences in node centrality or connectivity between pairs of subdivisions within the circuit. (A) For within-group maps with each subdivision, green represents regions showing

significant functional connectivity in controls; red in patients; and yellow represents the spatial overlap between two groups. (B) For between-group comparison maps, green represents regions where functional connectivity was decreased in patients, while red represents regions where connectivity was increased in patients. [Color figure can be viewed at wileyonlinelibrary.com.]

exhibited increased connectivity and was composed of anterior and medial thalamus (thalamus Clusters 4 and 5) and ventral and dorsal caudate (striatal Clusters 1, 2, and 5). Previous OCD studies have demonstrated that there is not only abnormal regional activity in the lateral and central parts of the OFC, the ventral and dorsomedial striatum (which encompass striatum Clusters 5 and 6), and medial thalamus but that there is also altered functional interactions between these regions [Harrison et al., 2009; Jung et al., 2014; Menzies et al., 2008]. These findings emphasize the crucial roles that these regions play in the pathophysiology of OCD. The lateral and central OFC areas, including areas 13l and 47/12, receive and integrate information from diverse sensory modalities and regulate stimulus-response associations and outcome-based decision-making in conjunction with the striatum [Carmichael and Price, 1995; Gourley et al., 2013; Reading et al., 1991]. Thus, altered FC between these regions may be involved in

the cognitive inflexibility of OCD patients due to problems in updating stimulus-response associations [Gu et al., 2008].

Between-group comparisons on seed-to-voxel FC revealed increased FC between the ventral striatum (striatum Clusters 3 and 5) and the medial PFC in patients, which agrees with previous findings [Harrison et al., 2009]. Consistent with the NBS results, patients exhibited decreased FC between the central OFC (OFC Cluster 1) and the dorsomedial striatum and increased FC between the medial thalamus (thalamus Cluster 5) and striatal areas.

Implications for Dysconnection Hypothesis of OCD

Recent optogenetic rodent studies have reported a causal relationship between abnormalities in the OFC-striatum pathways and OCD-like behavior (i.e., grooming) [Ahmari

et al., 2013; Burguière et al., 2013]. Ahmari et al. [2013] observed that the repeated hyperactivation of the ventromedial OFC to ventromedial striatum projections produces OCD-like behavior, whereas Burguière et al. [2013] found that the selective stimulation of the lateral OFC to dorsomedial striatum pathway can alleviate repetitive behaviors in a genetic model of compulsive behaviors. It is suggested that these opposing effects may depend on the interaction between specific targeted subdivisions in the OFC-striatum projection system. Consistent with these opposing effects, in our previous study we observed that during resting-state, patients' Y-BOCS scores were positively correlated with the FC strength between the ventral striatum and the medial OFC, while these scores were negatively correlated with the FC strength between the ventral striatum and lateral areas of the OFC [Jung et al., 2013]. According to the existing literature, the medial OFC is engaged to process positive valence (reward) and valuation [Elliott et al., 2000; Kable and Glimcher, 2007; O'Doherty et al., 2001], while the lateral OFC processes negative valence (punishment) and behavioral inhibition in a motivational context [Ursu et al., 2008]. Taken together, disrupted information exchange between the central OFC and dorsomedial striatum may be reflected by decreased FC between these two regions, suggesting that OC symptoms may result from the failures of inhibition, mediated by an interaction between these two regions. Furthermore, given that corticostriatal loops originate in the frontal cortex and project to the basal ganglia and finally to the thalamus [Tekin and Cummings, 2002], the disruption of FC between the OFC and striatum may subsequently result in that of FC between the striatum and thalamus. Future research is needed to confirm this hypothesis.

Limitations and Methodological Considerations

The present study has several methodological considerations that should be noted. First, though all patients were drug-free for at least 4 weeks, the history of medication exposure may be a possible confounder. Thus, we further investigated whether there were significant differences between the 25 drug-naïve patients in our study and 36 medication-free patients. This additional analysis revealed no significant group differences in any measures from GTA and NBS analyses, except for normalized BC (b_i) showing an increase in striatum Cluster 3 and a decrease in striatum Cluster 7 and thalamus Cluster 1 in drug-naïve patients relative to medication-free patients ($P < 0.05$, uncorrected; refer to Supporting Information Table S1). Thus, we cannot fully rule out the confounding effect of medication on our results; however, it does not appear to have impacted our main findings. Second, although this study focused on the connections among the OFC, striatum, and thalamus due to the limited spatial resolution of fMRI, the corticostriatal loops typically thought to be involved in OCD also include direct and indirect

pathways between other subcortical regions such as the globus pallidus, substantia nigra, and subthalamic nucleus. However, the anatomical definition of these subcortical structures is especially challenging, even when performed manually. Third, the issue of proper imaging duration to perform stable FC estimates may be of concern. While previous RSFC studies used data obtained for 5–7 minutes based on Van Dijk et al. [2010] study, recent studies have demonstrated improvements in FC estimates by increasing the scan duration to greater than 10 minutes [Anderson et al., 2011; Birn et al., 2013]. However, increasing the scan duration can lead to the increase of head motion that influences RSFC. Finally, while the majority of previous studies have used existing anatomical atlases (e.g., AAL atlas) to define the nodes for the network and connectivity analyses, we used nodes derived from connectivity-based segmented clusters, which allowed us to estimate the FC of each ROI at a finer level with increased functional homogeneity within each node (Supporting Information Figs. S2–S4, and S8).

In summary, using a multilevel FC approach in one of the largest sample sizes of unmedicated OCD patients, the present study revealed changes in the intrinsic functional network architecture of the OFST circuit in OCD patients. These findings suggest that the manifestation of OCD is due, at least in part, to altered network organization in this circuit, including reduced functional integration, and disruptive functional coupling, particularly among the lateral and central OFC, ventral and dorsomedial striatum, and medial thalamus. Based on recent finding showing the effect of pharmacological treatment on network properties [Shin et al., 2014], our results may aid in the identification of biomarkers to improve treatment for OCD and of treatment response.

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