Global Resting-State Functional Magnetic Resonance Imaging Analysis Identifies Frontal Cortex, Striatal, and Cerebellar Dysconnectivity in Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is associated with regional hyperactivity in cortico-striatal circuits. However, the large-scale patterns of abnormal neural connectivity remain uncharacterized. Resting-state functional connectivity studies have shown altered connectivity within the implicated circuitry, but they have used seed-driven approaches wherein a circuit of interest is defined a priori. This limits their ability to identify network abnormalities beyond the prevailing framework. This limitation is particularly problematic within the prefrontal cortex (PFC), which is large and heterogeneous and where a priori specification of seeds is therefore difficult. A hypothesis-neutral, data-driven approach to the analysis of connectivity is vital.

Methods: We analyzed resting-state functional connectivity data collected at 3T in 27 OCD patients and 66 matched control subjects with a recently developed data-driven global brain connectivity (GBC) method, both within the PFC and across the whole brain.

Results: We found clusters of decreased connectivity in the left lateral PFC in both whole-brain and PFC-restricted analyses. Increased GBC was found in the right putamen and left cerebellar cortex. Within regions of interest in the basal ganglia and thalamus, we identified increased GBC in dorsal striatum and anterior thalamus, which was reduced in patients on medication. The ventral striatum/nucleus accumbens exhibited decreased global connectivity but increased connectivity specifically with the ventral anterior cingulate cortex in subjects with OCD.

Conclusions: These findings identify previously uncharacterized PFC and basal ganglia dysconnectivity in OCD and reveal differentially altered GBC in dorsal and ventral striatum. Results highlight complex disturbances in PFC networks, which could contribute to disrupted cortical-striatal-cerebellar circuits in OCD.

Key Words: Basal ganglia, functional connectivity, global connectivity, obsessive-compulsive disorder, prefrontal cortex, resting-state fMRI

Obsessive-compulsive disorder (OCD) is characterized by intrusive, anxiety-producing thoughts and repetitive, compulsive behaviors, which cause enormous distress (1,2). Obsessive-compulsive disorder affects 2.7% of the population at some point during their lives (3,4). Of these, up to 65% report that their illness produces major functional impairment (4).

OCD was among the first neuropsychiatric conditions in which pathological activity in a defined brain circuit was identified. Positron emission tomography studies of glucose use (5–7), positron emission tomography and single photon emission computed tomography studies of brain perfusion (8,9), and functional/structural magnetic resonance imaging (MRI) investigations (10–14) suggest increased cerebral metabolism in cortico-striato-thalamo-cortical (CSTC) circuits, particularly in the caudate and putamen, the anterior thalamus, the orbitofrontal cortex (OFC), and (more variably) the anterior cingulate cortex (ACC) (11,15,16). This circuitry is activated after symptom provocation in patients (17–19); the hyperactivity is reduced in parallel with symptomatic improvement after either pharmacotherapy or psychotherapy (20–22).

The evolutionarily well-preserved CSTC circuitry is involved in diverse computations, including reward processing, action selection, habit formation, and motor control (23–26). To a first approximation, it consists of parallel loops (24,27,28). This parallel organization is complicated by heterogeneity within the striatum itself (29), by afferents from other structures (24), and by recently appreciated di-synaptic interactions with the cerebellum (30,31). Despite these complexities, the notion of parallel, functionally specialized information-processing loops remains of heuristic value for conceptualizing circuit-level disturbances.

Abnormal activity in a ventral striatum-OFC loop is well replicated in the OCD functional neuroimaging literature (11) and has been linked with symptom severity (32,33). Dysregulation in this "affective loop" might be associated with abnormal reward processing (34). Abnormal activity in the more dorsal striatum, especially the head of the right caudate and the putamen,

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implicates the "cognitive loop," communicating with the dorsolateral prefrontal cortex (PFC) (35), although functional imaging analyses of the dorsal PFC have been inconsistent (11).

Traditional functional magnetic resonance imaging (fMRI) studies analyze the blood oxygen level–dependent (BOLD) signal after stimulation or during a task. However, BOLD signal fluctuations at rest contain information about functional network architecture (36–39). Resting-state functional connectivity, defined as correlations between these spontaneous BOLD fluctuations, has been increasingly used to analyze neural circuit dynamics both in normal populations (28,40,41) and in pathological states (42). In particular, several recent studies have used seed-based analyses of resting-state data to probe functional connectivity within CSTC networks in both adult and pediatric OCD (32,33,43–50). These studies have provided confirmatory evidence of dysconnectivity within the networks previously identified with baseline or provocation-related perfusion measures (11,15,35). Differential patterns of dysconnectivity have been observed in dorsal and ventral striatal networks (32,33).

Most resting-state functional connectivity analyses in OCD have used seed-based approaches, in which specific regions of interest (ROIs) are identified on the basis of a priori anatomical considerations [e.g., (32,33)] or on task-based activation [e.g., (46)], and the activity of all other brain regions is correlated against those seeds. This approach is useful for testing regionally specific hypotheses of altered functional connectivity, but it has limited power to detect dysconnectivity not predicted a priori. This is particularly problematic when searching for dysconnectivity within large and heterogeneous regions such as basal ganglia or PFC, in which identifying appropriate seeds for connectivity analysis is challenging. Individual differences in anatomy further complicate seed definition. Independent component analyses represent an alternative to the a priori specification of a seed but have not been extensively applied in OCD (50).

An alternative, data-driven approach, successfully used in complex neuropsychiatric illness (51–53), has the potential to identify novel patterns of brain dysconnectivity independent of a priori seeds. This permits both independent support of established hypotheses and the discovery of new patterns of connectivity alterations that might be missed by seed-driven approaches. Such a "bottom-up" approach is particularly well-suited to characterization of abnormalities in PFC connectivity. Here we have applied an approach, derived from graph theory, in which the global connectivity of all voxels in the brain is determined, relative to all other voxels, and then compared between diagnostic groups (54–56). This global brain connectivity (GBC) analysis has proven powerful for detecting "hubs" of connectivity in healthy populations (57) and has also been successfully applied to studies of PFC dysconnectivity in schizophrenia and bipolar disorder (51–53) as well as following pharmacological challenge (58). A single recent study has examined global connectivity in OCD and identified predicted abnormalities in the OFC and the ventral striatum (59).

GBC addresses qualitatively different questions about brain connectivity than seed-based analyses. Areas of high GBC are maximally functionally connected with other areas and might play a role in coordinating large-scale patterns of brain activity (54,55). A significant between-group difference in GBC thus indicates areas and networks in which the large-scale coordination of information processing might be altered in a disease state. Decreased GBC in a disease state might suggest decreased participation of a particular brain region in broader networks, whereas increased GBC might suggest a pathological broadening or synchronization of functional networks. Importantly, such alterations in connectivity need not parallel the metabolic activity of the implicated brain areas. We examined alterations in network connectivity in 27 OCD patients, compared with 66 matched healthy comparison subjects (HCS), within the PFC and across the whole brain (to provide a fully unbiased, data-driven, and partially independent search). We predicted alterations both in prefrontal network connectivity and in the basal ganglia.

Methods and Materials

Participants

All procedures were approved by the Yale Human Investigations Committee. Adult OCD patients, 18–65 years of age, were recruited through the Yale OCD Research Clinic through referrals and advertising. Diagnoses were confirmed by clinical interview by a psychiatrist and the Structured Clinical Interview for DSM-IV (60). All patients met DSM-IV criteria for OCD. Comorbid DSM-IV depression and other anxiety disorders were permitted, to capture a representative sample. Patients with any psychotic illness, autism, history of substance abuse, major head trauma or neurological disease, unstable medical illness, or pregnancy were excluded. High-quality neuroimaging data that passed quality control criteria (Supplement 1) were acquired from 27 of 32 patients (84.6%) and are included in analysis (Table 1 and Supplement 1). Of these patients, 13 were medication-free for at least 8 weeks at the time of fMRI scanning; 14 were treated with a selective serotonin reuptake inhibitor antidepressant at a stable dose for $\geq$ 8 weeks at the time of scanning (Table 1). We examined the effect of medication and of comorbid depression in secondary analyses. The HCS, matched as a group for age and gender, were recruited through advertising; high-quality data were acquired from 66 of 80 subjects (83.5%) and included in analysis. The OCD symptom severity was evaluated with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (61,62); comorbid symptomatology was evaluated with the Hamilton Depression Rating Scale (HAM-D, 17-item version) (63) and the Hamilton Anxiety Rating Scale (HAM-A) (64). Ratings were performed on the same day as the scan in most cases, and always within 3 days of the day of scanning.

Data Acquisition

Imaging data were acquired on a Siemens Trio 3T scanner (Siemens, Munich, Germany). A standard 12-channel head coil was used, with foam padding to minimize head motion. Participants were instructed to rest with their eyes closed during scanning but were monitored to ensure they stayed awake. Images sensitive to BOLD signal were acquired with a T2*-weighted gradient-echo planar imaging sequence sensitive to BOLD contrast (repetition time/echo time = 2000/25 msec, flip angle = 85°, field of view = 220 × 220 mm, acquisition matrix = 64 × 64). Thirty-two axial slices (4 mm) were collected without gap; acquisition lasted 10 min and produced 300 volumetric images/subject with 3.4375 × 3.4375 mm voxels. For spatial normalization and structural segmentation, high-resolution images were acquired with a T1-weighted, three-dimensional fast spoiled gradient-echo sequence (repetition time/echo time = 2530/3.66 msec, flip angle = 7°, field of view = 256 × 256 mm, matrix = 256 × 256, 176 slices without gap, voxel size = 1 mm^3).

Global Brain Connectivity

All analyses followed our prior published approaches (51); see Supplement 1 for details. Briefly, GBC (55) was computed (51) as

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