The Effects of Pharmacological Treatment on Functional Brain Connectome in Obsessive-Compulsive Disorder

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Background: Previous neuroimaging studies of obsessive-compulsive disorder (OCD) have reported both baseline functional alterations and pharmacological changes in localized brain regions and connections; however, the effects of selective serotonin reuptake inhibitor (SSRI) treatment on the whole-brain functional network have not yet been elucidated.

Methods: Twenty-five drug-free OCD patients underwent resting-state functional magnetic resonance imaging. After 16-weeks, seventeen patients who received SSRI treatment were rescanned. Twenty-three matched healthy control subjects were examined at baseline for comparison, and 21 of them were rescanned after 16 weeks. Topological properties of brain networks (including small-world, efficiency, modularity, and connectivity degree) were analyzed cross-sectionally and longitudinally with graph-theory approach.

Results: At baseline, OCD patients relative to healthy control subjects showed decreased small-world efficiency (including local clustering coefficient, local efficiency, and small-worldness) and functional association between default-mode and frontoparietal modules as well as widespread altered connectivity degrees in many brain areas. We observed clinical improvement in OCD patients after 16 weeks of SSRI treatment, which was accompanied by significantly elevated small-world efficiency, modular organization, and connectivity degree. Improvement of obsessive-compulsive symptoms was significantly correlated with changes in connectivity degree in right ventral frontal cortex in OCD patients after treatment.

Conclusions: This is first study to use graph-theory approach for investigating valuable biomarkers for the effects of SSRI on neuronal circuitries of OCD patients. Our findings suggest that OCD phenomenology might be the outcome of disrupted optimal balance in the brain networks and that reinstating this balance after SSRI treatment accompanies significant symptom improvement.

Key Words: Connectivity, graph-theory, OCD, resting state fMRI, SSRI, treatment

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder typically associated with recurrent thoughts and repetitive behaviors (1). Without effective treatment, OCD patients experience substantial distress and impairment within social and occupational settings (2). It is recently thought that abnormal functional connectivity in the neurocircuitry comprising frontal-subcortical and parietal regions might underlie the illness, contributing to the formation of OCD symptoms (3–8).

Selective serotonin reuptake inhibitors (SSRI) are commonly used to treat OCD. Selective serotonin reuptake inhibitor treatment has been associated with various brain changes, such as reducing functional activity in the fronto-subcortical regions (9–13), decreasing thalamic volume (14), and increasing neuronal viability in frontal regions (15), according to previous longitudinal neuroimaging studies of OCD. However, the underlying therapeutic mechanism of SSRI on the functional neural circuitry of OCD patients remains controversial, owing to differences in the imaging techniques, analytic methods, and cognitive tasks employed. Furthermore, most previous studies are limited in examining changes in focal brain activity. Because the human brain is an interacting complex network with nontrivial topological properties (16–19), it is essential to examine the whole-brain functional networks of drug-free OCD patients before and after SSRI treatment to understand the pathophysiology and improve the treatment of this disorder. This might provide vital information that contributes to the establishment of reliable biomarkers of treatment response to SSRI and, more generally, results in better diagnostic practice and more individualized therapeutic strategies for patients.

When a person is at rest, the brain dynamically engages in a distinctive pattern of neural activity. Connectivity analysis of resting-state functional magnetic resonance imaging (rs-fMRI) suggests the brain functional system is composed of highly coherent spontaneous blood oxygen level dependent (BOLD) fluctuations among brain regions that subserve a specific function, such as motor (20,21), auditory (22), visual (21), language (23), default-mode (24), and attention system (25). The structure of the human brain ensures optimal balance between functional segregation and integration among these functional systems to facilitate real-time integration of information across segregated brain regions (26). This balance is central for the operation of distributed networks underlying cognitive function (27). An emerging focus is the disruptions in balance of the brain networks, which manifest in changed functional interactions between regions, circuits, and system (28) in disease states. Network-based analysis with graph theory has attracted growing interests for quantitatively investigating the topological features of the coherent brain activities during

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resting-state. With this approach, recent studies have uncovered significant properties underpinning the functional organization of the human brain, namely small-worldness (18,19,29), high efficiency at a low wiring cost (30,31), modular architecture (32,33), and highly connected hubs (19).

Small-worldness, modularity, and nodal connectivity degree measures are of particular importance in a neurobiological context, exploring local and global connectivity structure (34). The connectivity degree of a node evaluates strength of a node, indicating the impact of individual nodes on the overall functioning of the network (34). The measures of clustering and modularity demonstrate how well functionally specialized subsystems are segregated from each other in the network (26,35). Measure of shortest paths that link each node pair expresses the capacity of network nodes from different modules to cooperate and enable network-wide integration (26,35). Changes in these topological properties might reflect fragmentation or breakdown of the optimal balance in the human brain (36).

Topologies of a brain vary with aspects of a disorder, thus offering remarkable clinical implications. Prior neuroimaging studies have found disrupted small-world organization, modular architecture, and regional characteristics in the brains of people with numerous neuropsychiatric disorders, such as Alzheimer's disease (37) and schizophrenia (29). Such disruptions are also associated with cognitive and behavioral disturbances arising from disorders (31,33,36). Recent functional connectivity studies with rs-fMRI in OCD patients have identified that disturbances are predominantly associated with frontoparietal regions in the brain (7,8); however, only one study (8) used a graph-theory approach, and no study has examined rs-fMRI in OCD before and after treatment. Therefore, exploring the brain functional networks of drug-free OCD patients before and after SSRI treatment can provide new insights into the nature of the disorder and a basis for charting disease improvement after treatment.

We hypothesized that OCD disrupts functional balance in the organization of intrinsic brain networks, and the alterations would be most apparent in the frontoparietal regions. The effects of SSRI treatment would be conspicuous in medication-free OCD patients at the different levels of functional systems to restore the impaired balance in the brain networks. To test our hypothesis, we measured functional connectivity on the basis of the temporal correlation of regional BOLD signals with rs-fMRI. Brain functional networks were constructed with a graph-theory approach. Various aspects of topological properties such as small-worldness, modularity, and regional connectivity degree were computed for the networks to observe relevant alterations and treatment effects in the OCD group compared with healthy control subjects (HCs). Relationships between changes in topological properties and symptom improvement after treatment were also examined.

Methods and Materials

Subjects

We recruited 25 OCD patients (9 drug-naïve and 16 unmedicated) from the OCD clinic at Seoul National University Hospital and 25 comparison subjects matched for sex, age, IQ, and handedness via internet advertisement. No significant differences with regard to age, education, or mean IQ were found between the two groups (Table 1). The detailed inclusion and exclusion criteria are described in Supplement 1. We used the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to assess OCD symptom severity. The Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) were used to rate the severity of depressive and anxiety symptoms, respectively. After completion of clinical assessments and baseline fMRI scans, 20 patients with OCD received the routine outpatient treatment at OCD Clinic of Seoul National University Hospital. They received pharmacological treatment with SSRI for 16-weeks (escitalopram, range 10–60 mg/day). Two of these patients were concomitantly medicated with clonazepam. None of the patients was engaged in cognitive behavioral therapy or psychoanalytic psychotherapy during the study period. After 16-weeks, of the enrolled subjects, 17 patients and 21 HCs participated in the follow-up fMRI scans (Figure S1A in Supplement 1). The Clinical Global Impression-Severity and -Improvement scales were used to evaluate symptom severity and improvement, respectively, after treatment. The mean interval between the two fMRI scans was 120.9 (SD, 16.1) days for OCD patients and 120.7 (SD, 22.9) days for HCs.

Table 1. Demographic and Clinical Characteristics of the Subjects at Baseline and Follow-Up

	Baseline			Follow-up		
Variable	HCs (n = 23)	OCD[a] (n = 25)	p	HCs (n = 21)	OCD (n = 17)	p
Age (yrs)	26.9 (5.5)	26.3 (6.2)	.35	26.0 (5.3)	26.4 (6.0)	.23
Gender (M/F)	13/10	17/8	.41	11/10	12/5	.25
Handedness (R/L)	19/4	21/4	.9	19/2	16/1	.68
IQ	114.5 (10.2)	111.6 (8.6)	.35	113.2 (11.0)	112.4 (9.6)	.44
Education (yrs)	15.8 (2.2)	14.4 (2.7)	.14	15.4 (1.7)	14.3 (2.2)	.11
Age of Onset (yrs)		17.4 (5.9)			16.6 (6.0)	
Duration of Illness (yrs)		8.9 (6.6)			9.9 (6.8)	
Y-BOCS Score						
Obsessive		15.8 (2.5)			11.3 (4.3)	
Compulsive		14.3 (2.5)			10.0 (3.6)	
Total		30.1 (4.7)			21.2 (7.6)	
HAM-D Score		10.7 (5.3)			6.8 (5.6)	
HAM-A Score		11.3 (7.2)			7.2 (6.2)	

Data are given as mean (SD).

HCs, healthy control subjects; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Rating Scale for Depression; M/F, male/female; OCD, obsessive-compulsive disorder; R/L, right/left; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a]Nine patients were drug-naïve, and 16 patients were unmedicated for more than 4 weeks.