ARCHIVAL REPORT

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.

The OCD patients had mean illness duration of 9.8 years (SD, 6.8). One patient scored over 17 on the HAM-D self-report, but no patient met criteria for major depressive disorder by SCID I. Six patients had comorbid depressive disorder not otherwise specified, and three patients had comorbid dysthymic disorder. The remaining 16 patients were not diagnosed with any comorbid Axis I or II disorders (SCID II) (38). The study was approved by the Institutional Review Board of Seoul National University Hospital. Written informed consent was obtained from all subjects after the procedures had been fully explained.

Image Acquisition and Preprocessing

Resting-state BOLD images of the whole-brain were acquired on a 3.0 T scanner (Siemens Magnetom Trio, Erlangen, Germany) with echo-planar imaging sequence. Each functional run contained 116 image volumes. The parameters were: echo time = 30 msec, repetition time = 3.5 sec, flip angle = 90°, matrix size = 128 × 128, field of view = 24 × 24 cm, voxel dimensions = 1.9 × 1.9 × 3.5 mm, slice thickness = 3.5 mm, and .7 mm slice gap. During the scan, we instructed all participants to keep their eyes closed without falling asleep and to move as little as possible. All rs-fMRI images were preprocessed with the SPM8 package (www.fil.ion.ucl.ac.uk/spm). After discarding the first four images, we subjected the remaining echo-planar imaging images to slice-timing correction, realignment, spatial normalization, and smoothing procedures. The criterion for excessive head motion was spatial movement > 1 voxel (3 mm) in any direction. Two HCs were excluded at baseline for excessive head motion. Statistical tests confirmed that the remainder of the participants demonstrated no significant group differences in the head-motion parameters. Then, the REST toolkit (39) (http://www.http://restfmri.net/forum/) was used to remove the linear trend of time courses and for temporal band-pass filtering (.01–.08 Hz). The estimated head-motion profiles and global signal activity were also removed to eliminate sources of spurious variance. Further details are provided in Supplement 1.

Brain Network Construction

A total of 142 functionally defined regions of interest covering the whole-brain were adopted from a previous study conducted by Dosenbach *et al.* (40) Functional connectivity among regions was measured by computing the Pearson correlation coefficient for every possible pair of regional residual time series, producing a continuously-weighted network G (142 × 142) for each subject (Figure S1B in Supplement 1). For the constructed brain networks, we calculated small-world parameters (including clustering coefficient, path length, small-worldness, local and global efficiencies), modular characteristics (including modularity, intra- and inter-modular connectivity), and regional connectivity degree (i.e., the sum of all connectivity strength within a node) to examine both global and regional topological characteristics. For small-world analysis, we used sparsity threshold S to define small-world regime ($.08 \leq S \leq .48$). Each small-world attribute was compared with those of 100 random networks, and the area under the curve (AUC) was calculated for statistical comparison. For modular and degree analyses, the normalized positive correlation map ($r > 0$, where r is Pearson correlation coefficient) for each participant was used. See Supplement 1 for the detailed analytic procedures and the formulas.

Clinical Symptom Correlation

The percentage changes in the clinical scales (Y-BOCS, HAM-D, HAM-A, and the illness-duration scalar) and the percentage changes in the graph-theory parameters (the AUC of each small-world attribute, modular characteristic, and connectivity degrees of each node) that showed either significant baseline between-group differences or significant within-group differences in OCD patients were taken for the Pearson correlation analysis. The Bonferroni correction was applied to account for multiple testing.

Statistical Analysis

Before computation, multiple linear regression analyses were applied to remove the confounding effects of age and gender for each graph-theory parameter. Then, we performed 1000 iterations of permutation tests to determine significant between- and within-group differences in graph-theory parameters. Briefly, between-group differences in network parameters were measured with the nonparametric permutation test, whereas residual differences in network parameters between baseline and follow-up were computed for a one-sample permutation test to assess longitudinal differences within each group. A threshold of .05 was used to confirm significance.

Results

Treatment Response

After 16 weeks, OCD patients who were treated with SSRI showed significant clinical improvement compared with their baseline assessments (Table S1 in Supplement 1). The Y-BOCS scores decreased significantly, by 30.4% ± 23.2%, and five patients showed a >50% reduction in the Y-BOCS score ($p < .001$). Significant reductions in Clinical Global Impression-Severity, HAM-D, and HAM-A scores were also observed in OCD patients at follow-up ($p < .001$).

Changes in Small-World Properties

The whole-brain networks of both OCD patients and HCs at baseline and follow-up demonstrated small-world network architecture over a small-world regime sparsity range. However, the statistical analyses showed that, at baseline, OCD patients exhibited significantly decreased AUC values in small-world efficiency (including local clustering coefficient [$p = .002$], small-worldness [$p = .005$], and local efficiency [$p = .01$]) relative to HCs (Figures 1A–D).

After 16-weeks of treatment with SSRI, small-world efficiency increased significantly (Figure 1D) in OCD patients and showed no significant difference compared with HCs. No significant changes in network parameters were observed in HCs between baseline and follow-up.

Changes in Modular Structures

At baseline, five functionally oriented modules were identified in the brain networks of HCs (Figure 2A): default-mode, sensorimotor, occipital, cingulo-opercular, and frontoparietal (for details, see Supplement 1). In OCD patients, however, the brain regions that had been associated with the two distinct default-mode and frontoparietal modules in HCs were clustered to form a single module, resulting in four functional modules in the whole-brain network (Figure 2B): sensorimotor, occipital, cingulo-opercular, and a combined module consisting of default-mode and frontoparietal.

Although statistically nonsignificant, reduced modularity in the brain networks of OCD patients compared with those of HCs was observed at baseline (−6.9%), and this difference decreased after

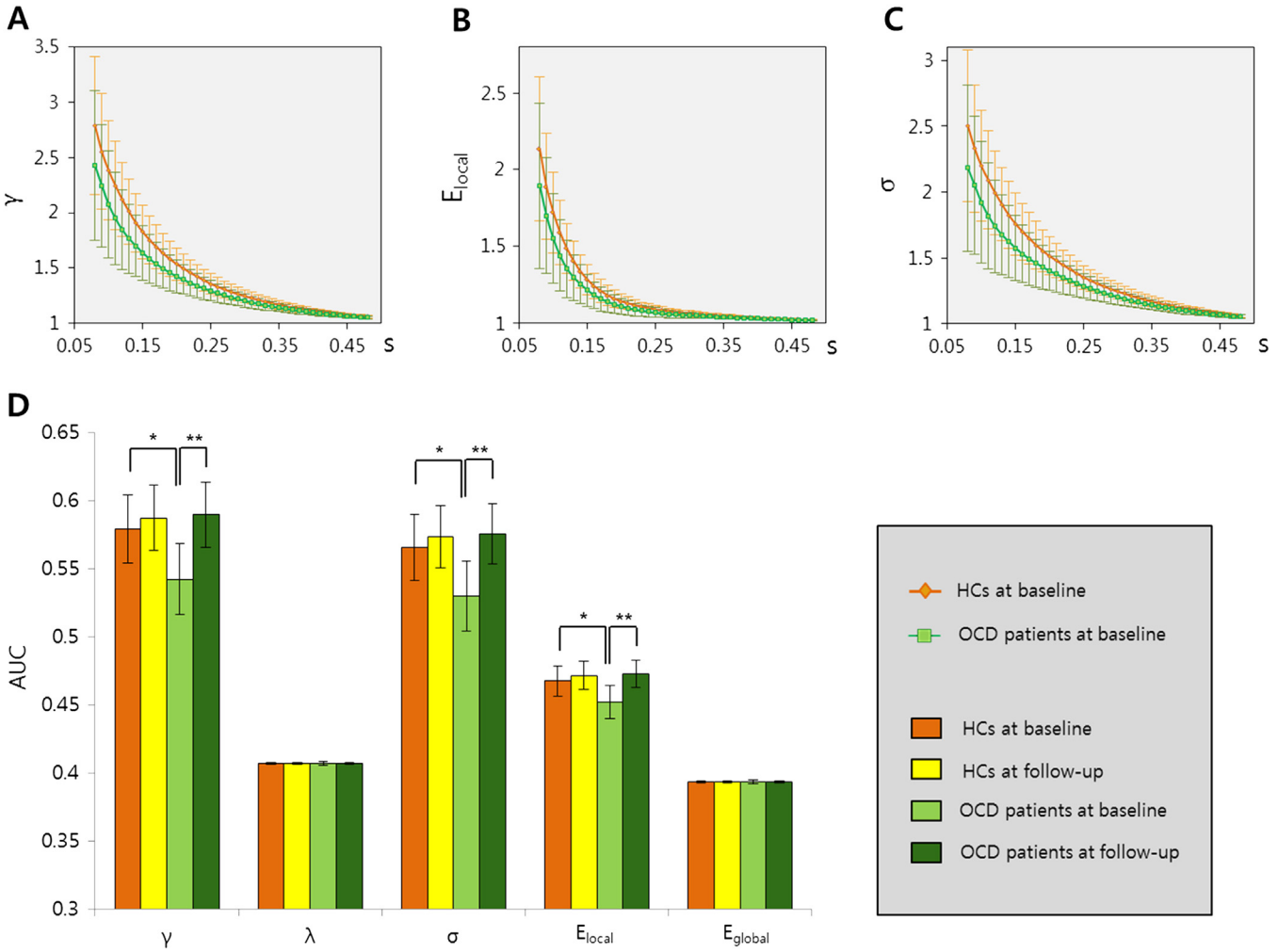

Figure 1. Small-world whole-brain networks in healthy control subjects (HCs) and obsessive-compulsive disorder (OCD) patients. The graphs **(A–C)** show normalized mean **(A)** clustering coefficient, **(B)** local efficiency, **(C)** small-worldness in the HCs and OCD patients at baseline. **(D)** The bars showed between- and within-group differences in the area under the curves (AUC). The OCD patients showed significantly decreased clustering coefficient ($p = .002$), small-worldness ($p = .005$), and local efficiency ($p = .01$). After selective serotonin reuptake inhibitor treatment, clustering coefficient ($p = .004$), small-worldness ($p = .008$), and local efficiency ($p = .01$) in OCD patients increased significantly. Error bars correspond to SD of each parameter. For cross-sectional analyses, HCs ($n = 23$) and OCD patients ($n = 25$) at baseline and HCs ($n = 21$) and OCD patients ($n = 17$) at follow-up were included. For longitudinal analyses, HCs ($n = 19$) and OCD patients ($n = 17$) were included. E_{global}, normalized global efficiency; E_{local}, normalized local efficiency; γ, normalized clustering coefficient (C_p^{real}/C_p^{rand}); λ, normalized characteristic path length (L_p^{real}/L_p^{rand}); s, sparsity threshold; σ, normalized small-world (γ/λ). *$p < .05$, with permutation test; **$p < .05$, with paired permutation test.

treatment (−3.4%) (Figure S3A in Supplement 1). The networks of OCD patients demonstrated reduced intra-modular connectivity in the frontoparietal module at baseline ($p = .011$), and this was significantly normalized at follow-up ($p = .009$) (Figure S3B in Supplement 1). Additionally, a reduction in inter-modular connectivity between the occipital and frontoparietal modules in the OCD group was observed at baseline ($p = .018$), whereas enhanced inter-modular connectivity was found between the sensorimotor and cingulo-opercular modules at follow-up ($p = .017$) (Figure S3C in Supplement 1).

Changes in Regional Connectivity Degrees

We investigated connectivity degree changes of each brain region and its associated module defined by Dosenbach in HCs and OCD patients before and after treatment. Compared with HCs, OCD patients showed changed nodal connectivity degrees in brain regions associated with the default-mode, sensorimotor, occipital, and cingulo-opercular modules at baseline (Figure 3A). At follow-up, no significant between-group differences in nodal connectivity degrees were noted. Further paired permutation test revealed that HCs showed significant changes in the nodal connectivity degrees of several regions in the default-mode and sensorimotor modules between baseline and follow-up (Figure 3B); however, no statistical trend (i.e. increasing or decreasing) distinguishing these degree changes was observed. The OCD patients, by contrast, showed a coherent SSRI treatment effect of increasing nodal degrees within the frontoparietal module (Figure 3C) (for details, see Supplement 1).

Clinical Symptom Correlation

The correlation analysis revealed a strong negative correlation between the percentage connectivity degree changes in the right ventral frontal cortex (rvFC) and the percentage changes in all obsession, compulsion, and total scores on the Y-BOCS (Bonferroni

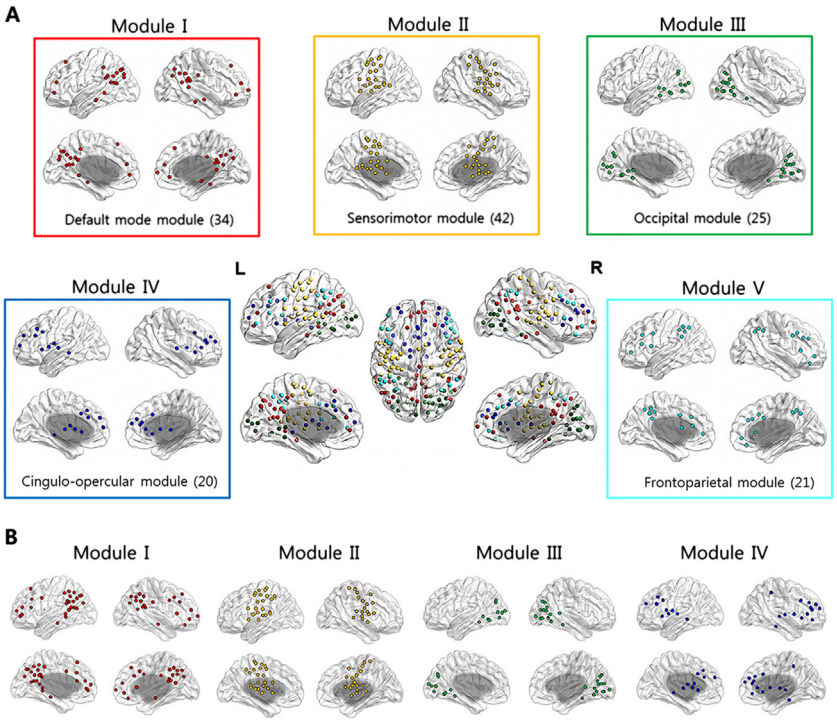

Figure 2. Modular organization of the brain functional network in both healthy control subjects and obsessive-compulsive disorder patients at baseline. **(A)** The five functionally interconnected modular structures in brain network of healthy control subjects at baseline: default-mode (Module I), sensorimotor (II), occipital (III), cingulo-opercular (IV), and frontoparietal (V). **(B)** The four modules identified in obsessive-compulsive disorder patients at baseline, corresponding to a combined module consisting of default-mode and frontoparietal modules (Module I), sensorimotor (II), occipital (III), and cingulo-opercular (IV).

corrected, $p < .05/19 = .0026$) (Figure S5 in Supplement 1). No correlation between the percentage changes in clinical scales and the percentage changes in small-world and modular parameters was found.

Discussion

To our knowledge, this is the first longitudinal study investigates that disrupted optimal balance between functional integration and segregation in drug-free patients with OCD could be restored after SSRI treatment. Our results suggest that the functional brain networks of OCD patients are characterized by deviant topological properties at both the global and local scales before pharmacotherapy, most apparently in the frontoparietal regions. These deviances reflect disturbances in the brain network balance. Along with symptom improvement, the normalizations in topological properties that indicate the retrieval of the functional balance were observed after SSRI treatment.

Abnormal Small-World Networks in OCD

The human brain is a dynamically interconnected functional system with economical small-world architecture (29). In the present study, we used small-world attributes to investigate the global topological characteristics in OCD patients before and after treatment. Compared with HCs, OCD patients exhibited significantly reduced small-world efficiency at baseline. These anomalies suggest impaired functional segregation but spared functional integration in the organization and information processing within the whole-brain network of OCD patients. Abnormal segregation has also been observed in the functional and structural networks of individuals with schizophrenia (41,42) and Alzheimer's disease (37). The abnormal small-world properties observed in OCD patients indicate a breakdown of optimal topological organization of the functional networks of the brain. After treatment, we observed both symptom improvement and significant amelioration of these anomalies. Most functional neuroimaging studies of OCD report both baseline deficits and treatment effects in localized brain regions. Zhang *et al.* (8) emphasized that OCD is related to local small-world network abnormality rather than to disturbance in the whole-brain small-world network. Direct comparisons between that study and our current analysis are impossible, because some of the OCD patients included in Zhang's study were receiving medication at the time of their participation. Our results might explain the finding by Zhang of no between-group differences in the whole-brain small-world attributes when patients were treated with SSRI. Furthermore, the present study proposes that drug-free OCD patients exhibit imbalance in whole-brain functional network systems and that these can be reversed by SSRI treatment.

Disturbances in Modular Architecture of OCD

The modular structure of the brain demonstrates tighter links among nodes in the same module and sparser connections between nodes in different modules (32). This structure provides a balance between functional segregation and integration. Changes in the modular structure were found in people with synesthesia (43), Alzheimer's disease (44), schizophrenia (41), and normal aging (33,45). Our results showed that HCs represent five modules that are compatible with those found in previous studies (18,32,33,40). By contrast, OCD patients demonstrated reduced frontoparietal intra-modular connectivity and less functionally segregated brain modular organization, especially in the default-mode and frontoparietal modules, at baseline. Dissociable functions of detecting salient events and maintaining attention and executive functions involve the frontoparietal module (46–49), whereas states of rest and reflection involve the default-mode module (50–52). Recently, Stern *et al.* (7) reported reduced anti-correlation between regions within the two networks, whereas Zhang *et al.* (8) proposed increased short-range and decreased long-range connections within frontoparietal regions in partially medicated OCD patients during rest. Our findings

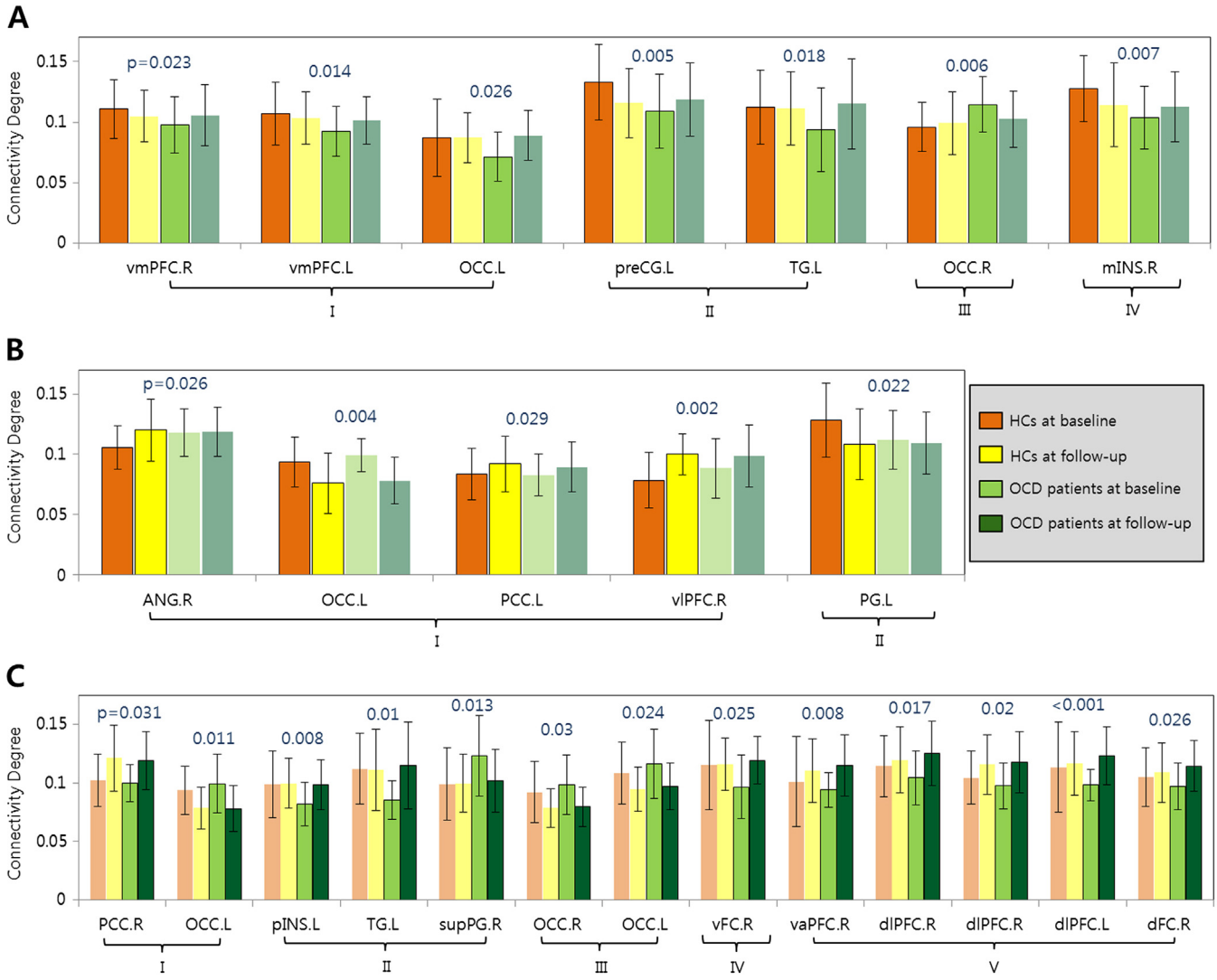

Figure 3. Brain regions showing significant differences in regional connectivity degree between- and within-group (see Figures S4A–D in Supplement 1 for the complete version). **(A)** The graph represented the significant differences ($p < .05$) in the regional degrees between obsessive-compulsive disorder (OCD) patients and healthy control subjects (HCs) at baseline by permutation test. **(B)** The brain regions that showed significant within-group differences ($p < .05$) in HCs between baseline and follow-up by paired permutation test. **(C)** The graph illustrated brain regions that showed significant within-group differences in OCD patients before and after selective serotonin reuptake inhibitor treatment with paired permutation test. The outlined bars demonstrate significant between- or within-group differences, whereas transparent bars are supplemental. For cross-sectional analyses, HCs ($n = 23$) and OCD patients ($n = 25$) at baseline and HCs ($n = 21$) and OCD patients ($n = 17$) at follow-up were included. For longitudinal analyses, HCs ($n = 19$) and OCD patients ($n = 17$) were included. The bar represents the mean values and the error bar represents SDs. The p values are denoted above the bars of each region. The associated module of each brain region defined from modular structure of HCs is shown below the x-axis. I, Default-mode; II, Sensorimotor; III, Occipital; IV, Cingulo-opercular; V, Frontoparietal; ANG, angular gyrus; dFC, dorsal frontal cortex; dlPFC, dorsolateral prefrontal cortex; L, left hemisphere; mFC, middle frontal cortex; mINS, middle insula; OCC, occipital; PCC, posterior cingulate cortex; PG, parietal gyrus; pINS, posterior insula; preCG, precentral gyrus; R, right hemisphere; supPG, superior parietal gyrus; TG, temporal gyrus; vaPFC, ventral anterior prefrontal cortex; vFC, ventral frontal cortex; vlPFC, ventralateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

expand both works by proposing that drug-free OCD patients demonstrate a network-level loss of functional segregation between the two networks and reduced intraregional connectivity within frontoparietal module. These abnormities could form the basis of the inability of OCD patients to disengage from reverberating internal stimuli, which further propagates to executive function deficits in patients. After 16 weeks of pharmacotherapy, no significant between-group differences in intra/inter modular connectivity were observed between OCD patients and HCs, indicating network-wide improvement after successful treatment.

Flexibility of Regional Connectivity Degree

The connectivity degree of a node quantifies weighted connections to all other nodes (strength), thereby indicating the role of individual elements in the whole network (34). Before pharmacotherapy, decreases in nodal connectivity degree were found in several brain regions within the default-mode, sensorimotor, and occipital modules of OCD patients. After 16 weeks of SSRI treatment, the regional connectivity degree changed in effects of both time and drug treatment. It is likely that these changes in subjects arise from the re-organization of the brain network to maintain the most functionally stable state at the time

of fMRI scan. Prior studies have shown that changes in neuronal connectivity entail homeostatic mechanisms for functional balance (53). Although patterns of functional connectivity between brain regions are highly responsive to perturbations, such as sensory input or cognitive tasks, these changes do not affect global topological stability (54,55). Moreover, these changes occur within hundreds of milliseconds. The current result shows that, on a much longer timescale of months, regional connectivity flexibly reconfigures to account for internal and external dynamics while preserving the stability of whole-brain functional system, as reflected in the stable small-world and modular characteristics of HCs between baseline and follow-up. The longitudinal analysis of data from HCs revealed no trends in connectivity degree changes; however, OCD patients demonstrated pronounced pharmacotherapy effects of increasing degree within the frontoparietal module. Previous longitudinal studies of OCD have also pointed out that effects of treatment were associated with increased neuronal viability (15), lower activation, and metabolic decreases in frontal-subcortical and parietal-cerebellar regions (9–11,56). Thus, our results raise the possibility that enhanced connectivity degree in frontoparietal regions might underlie the different therapeutic changes in the same area where changes have been detected by previous studies. Nonetheless, the relationship between changes in regional connectivity and variations in neural activity needs to be substantiated.

In this study, improvement in symptoms was negatively correlated with connectivity degree changes in the rvFC. Previous studies suggested that the rvFC is involved in reorienting attention toward salient sensory stimuli (25) and in response to errors and that OCD patients showed greater activation in the region during error commission (57,58). Thus, improvements in obsessive-compulsive symptoms after pharmacotherapy might be involved with reduced activity of the rvFC, serving to ease compulsive behaviors by abating the failure of patients to shift attention from obsessive thoughts that stem from a constant feeling of erroneous. However, this finding should be interpreted with caution, because no abnormality in the rvFC was observed in OCD patients at baseline.

Clinical Implication of Functional Network Analysis in the Treatment of OCD Patients

From a network perspective, the current findings provide a conceptualization of OCD as a network disease, impairment in the normal balance of brain networks. With a recent shift of view toward looking at psychiatric disorders as dysfunctions that lie on the brain network-level during resting-state, the role of medication in modulating the brain networks is largely unexplored area. The current study gives the first investigation of alterations in resting-state functional networks after the short-term SSRI treatment of medication-free OCD patients with various network measures. These measures provided convergent results, showing that SSRI treatment normalized OCD-related abnormal frontoparietal network connectivity and impaired segregation in the whole-brain functional network. Each network measure in the present study assessed different levels of topological features to address the effects of both illness and treatment. The connectivity degree of each region can be highly informative about not only how individual regions respond differently to various factors but also how these changes impact the overall functioning of the network. Small-worldness and modularity are attractive models to characterize the brain, because the attributes support a structural substrate for two fundamental organizational principles of the brain: functional segregation; and functional integration (36). Segregation and integration capture different dimensions of how neural information is distributed and integrated (59). High segregation means having many specialized communities (59). High integration means having information stream both within and between communities (e.g., the involvement of multiple brain regions in higher-level cognition and consciousness) (59). The high level of complexity of the brain is realized when these two principles are jointly expressed (59). Consonant with the present study, there is increasing evidence that perturbations in the balance between functional segregation and integration are associated with system-wide alterations in the structural and functional connectivity in different disease states, which might offer new avenues for objective diagnosis and potential therapeutic intervention. Although clinical applications of network approaches are still in the beginning stage, earlier studies have reported promising results, suggesting that network measures can help to understand recovery from brain injury (60,61), heritability (62), and responses to drugs (30). In this sense, the current study expands the spectrum of network science to potential clinical applications by proposing that the impairing of the most favorable intrinsic functional structure, predominantly in the frontoparietal module, of the brain in OCD patients might underlie abnormal thinking and behavioral outcomes in the patients, and improvement in these anomalies—most evidently in ventral frontal regional activity—might be attributable to symptom improvement after SSRI treatment.

Study Limitation and Summary

This study has several limitations. First, some participants dropped out between the baseline and follow-up assessments, and the decreased number of subjects might have affected the statistical power of the results. Second, nine patients had comorbid axis I disorders such as depressive disorder not otherwise specified or dysthymic disorder. Although the correlation analysis revealed no effects of depression or anxiety as measured by the HAM-D and HAM-A, respectively, on network parameters, we cannot rule out the possible influence of comorbid axis I disorders. Future studies should investigate the effects of these variables on brain connectivity. Third, we included only positive correlations in the modularity and connectivity degree analyses to minimize any potential confounding effects of global signal regression (63,64). Therefore, some network interactions characterized by anti-correlations are not figured into the analyses. Fourth, we used fixed size spheres to define brain regions of interest. However, the limitation of this approach is that it does not provide coverage over the whole-brain, and many cortical voxels might have been left uninvestigated (65–67). Future studies could benefit from using alternative node definitions (e.g., anatomical or random parcellations). Lastly, the small-world parameters in this study were normalized with degree-matched random networks generated with the Maslov-Sneppen rewiring algorithm (68). Nonetheless, recent evidence pointed out that this topology randomization can overestimate the degree to which brain networks are small-world networks (69). This suggests future strategies for examining the small-world networks with more realistic random networks, such as random networks generated with the H-Q-S algorithm, for normalization (69,70).

In summary, the current study demonstrated that 16 weeks of treatment with an SSRI leads to the restoration of optimal balance between functional segregation and integration in the brain networks, most evidently in the frontoparietal regions. These findings contribute important new information about the effects

of SSRI on the functional neural system. Long-term longitudinal study might help clarify the development of treatment resistance and prolonged symptomatology in OCD patients. Our findings offer hope in clinical applications that might use novel neuroimaging approaches to examine the essential biomarkers of OCD and to track the effects of drugs in the service of optimal diagnostic and therapeutic practice.

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1. American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorder: DSM-IV*. Washington, DC: American Psychiatric Association.
2. Blanco C, Olfson M, Stein DJ, Simpson HB, Gameroff MJ, Narrow WH (2006): Treatment of obsessive-compulsive disorder by U.S. psychiatrists. *J Clin Psychiatry* 67:946–951.
3. Sakai Y, Narumoto J, Nishida S, Nakamae T, Yamada K, Nishimura T, *et al.* (2011): Corticostriatal functional connectivity in non-medicated patients with obsessive-compulsive disorder. *Eur Psychiatry* 26: 463–469.
4. Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, Lopez-Sola M, Hernandez-Ribas R, *et al.* (2009): Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Arch Gen Psychiatry* 66:1189–1200.
5. van den Heuvel OA, Veltman DJ, Groenewegen HJ, Cath DC, van Balkom AJ, van Hartskamp J, *et al.* (2005): Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Arch Gen Psychiatry* 62:301–309.
6. Stein DJ (2002): Obsessive-compulsive disorder. *Lancet* 360:397–405.
7. Stern ER, Fitzgerald KD, Welsh RC, Abelson JL, Taylor SF (2012): Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PloS One* 7: e36356.
8. Zhang T, Wang J, Yang Y, Wu Q, Li B, Chen L, *et al.* (2011): Abnormal small-world architecture of top-down control networks in obsessive-compulsive disorder. *J Psychiatry Neurosci* 36:23–31.
9. Kang DH, Kwon JS, Kim JJ, Youn T, Park HJ, Kim MS, *et al.* (2003): Brain glucose metabolic changes associated with neuropsychological improvements after 4 months of treatment in patients with obsessive-compulsive disorder. *Acta Psychiatr Scand* 107:291–297.
10. Han JY, Kang DH, Gu BM, Jung WH, Choi JS, Choi CH, *et al.* (2011): Altered brain activation in ventral frontal-striatal regions following a 16-week pharmacotherapy in unmedicated obsessive-compulsive disorder. *J Korean Med Sci* 26:665–674.
11. Perani D, Colombo C, Bressi S, Bonfanti A, Grassi F, Scarone S, *et al.* (1995): [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. *Br J Psychiatry* 166: 244–250.
12. Saxena S, Brody AL, Ho ML, Alborzian S, Maidment KM, Zohrabi N, *et al.* (2002): Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs major depression. *Arch Gen Psychiatry* 59:250–261.
13. Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, *et al.* (2005): Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: A functional magnetic resonance imaging study. *Biol Psychiatry* 57:901–910.
14. Gilbert AR, Moore GJ, Keshavan MS, Paulson LA, Narula V, Mac Master FP, *et al.* (2000): Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. *Arch Gen Psychiatry* 57:449–456.
15. Jang JH, Kwon JS, Jang DP, Moon WJ, Lee JM, Ha TH, *et al.* (2006): A proton MRSI study of brain N-acetylaspartate level after 12 weeks of citalopram treatment in drug-naive patients with obsessive-compulsive disorder. *Am J Psychiatry* 163:1202–1207.
16. He Y, Chen ZJ, Evans AC (2007): Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* 17:2407–2419.
17. Sporns O, Chialvo DR, Kaiser M, Hilgetag CC (2004): Organization, development and function of complex brain networks. *Trends Cogn Sci* 8:418–425.
18. Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E (2005): Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb Cortex* 15:1332–1342.
19. Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E (2006): A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci* 26:63–72.
20. Jiang T, He Y, Zang Y, Weng X (2004): Modulation of functional connectivity during the resting state and the motor task. *Hum Brain Mapp* 22:63–71.
21. Lowe MJ, Mock BJ, Sorenson JA (1998): Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage* 7:119–132.
22. Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, *et al.* (2001): Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. *AJNR Am J Neuroradiol* 22: 1326–1333.
23. Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC (2002): Detection of functional connectivity using temporal correlations in MR images. *Hum Brain Mapp* 15:247–262.
24. Greicius MD, Krasnow B, Reiss AL, Menon V (2003): Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100:253–258.
25. Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME (2006): Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci U S A* 103:10046–10051.
26. Sporns O, Zwi JD (2004): The small world of the cerebral cortex. *Neuroinformatics* 2:145–162.
27. Bassett DS, Bullmore E (2006): Small-world brain networks. *Neuroscientist* 12:512–523.
28. Sporns O (2013): Network attributes for segregation and integration in the human brain. *Curr Opin Neurobiol* 23:162–171.
29. Liu Y, Liang M, Zhou Y, He Y, Hao Y, Song M, *et al.* (2008): Disrupted small-world networks in schizophrenia. *Brain* 131:945–961.
30. Achard S, Bullmore E (2007): Efficiency and cost of economical brain functional networks. *PLoS Comput Biol* 3:e17.
31. Wang L, Zhu C, He Y, Zang Y, Cao Q, Zhang H, *et al.* (2009): Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. *Hum Brain Mapp* 30:638–649.
32. He Y, Wang J, Wang L, Chen ZJ, Yan C, Yang H, *et al.* (2009): Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PloS One* 4:e5226.
33. Chen ZJ, He Y, Rosa-Neto P, Gong G, Evans AC (2011): Age-related alterations in the modular organization of structural cortical network by using cortical thickness from MRI. *Neuroimage* 56:235–245.
34. Sporns O (2011): The non-random brain: Efficiency, economy, and complex dynamics. *Front Comput Neurosci* 5:5.
35. Sporns O (2011): *Networks of the Brain*. Cambridge, MA: MIT Press.
36. Zhang J, Wang J, Wu Q, Kuang W, Huang X, He Y, *et al.* (2011): Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biol Psychiatry* 70:334–342.
37. Supekar K, Menon V, Rubin D, Musen M, Greicius MD (2008): Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol* 4:e1000100.
38. First MB SR, Gibbon M (1997): *Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press.
39. Song XW, Dong ZY, Long XY, Li SF, Zuo XN, Zhu CZ, *et al.* (2011): REST: A toolkit for resting-state functional magnetic resonance imaging data processing. *PloS One* 6:e25031.
40. Dosenbach NU, Nardos B, Cohen AL, Fair DA, Power JD, Church JA, *et al.* (2010): Prediction of individual brain maturity using fMRI. *Science* 329:1358–1361.
41. Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A (2008): Hierarchical organization of human

cortical networks in health and schizophrenia. *J Neurosci* 28: 9239–9248.
42. Micheloyannis S, Pachou E, Stam CJ, Breakspear M, Bitsios P, Vourkas M, *et al.* (2006): Small-world networks and disturbed functional connectivity in schizophrenia. *Schizophr Res* 87:60–66.
43. Hanggi J, Wotruba D, Jancke L (2011): Globally altered structural brain network topology in grapheme-color synesthesia. *J Neurosci* 31: 5816–5828.
44. de Haan W, van der Flier WM, Koene T, Smits LL, Scheltens P, Stam CJ (2012): Disrupted modular brain dynamics reflect cognitive dysfunction in Alzheimer's disease. *Neuroimage* 59:3085–3093.
45. Meunier D, Achard S, Morcom A, Bullmore E (2009): Age-related changes in modular organization of human brain functional networks. *Neuroimage* 44:715–723.
46. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27:2349–2356.
47. Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, *et al.* (2007): Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci U S A* 104:11073–11078.
48. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102: 9673–9678.
49. Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A* 105:12569–12574.
50. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. *Proc Natl Acad Sci U S A* 98:676–682.
51. Buckner RL, Andrews-Hanna JR, Schacter DL (2008): The brain's default network: Anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124:1–38.
52. Raichle ME, Snyder AZ (2007): A default mode of brain function: A brief history of an evolving idea. *Neuroimage* 37:1083–1090; discussion 1097–1089.
53. Marder E, Goaillard JM (2006): Variability, compensation and homeostasis in neuron and network function. *Nat Rev Neurosci* 7: 563–574.
54. Bassett DS, Meyer-Lindenberg A, Achard S, Duke T, Bullmore E (2006): Adaptive reconfiguration of fractal small-world human brain functional networks. *Proc Natl Acad Sci U S A* 103:19518–19523.
55. Valencia M, Martinerie J, Dupont S, Chavez M (2008): Dynamic small-world behavior in functional brain networks unveiled by an event-related networks approach. *Phys Rev E Stat Nonlin Soft Matter Phys* 77: 050905.
56. Swedo SE, Pietrini P, Leonard HL, Schapiro MB, Rettew DC, Goldberger EL, *et al.* (1992): Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder: Revisualization during pharmacotherapy. *Arch Gen Psychiatry* 49:690–694.
57. Stern ER, Welsh RC, Fitzgerald KD, Gehring WJ, Lister JJ, Himle JA, *et al.* (2011): Hyperactive error responses and altered connectivity in ventromedial and frontoinsular cortices in obsessive-compulsive disorder. *Biol Psychiatry* 69:583–591.
58. Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I, *et al.* (2005): Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biol Psychiatry* 57:287–294.
59. Sporns O (2011): The human connectome: A complex network. *Ann N Y Acad Sci* 1224:109–125.
60. Nakamura T, Hillary FG, Biswal BB (2009): Resting network plasticity following brain injury. *PloS One* 4:e8220.
61. Wang L, Yu C, Chen H, Qin W, He Y, Fan F, *et al.* (2010): Dynamic functional reorganization of the motor execution network after stroke. *Brain* 133:1224–1238.
62. Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, *et al.* (2010): Genetic control over the resting brain. *Proc Natl Acad Sci U S A* 107:1223–1228.
63. Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA (2009): The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *Neuroimage* 44:893–905.
64. Guo CC, Kurth F, Zhou J, Mayer EA, Eickhoff SB, Kramer JH, *et al.* (2012): One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. *Neuroimage* 61:1471–1483.
65. Wang J, Wang L, Zang Y, Yang H, Tang H, Gong Q, *et al.* (2009): Parcellation-dependent small-world brain functional networks: A resting-state fMRI study. *Hum Brain Mapp* 30:1511–1523.
66. Zalesky A, Fornito A, Harding IH, Cocchi L, Yucel M, Pantelis C, *et al.* (2010): Whole-brain anatomical networks: Does the choice of nodes matter? *Neuroimage* 50:970–983.
67. Wig GS, Schlaggar BL, Petersen SE (2011): Concepts and principles in the analysis of brain networks. *Ann N Y Acad Sci* 1224:126–146.
68. Maslov S, Sneppen K (2002): Specificity and stability in topology of protein networks. *Science* 296:910–913.
69. Zalesky A, Fornito A, Bullmore E (2012): On the use of correlation as a measure of network connectivity. *Neuroimage* 60:2096–2106.
70. Bialonski S, Wendler M, Lehnertz K (2011): Unraveling spurious properties of interaction networks with tailored random networks. *PloS One* 6:e22826.