Abnormal small-world architecture of top–down control networks in obsessive–compulsive disorder

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Background: Obsessive–compulsive disorder (OCD) is a common neuropsychiatric disorder that is characterized by recurrent intrusive thoughts, ideas or images and repetitive ritualistic behaviours. Although focal structural and functional abnormalities in specific brain regions have been widely studied in populations with OCD, changes in the functional relations among them remain poorly understood. This study examined OCD–related alterations in functional connectivity patterns in the brain's top–down control network. **Methods:** We applied resting-state functional magnetic resonance imaging to investigate the correlation patterns of intrinsic or spontaneous blood oxygen level–dependent signal fluctuations in 18 patients with OCD and 16 healthy controls. The brain control networks were first constructed by thresholding temporal correlation matrices of 39 brain regions associated with top–down control and then analyzed using graph theory-based approaches. **Results:** Compared with healthy controls, the patients with OCD showed decreased functional connectivity in the posterior temporal regions and increased connectivity in various control regions such as the cingulate, precuneus, thalamus and cerebellum. Furthermore, the brain's control networks in the healthy controls showed small-world architecture (high clustering coefficients and short path lengths), suggesting an optimal balance between modularized and distributed information processing. In contrast, the patients with OCD showed significantly higher local clustering, implying abnormal functional organization in the control network. Further analysis revealed that the changes in network properties occurred in regions of increased functional connectivity strength in patients with OCD. **Limitations:** The patient group in the present study was heterogeneous in terms of symptom clusters, and most of the patients with OCD were medicated. **Conclusion:** Our preliminary results suggest that the organizational patterns of intrinsic brain activity in the control networks are altered in patients with OCD and thus provide empirical evidence for aberrant functional connectivity in the large-scale brain systems in people with this disorder.

Introduction

Obsessive–compulsive disorder (OCD) is a relatively common, chronically disabling neuropsychiatric disorder with an average lifetime prevalence of 2%–3%.[1] This disorder is characterized by thoughts and ideas that are recurrent, intense and intrusive, which are often accompanied by urges to perform repetitive, ritualistic behaviours.[2] Cognitive behavioural models incorporating the symptoms and psychology of OCD posit a dysfunction of inhibitory control systems.[3] Neuropsychological

studies have demonstrated OCD–related abnormalities during various control tasks, such as motor inhibition and cognitive flexibility.[4,5] Neuroimaging studies of OCD have also reported focal abnormalities in many brain regions associated with the top–down control system, such as the anterior prefrontal cortex (APFC),[6] dorsolateral prefrontal cortex (DLPFC),[6–8] cingulate cortex,[9,10] insula,[6] parietal regions[10,11] and thalamus.[12–14] Despite these advances, however, very few studies directly examined OCD–related changes in functional integrity of the brain's control system.

In this study, we used resting-state functional connectivity magnetic resonance imaging (rs-fcMRI)[15] to investigate changes in topological organization in intrinsic or spontaneous brain activities in top–down control networks in patients with OCD. This imaging method measures the synchronization in slow blood oxygen level–dependent (BOLD) signal fluctuations (typically < 0.1 Hz)[15] between different brain regions during rest. These low-frequency oscillations in BOLD signal are vital for the study of brain function since they are generally thought to reflect intrinsic or spontaneous neuronal activity in the absence of specific external stimuli.[16] Recent advances in graph theoretical analysis of rs-fcMRI data have allowed us to map the topological organization of these spontaneous brain functional networks under normal and pathologic conditions.[17,18] It is worthy to mention that Dosenbach and colleagues[19] conducted 10 different control tasks on 183 human participants and identified a large set of brain regions (*n* = 39), mainly involving the frontal and parietal regions, cingulate cortex, thalamus and cerebellum (Appendix 1, available at cma.ca/jpn). Using rs-fcMRI and graph theoretical analysis, Dosenbach and colleagues[20] further demonstrated that the top–down control network of the healthy brain follows a small-world network structure[21] characterized by dense local clustering and short path lengths between regions, which is suggestive of a highly segregated and integrative connectivity pattern in the large-scale brain system. Very recently, 2 rs-fcMRI studies have demonstrated that resting-state functional connectivity pattern in the brain's control networks changes with normal development[22] and during pediatric Tourette syndrome.[23] Yet no studies reported OCD–related changes in topological organization of functional connectivity in the top–down control network.

We hypothesized that patients with OCD would show abnormal functional connectivity and small-world attributes in the brain's top–down control networks. To test our hypothesis we used rs-fcMRI to construct the brain's control networks in patients with OCD and healthy controls and then conducted a graph theoretical analysis. Using these approaches, we sought to determine whether patients with OCD show alterations in functional connectivity among the brain regions within the control network and in small-world network parameters in the top–down control network.

Methods

Participants

We recruited patients with OCD from the Mental Health Center, West China Hospital, Sichuan University, Chengdu, China. They fulfilled DSM-IV criteria for OCD, as diagnosed using the Structured Clinical Interview for DSM-IV Axis I disorders.[24] Patients were diagnosed by 2 experienced psychiatrists (Y.Y. and B.L.) and had no relevant neurologic diseases (e.g., brain tumour, epilepsy), history of significant head injury, alcohol or drug abuse, mental retardation or other major psychiatric diseases. Specifically, no patients in this study met the criteria for major depressive disorder, Tourette syndrome or other tic-related conditions. We used the Yale–Brown Obsessive Compulsive Scale (Y–BOCS) and a clinician-rated Yale-Brown Obsessive Compulsive Scale symptom checklist to assess disease severity and to characterize the clinical expression of OCD.[25] In addition, we used the 17-item Hamilton Rating Scale for Depression (HAM-D[26]) and the Hamilton Anxiety Rating Scale (HARS[27]) to rate the severity of depressive and anxiety symptoms in the patients with OCD.

We recruited age- and sex-matched heathy controls from the local community by poster advertisement, and we screened them using the Structured Clinical Interview for the DSM-Non-Patient edition (SCID-NP)[28] to confirm the lifetime absence of psychiatric and neurologic illness. There was no history of psychiatric illness in the controls or any of their first-degree relatives. No gross abnormalities were observed for any of the participants when brain magnetic resonance images (T_1- and T_2-weighted images) were inspected by an experienced neuroradiologist (Q.Y. and S.L.). All participants gave written informed consent, and the institutional ethical review board of West China Hospital, Sichuan University approved this study.

Image acquisition and preprocessing

We acquired all images using a 3.0 T GE scanner (EXCITE, General Electric) with an 8-channel phase array head coil. Resting state BOLD images of the whole brain were acquired using a gradient-echo echo-planar imaging (EPI) sequence in 30 axial slices: repetition time (TR) 2000 ms, echo time (TE) 30 ms, flip angle 90°, slice thickness 5 mm (no slice gap), matrix 64 × 64, field of view (FOV) 240 × 240 mm². We obtained T_1-weighted structural images using a 3-dimensional spoiled gradient echo recall (SPGR) sequence for each participant: TR 8.5 ms, TE 3.4 ms, flip angle 12°, slice thickness 1.0 mm, FOV 240 × 240 mm². During the MRI scan, we instructed all participants to lie quietly awake with their eyes closed (confirmed by participants immediately after the experiment) and to move as little as possible. Each functional run contained 200 image volumes. The rs-fcMRI time was 6 minutes and 40 seconds, and the total acquisition time of the MRI scan was about 20 minutes.

All rs-fcMRI preprocessing was carried out using the SPM5 package (www.fil.ion.ucl.ac.uk/spm). To allow for magnetization equilibrium, we discarded the first 10 images. For each participant, the remaining 190 EPI images were subjected to slice-timing correction, realigned to the first image in the first series and then subsequently unwarped to correct for susceptibility-by-movement interactions. We obtained the time course of head motions by estimating the translations in each direction and the rotations in angular motion about each

axis for each of the 190 consecutive volumes. All the participants included in this study exhibited a maximum displacement of less than 1.5 mm at each axis and an angular motion of less than 1.5° for each axis. All the realigned images were further spatially normalized to the Montreal Neurological Institute (MNI) EPI template in SPM5, resampled to $3 \times 3 \times 3$ mm^3 and smoothed with a 4-mm full-width at half-maximum Gaussian kernel. Finally, the data were temporally band-pass filtered (0.01–0.1 Hz; http//resting-fmri.sourceforge.net) to reduce the effects of low-frequency drift and high-frequency noise.

Definition of region of interest

Thirty-nine regions of interest (ROIs) with 12-mm diameters[19] were created around centre of mass coordinates previously identified from cross-study analysis of task-control signals. These ROIs have been recently used in several rs-fcMRI studies.[20,22,23]

Measurement of interregional functional connectivity

For each of the 39 ROIs, we obtained a representative time series by averaging the time series of all voxels within that ROI. Several sources of spurious variances arising from estimated head-motion profiles and global signal activity were further removed by multiple linear regression analysis.[29] To measure functional connectivity among regions, we computed the Pearson correlation coefficients between every possible pair of regional residual time series, yielding a correlation matrix (39×39) for each participant (Appendix 1).

Graph theoretical approaches

Network construction
To construct the brain's control networks, we thresholded individual correlation matrices (obtained above) into undirected binarized graphs (networks). To avoid the differences in correlation levels between the OCD and control groups, we employed sparsity, (S; defined as the existing number of edges in a graph divided by the maximum possible number of edges) instead of correlation coefficients as threshold metrics. Setting a sparsity-specific threshold ensures that the graphs of both groups have the same number of edges or wiring cost.[30–32] In this study, we computed the network properties over a wide range of sparsity ($0.10 \leq S \leq 0.50$) in which small-world parameters could be properly estimated and the number of spurious edges was minimized, as indicated in previous studies.[33,34]

Small-world analysis
Small-world models can be characterized by the clustering coefficient C_p and the characteristic path length L_p,[21] which quantify the extent of interconnectivity of a network at local and global levels, respectively. Here, we used a "harmonic mean" distance measure to compute the L_p since it considers more than one component in a graph.[35] To test the small-world properties of the control networks, the values of C_p and L_p were compared with those of 100 degree-matched random networks ($\gamma = C_p/C_p^{rand}$ and $\gamma = L_p/L_p^{rand}$ with C_p^{rand} and L_p^{rand} de-

noting the mean C_p and L_p of 100 random networks). Typically, a network could be considered small-world if it met the following conditions: > 1 and ~1.[21]

Statistical analysis

Differences in functional connectivity
To determine whether the correlations between regions were significantly nonzero across participants, we performed 1-sample t tests in an element-by-element manner on Fisher's transformed correlation matrices in both the OCD and control groups. To account for the multiple comparisons, a false discovery rate (FDR) procedure[36] was performed at a q value of 0.05. Furthermore, we analyzed functional connectivity differences between the OCD and control groups in 2 different ways. First, as in previous studies,[20,22] we selected the 75 strongest positive connections from each group and visualized these in graphs. This process makes the 2 groups of networks have the exact same number of nodes and connections, ensuring that any differences among graphs would reflect topological changes rather than low-level correlation differences. Second, we performed further direct comparisons using 2-tailed 2-sample t tests on the significant nonzero connections in the OCD or control groups.

Differences in network parameters
We performed statistical comparisons between groups using 2-tailed 2-sample t tests over a wide range of S ($0.10 \leq S \leq 0.50$). In addition, we evaluated the areas under the curves of these metrics as the summarized measures of the networks over a preselected range of S and then conducted Student t tests.

Whole-brain network analysis

In addition to the specific top–down control network, we also investigated the topological organization of the whole-brain network in patients with OCD and healthy controls. The network construction and characteristics involved have been described previously.[37] Briefly, the brain was first parcellated into 90 ROIs (45 for each hemisphere) using Automated Anatomical Labeling.[38] The mean time series of each region was then acquired by averaging the time series of all voxels within that region. The following preprocessing and graph theoretical analyses were similar to those previously described for the control networks.

Results

Demographic and clinical characteristics

Eighteen patients with OCD and 16 age- and sex-matched healthy controls participated in this study. According to clinical dimensions, we found that the patients with OCD were categorized as follows: symmetry/ordering, $n = 2$; hoarding, $n = 3$; contamination/cleaning, $n = 5$; aggressive/checking, $n = 7$; and sexual/religious, $n = 1$. Five of the patients were drug-naïve, 10 were prescribed selective serotonin reuptake inhibitors and 3 were prescribed clomipramine.

Table 1 summarizes the demographic and clinical characteristics of both the OCD and control groups. There were no significant differences in the distributions of age ($t_{32} = -0.48$, $p = 0.64$), sex ($\chi^2_1 = 0.036$, $p = 0.85$), years of education ($t_{32} = -0.28$, $p = 0.78$) and handedness between the groups. The mean Y-BOCS total score for the OCD group indicated that the patients were in the moderate range of OCD severity.

Interregional functional connectivity in the control networks

Among the 75 strongest positive connections in both groups, there were 58 overlapping edges and 17 group-specific connections, as shown in Figure 1. Visual examination indicated that a considerable proportion of the OCD–related increases in functional connections were short-range, whereas the OCD–related decreases in connections were mainly associated with different lobes (i.e., long-range connections, especially between the frontal and temporal lobes, and the frontal and parietal lobes). Further comparisons of connections with nonzero connectivity strength revealed significant between-group differences in the connections between various regions (Table 2 and Fig. 2). For instance, compared with the controls, patients with OCD showed decreased positive correlations between the left APFC and left posttemporal and between the left posttemporal and left anterior fusiform, and increased positive correlations between many pairs of brain regions, including the midcingulate–postcingulate, fronto–thalamus, intraparietal sulcus–precuneus, cingulate–temporal and cerebellum–cerebellum. Additionally, we noted several abnormal negative correlations in patients with OCD (Appendix 2, available at cma.ca/jpn).

Small-world top–down control networks

Using graph theoretical approaches, we further investigated the topological properties of the brain top–down control networks in patients with OCD and healthy controls. The small-world network parameters (normalized clustering coefficient, γ, and normalized shortest path length, λ) were computed as a function of network sparsity, S. As expected, both groups

demonstrated small-world network architecture over a wide range of sparsity ($0.10 \leq S \leq 0.50$) as they had an almost identical path length ($\lambda \approx 1$) but were more locally clustered ($\gamma > 1$)
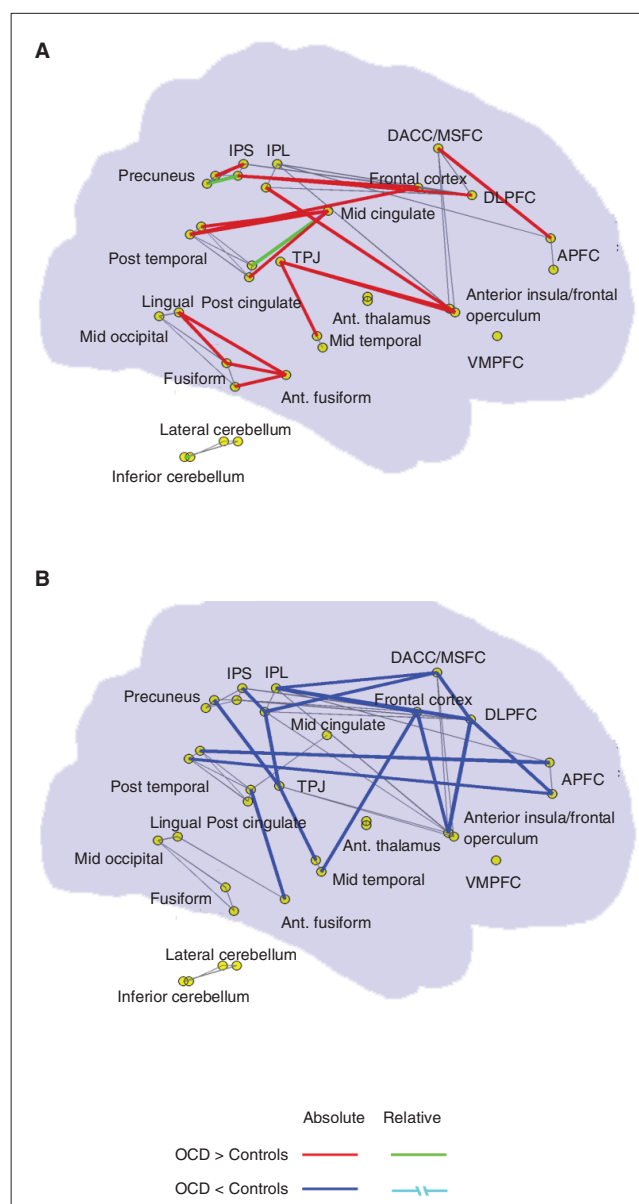

Fig. 1: An anatomic representation of the 75 strongest positive connections in (**A**) patients with obsessive–compulsive disorder (OCD) and (**B**) control groups mapped onto sagittal views of a transparent brain. The red and blue lines highlight those connections only existing in either OCD or control groups (i.e., absolute difference). Green lines highlight those connections present in both groups but with significant between-group differences in connection strengths (i.e., relative differences). Gray lines represent those connections present in both groups but without significant between-group differences. APFC = anterior prefrontal cortex; DACC/MSFC = dorsolateral anterior cingulate cortex/medial superior frontal cortex; DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; IPS = intraparietal sulcus; TPJ = temporo-parietal conjunction; VMPFC = ventral medial prefrontal cortex.

Table 1: Demographic and clinical characteristics of OCD and control groups

Characteristic	Group; mean (SD)*	
	OCD, $n = 18$	Control, $n = 16$
Age, yr	23.3 (5.0)	24.1 (5.4)
Sex, no. male:female	14:4	12:4
Handedness, no. right:left	18:0	16:0
Education, yr	13.6 (3.0)	13.9 (2.6)
Illness duration, yr	4.7 (3.7)	
Total Y–BOCS severity score (range 16–33)	24.0 (5.7)	
HARS score	7.5 (1.9)	
HAM-D score	9.2 (2.2)	

OCD = obsessive–compulsive disorder; HAM-D = Hamilton Rating Scale for Depression;[26] HARS = Hamilton Anxiety Rating Scale;[27] SD = standard deviation; Y–BOCS = Yale–Brown Obsessive Compulsive Scale.[25]
*Unless otherwise indicated.

in comparison with the matched random networks (Fig. 3).

Despite the regime of small-worldness in both groups, patients with OCD showed significant changes in the small-world network parameters compared with controls. As shown in Figure 3A, we found that both γ and λ of patients
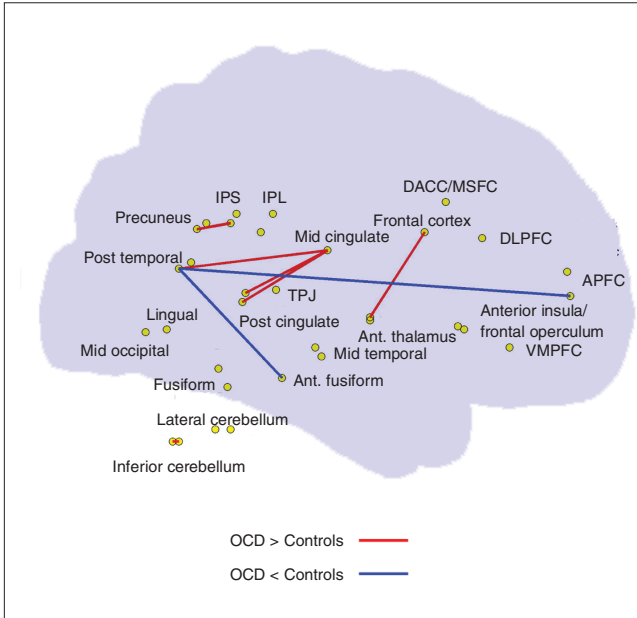

Fig. 2: Significant differences in interregional positive correlations between patients with obsessive–compulsive disorder (OCD) and controls. Compared with the controls, the patients with OCD showed increased (red lines) and decreased (blue lines) positive correlations in several brain regions associated with top–down control. Both left- and right-hemispheric regions are placed on a transparent brain to aid with visualization. APFC = anterior prefrontal cortex; DACC/MSFC = dorsolateral anterior cingulate cortex/medial superior frontal cortex; DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; IPS = intraparietal sulcus; TPJ = temporoparietal conjunction; VMPFC = ventral medial prefrontal cortex.
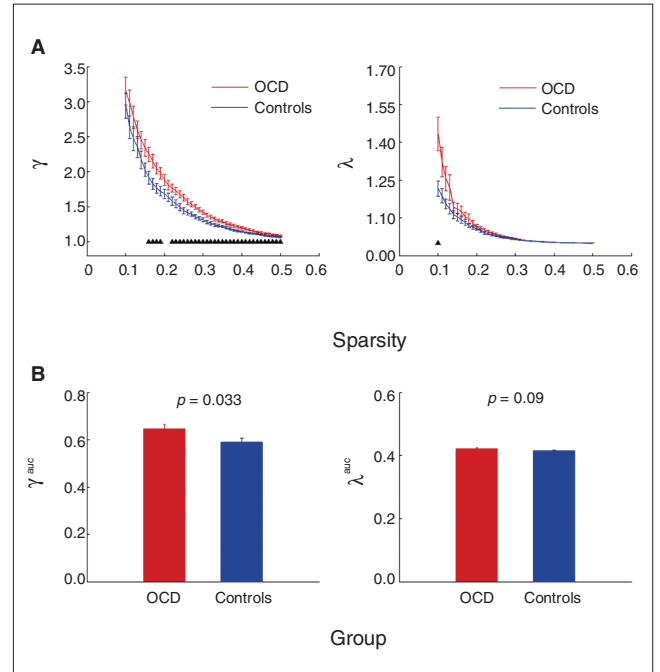

Fig. 3: Small-world top–down control networks in healthy controls and patients with obsessive–compulsive disorder (OCD). (**A**) The graph shows significant between-group differences in the normalized clustering coefficient (γ, C_p^{real}/C_p^{rand}; left panel) as a function of sparsity thresholds. Blue lines represent the controls and red lines represent the OCD group. Black triangles indicate significant (*t* test, $p < 0.05$) differences between the 2 groups. There were no significant between-group differences in the normalized shortest path length (λ, L_p^{real}/L_p^{rand}; right panel) at most sparsity values (besides at a sparsity of 0.10). Of note, both networks have $\gamma > 1$ and $\lambda \approx 1$, which implies prominent small-world properties in the top–down control networks. (**B**) The bars show significant differences ($p = 0.033$) in the area under the γ curves (γ^{auc}) (left panel) between the controls (blue bars) and OCD patients (red bars). There were no significant differences ($p = 0.09$) in the area under the λ curves (λ^{auc}; right panel) between the 2 groups.

Table 2: Abnormal functional connectivity in patients with OCD*

Correlation; brain regions	Group; mean (SD) correlation *r*		*t* value	*p* value	Distance
	Control	OCD			
Decreased positive correlation in OCD					
Left posttemporal and left anterior fusiform	**0.193 (0.166)**	0.037 (0.206)	2.306	0.028	51.740
Left posttemporal and left anterior prefrontal cortex	**0.293 (0.267)**	0.087 (0.294)	2.114	0.042	129.869
Increased positive correlation in OCD					
Midcingulate and left postcingulate	**0.247 (0.189)**	**0.469 (0.193)**	−3.395	0.002	34.554
Right frontal cortex and right anterior thalamus	0.010 (0.206)	**0.193 (0.211)**	−2.586	0.014	45.486
Midcingulate and right postcingulate	**0.278 (0.219)**	**0.432 (0.179)**	−2.289	0.029	32.016
Right intraparietal sulcus and left precuneus	**0.271 (0.163)**	**0.404 (0.212)**	−2.115	0.042	40.571
Midcingulate and left posttemporal	0.135 (0.272)	**0.320 (0.238)**	−2.096	0.044	63.537
Right inferior cerebellum and left inferior cerebellum	0.337 (0.310)	**0.545 (0.204)**	−2.079	0.046	37.054

OCD = obsessive–compulsive disorder; SD = standard deviation.
*The *r* values indicate Pearson correlation coefficients of the resting state blood oxygen level–dependent (BOLD) signal between regions in either the patients with OCD or controls. Correlation coefficients in bold indicate significant interregional association of resting state BOLD signal within group ($p < 0.05$, false discovery rate [FDR]–corrected). The *t* and *p* values showed significant differences in correlation between the 2 groups ($p < 0.05$, uncorrected). Note that pairs of regions were only listed if they met the following criteria: they were significantly nonzero in either the OCD group, control group, or both at $p < 0.05$ (FDR–corrected), and they showed significant between-group differences at $p < 0.05$ (uncorrected). The table shows the changes in positive correlations in the OCD group. For changes in negative correlations, see Appendix 2, available online at cma.ca/jpn.

with OCD were larger than those of the controls. Further statistical comparisons revealed significant between-group differences in the γ values over a wide range of sparsity ($0.16 \leq S \leq 0.50$), and differences in the λ values at $S = 0.10$ ($p = 0.008$). Moreover, patients with OCD exhibited a significantly ($t_{32} = 2.22$, $p = 0.033$) larger area under the γ curves. There were no significant differences in area under the λ curves between the groups, although there was a smaller increased trend ($t_{32} = 1.73$, $p = 0.09$; Fig. 3B). This combination of significantly increased γ with slightly changed λ indicates a tendency for the large-scale brain control system in patients with OCD to shift toward a more regular organization, implying abnormalities of small-world network characteristics. Finally, we demonstrated that the increase in the area under the γ curve is significantly correlated ($r = 0.46$, $p = 0.006$) with increases in mean functional connectivity that are mainly associated with short-range functional connections (Appendix 3, available at cma.ca/jpn).

Small-world whole-brain functional networks

Several previous studies of rs-fcMRI have shown that the small-world topology demonstrated in the whole-brain functional network in healthy participants[33,39] is significantly altered in conditions such as Alzheimer disease[40] and schizophrenia.[41] We found no significant between-group differences in the small-world parameters for the whole brain networks, even though both groups displayed significant small-world properties. This result suggests that OCD may be mainly associated with disruptive integrity of the specific brain control system rather than of the whole-brain network.

Discussion

To our knowledge, this is the first study to demonstrate OCD–related changes in functional connectivity patterns in the brain's control network using rs-fcMRI. Compared with controls, the patients with OCD not only showed abnormalities in functional connectivity among the brain's control regions, but also exhibited topological alterations in the control network characterized by abnormal small-world parameters. Taken together, these results strongly suggest that OCD is associated with disruptive functional integrity in the large-scale brain control system, thus providing new insights into the understanding of the pathophysiology of this disorder.

Abnormal small-world architecture in the control networks in OCD

Both the OCD and control groups displayed a small-world topology in the brain's control networks, which was consistent with a previous fMRI study.[20] The small-world model was introduced by Watts and Strogatz,[21] and has made a tremendous impact on the studies of complex brain networks (for a review, see Bullmore and Sporns[17]). The 2 main features of a small-world topology, high clustering and short paths, refer to a dense local clustering or cliquishness and a small number of connections between any pair of regions. High clustering en-

sures functionally segregated processing, whereas short paths ensure effective integrity and the rapid transfers of information between distant brain regions that are thought to constitute the basis of cognitive processes. Thus, when the human brain is taking part in a top–down control task, the coexistence of functional segregation and integration facilitates the effective integration of multiple segregated sources of information.[42,43]

Although both groups exhibited small-world topology in their brains' control networks, those in the OCD group had significantly larger clustering coefficients (γ), suggesting a disturbance in the organization of the control network and a shift toward a more regular organization. This result was similar to our recent finding in patients with attention-deficit/hyperactivity disorder.[44] It has been suggested that regular lattices reduce signal propagation speed and synchronizability across distant regions compared with small-world networks.[45] Therefore, the alterations in the small-world attributes observed here may reflect a less optimal topological brain network organization in patients with OCD. Interestingly, we also found that the changes in γ were correlated with increased positive correlations in connections that are mainly short-ranged. The abnormalities in the short-range connections could be the predominant contributors to the alterations of topological organization in the top–down control network. Of note, Vul and colleagues[46] suggest that the correlations between brain activation and personality measures could be greatly inflated because of nonindependent analysis error in fMRI studies, such as cognitive neuroscience and clinical neuroscience. However, there is larger debate about the effect size of correlation. Lieberman and colleagues[47] argued that whatever inflation does exist may be far more modest. Such correlations in neuroscience may reflect meaningful biological relations when valid multiple comparisons procedures are applied in a reasonable sample size. In this study, we did not observe significant changes in the small-world organization in the whole-brain system in patients with OCD, suggesting that the disorder could mainly be associated with disruptive integrity in the brain control network. This result provides further support for our recent finding that the topological organization of specific brain functional clusters cannot be captured by computing network properties on a whole-brain scale.[48]

Abnormal intrinsic functional connectivity in OCD

In addition to the above-mentioned abnormalities in network attributes in patients with OCD, We also observed interregional correlation changes. Decreased positive correlations in the OCD group were located in the APFC/posttemporal and posttemporal/fusiform connections. The APFC plays a vital role in integrating the outcomes of 2 or more separate higher cognitive tasks.[49] Using fMRI, Remijnse and colleagues[6] reported reduced APFC activity in patients with OCD during affective switching. Using structural MRI, Narayan and colleagues[50] showed a thicker posterior temporal gyrus in patients with OCD. They argued that the structural abnormalities might underlie poor neuronal connectivity, which in turn could affect information integration and cognitive functions in patients with OCD.

We found increased positive correlations in patients with OCD mainly in the cingulate cortex (middle cingulate cortex MCC/posterior cingulate cortex [PCC]), frontal–thalamic circuit and cerebellum. The MCC is vital in response selection during fear avoidance, whereas the PCC plays a role in personal visuospatial orientation, self-relevance assessment and episodic memory processes.[51] Recent studies have demonstrated that patients with OCD exhibit excessive activation in the PCC during errors of commission and high-conflict trials[9] and increased grey matter concentration in both the MCC and PCC that was positively correlated with variability in stop-signal task performance (response inhibition).[10] A diffusion tensor imaging study has also shown OCD-associated increases in fractional anisotropy (a measure of the directional diffusivity of water) in the cingulum bundles linking the PCC and MCC,[52] which provides support for our finding of increased functional correlations between the 2 regions. Other studies have shown that patients with OCD have greater activation in the frontal cortex during planning tasks,[53] higher glucose metabolism and grey matter concentration in the thalamus[13,14] and higher fractional anisotropy in the anterior limb of the internal capsule (the final pathway for all higher cognitive feedback loops connecting the frontal lobe and the thalamus).[54] Thus, increased frontal–thalamus connectivity in patients with OCD observed here are consistent with previous studies, which provides further support for the presence of abnormal frontal–striatal–thalamic–cortical circuitry in patients with OCD.[55,56] We also found increased positive correlations in 2 parietal regions (intraparietal sulcus and precuneus) and in the cerebellum, compatible with previous studies.[12,14,57]

An interesting finding was that the increased positive correlations in patients with OCD were mainly associated with short-range connections (i.e., segregation), whereas decreases in correlations were associated with long-range connections (i.e., integration). Previous studies have suggested that OCD is a developmental disorder that is usually accompanied by recurrent, intense and intrusive thoughts or ideas accompanied by a delay or inefficiency of synaptic pruning in brain regions.[2,58] Using rs-fcMRI, Fair and colleagues[22] showed that children have a larger proportion of short-range functional connections in the brain's control system, which decreases with age. In contrast, long-range connections tend to increase in strength with age. Another developmental disorder study by Church and colleagues[23] showed that in adolescents (10–15 years of age) with Tourette syndrome, the patterns of resting state functional connectivity in the brain's control network resembled those in children (7–9 years of age). Thus, our preliminary results of increased short-range connections and decreased long-range connections in patients with OCD may provide new evidence for the delay or disruption of segregated and integrative processing in the brain's control system, which might help to understand the defect in the inhibition of unwanted thoughts and behaviours observed in populations with this disorder. Further study with larger samples and more representative younger patients is necessary to confirm these preliminary findings.

In this study, we also observed altered negative correlations in patients with OCD, which were predominately involved in the frontal, inferior parietal lobule, dorsolateral anterior cingulate cortex/medial superior frontal cortex and anterior insula/frontal operculum regions. Although the phenomenon of negative correlations of spontaneous brain activity has been frequently observed in healthy participants,[29] it remains unclear as to what they precisely reflect. It is worthy to note that there has been controversy regarding a definitive source of negative correlations. Murphy and colleagues[59] suggested that global signal regression during rs-fcMRI data preprocessing is most likely the cause of negative correlations. However, Fox and colleagues[60] showed that various characteristics of negative correlations are not determined by global regression. Moreover, the removal of global signals could reduce the effect of physiologic artifacts and facilitate the observation of true physiologic relations. Of note, a previous structural MRI study[57] showed that patients with OCD had abnormal negative correlations between the grey matter volumes of cortical and subcortical structures. Based on these findings, we speculated that the abnormal negative correlations in patients with OCD might be of physiologic significance. Further studies still need to be conducted to clarify biological mechanisms of altered negative correlations in populations with OCD.

Limitations

Several methodologic issues need to be further addressed. First, head motion of participants during the scans may have affected our results. Recently, Salvador and colleagues[61] showed that the residuals of head motion were associated with the functional connectivity of brain regions predominantly at high frequency (0.17~0.25 Hz), but there were no strong correlations with that at middle (0.08~0.17 Hz) and low (< 0.08 Hz) frequencies. When analyzing the head motions of participants, we did not observe significant differences between the 2 groups or correlations with network parameters. Second, we reported uncorrected results for between-group analysis in functional connectivity (Table 2). We found that the results were not significant after a multiple comparison correction ($p > 0.05$, FDR–corrected). However, we still reported the uncorrected results and thus these results could be considered exploratory in nature. To further increase statistical power, future studies need to be conducted by using a large sample of patients with OCD or by selecting a limited number of ROIs. Third, the patient group in the present study is heterogeneous in terms of symptom clusters. A previous fMRI study[12] suggested that different OCD symptom dimensions could have distinct neural mechanisms. In the future, it would be interesting to investigate whether patients with different OCD symptoms show distinct connectivity patterns in the top–down brain control network. Fourth, in the present investigation, most of the patients with OCD (13 of 18) were medicated, thus we cannot completely rule out the possibility that our results were influenced by drug effects. However, it has been noted previously that brain abnormalities involving brain structure,[54] function[62] and metabolism[63] in patients with OCD were gradually restored and tended to normalize after treatment

with selective serotonin reuptake inhibitors. Further investigations using large, drug-naïve samples or longitudinal studies are warranted to confirm our preliminary results of intrinsic or spontaneous changes in brain function. Fifth, in this study, the participants were scanned during rest. It is generally thought that resting is a natural state in which participants are not performing any specific demanding tasks. However, we cannot completely rule out the possibility that the patients with OCD have experienced pervasive intrusive thoughts during the scan, thereby affecting our results of functional analysis. Of note, this is a common question for rs-fcMRI studies in populations with neuropsychiatric diseases. Finally, the top–down brain control network studied here includes only 39 regions. It could be further extended to contain more regions, such as the orbitofrontal cortex and striatal regions, which have been found to exhibit OCD–related abnormalities.[6,11]

Conclusion

In the present study, we used rs-fcMRI and graph theoretical approaches to show that patients with OCD have abnormal intrinsic functional connectivity in the brain's control network, thus providing novel insights into the understanding of the underlying pathophysiology of OCD. Future studies combining rs-fcMRI with structural MRI and diffusion MRI techniques will be vital to explore how the functional changes shown here are associated with structural alterations, and whether these changes could be used to characterize different clinical subtypes, disease progressions and medication effects in patients with OCD.

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