Brain Corticostriatal Systems and the Major Clinical Symptom Dimensions of Obsessive-Compulsive Disorder

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Background: Functional neuroimaging studies have provided consistent support for the idea that obsessive-compulsive disorder (OCD) is associated with disturbances of brain corticostriatal systems. However, in general, these studies have not sought to account for the disorder's prominent clinical heterogeneity.

Methods: To address these concerns, we investigated the influence of major OCD symptom dimensions on brain corticostriatal functional systems in a large sample of OCD patients ($n = 74$) and control participants ($n = 74$) examined with resting-state functional magnetic resonance imaging. We employed a valid method for mapping ventral and dorsal striatal functional connectivity, which supported both standard group comparisons and linear regression analyses with patients' scores on the Dimensional Yale-Brown Obsessive-Compulsive Scale.

Results: Consistent with past findings, patients demonstrated a common connectivity alteration involving the ventral striatum and orbitofrontal cortex that predicted overall illness severity levels. This common alteration was independent of the effect of particular symptom dimensions. Instead, we observed distinct anatomical relationships between the severity of symptom dimensions and striatal functional connectivity. Aggression symptoms modulated connectivity between the ventral striatum, amygdala, and ventromedial frontal cortex, while sexual/religious symptoms had a specific influence on ventral striatal-insular connectivity. Hoarding modulated the strength of ventral and dorsal striatal connectivity with distributed frontal regions.

Conclusions: Taken together, these results suggest that pathophysiological changes among orbitofrontal-striatal regions may be common to all forms of OCD. They suggest that a further examination of certain dimensional relationships will also be relevant for advancing current neurobiological models of the disorder.

Key Words: Basal ganglia, fMRI, functional connectivity, OCD, striatum, symptom dimensions

Prevailing ideas about the neurobiology of obsessive-compulsive disorder (OCD) continue to emphasize the role of brain corticostriatal systems: large-scale topologically organized neural circuits that connect the basal ganglia, thalamus, and cortex (1). Of most apparent relevance to OCD are partly overlapping systems that connect the ventral and dorsal striatum with frontal cortical areas implicated in motivational-emotional and cognitive aspects of behavior, respectively. Evidence linking OCD to a disturbance of these brain systems has accumulated from a variety of sources (2–6), although the specific mechanisms and vulnerability factors that give rise to these relationships are not fully understood. Additionally, one common criticism of the corticostriatal model is that it fails to explain the prominent clinical heterogeneity of OCD, referring to the fact that individual diagnoses often reflect very diverse symptom patterns. This criticism has led to the call for revised neurobiological models able to better account for its complex clinical phenotype (7). However, to date, few studies have compared neurobiological correlates of OCD when it is unitarily defined with when its heterogeneity is unpacked in terms of different symptoms or other features.

One perspective that has received much interest over the past decade in addressing the heterogeneity of OCD relates to the so-called multidimensional model ([8,9], see initially [10]). Its premise is that OCD can be reliably summarized with a few consistent and temporally stable symptom dimensions—derived from factor analytic studies—that may co-exist within individual patients (9,11). From this perspective, some neuroimaging studies have examined direct links between major OCD symptom dimensions and brain structural and functional indices (12–18). Notably, in the largest studies to date, Pujol *et al.* (15) and van den Heuvel *et al.* (17) reported significant associations between aggression/checking symptoms and temporolimbic volume reductions, including the amygdala (15), while greater severity of contamination/cleaning symptoms and symmetry/ordering symptoms predicted decreased volume of the dorsal caudate nucleus and sensorimotor cortex, respectively (17). In both studies, these dimensional effects were anatomically distinct from brain structural differences that characterized patients as a whole, including changes in the orbitofrontal cortex (15,17) and ventral striatum (15).

In a recent hypothesis-driven functional imaging study, we confirmed that OCD patients exhibit system-wide differences in the coordinated activity, or functional connectivity, of both

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ventral and dorsal corticostriatal systems when assessed under resting-state conditions (19). Our findings, in particular, emphasized heightened connectivity of the ventral caudate/nucleus accumbens with the anterolateral and medial orbitofrontal cortices in patients, findings that have received good support in subsequent studies (20–22). Despite our former results demonstrating a direct link between ventral corticostriatal connectivity and overall symptom severity, we were unable to assess the influence of certain symptom dimensions on these findings due to inadequate sample size. This limitation therefore remains an important caveat to address.

The goal of this study was to investigate the contribution of major OCD symptom dimensions to a disturbance of brain corticostriatal systems in OCD patients using resting-state functional magnetic resonance imaging. We were most interested in the idea that a more rich characterization of our imaging findings might be achieved when adopting a dimensional approach (7,9). To do so, we recruited a large sample of patients who additionally completed the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) (23), which provides comprehensive ratings of six hypothesized major symptom dimensions (24). Based on past work, we made two specific predictions: OCD patients would show significant common functional alterations of ventral corticostriatal regions that would be associated with overall illness severity; and the influence of major symptom dimensions would be mostly distinct from such common disorder effects but nevertheless implicate brain regions of existing theoretical interest to neurobiological models of OCD.

Methods and Materials

Participants

Seventy-four adult outpatients were recruited from the Obsessive-Compulsive Disorders Unit of the University Hospital of Bellvitge, Barcelona, Spain. Patients were selected from a slightly larger cohort after having satisfied DSM-IV diagnostic criteria for OCD (for at least 1 year before the study), in the absence of relevant medical, neurologic, and other major psychiatric illness, as well as imaging data quality control checks (see below). Nineteen of these patients (26%) were included in our original report (19). Diagnosis was confirmed by two senior psychiatrists (P.A. and C.S.) through separate interviews 1 month apart, using the Structured Clinical Interview for DSM-IV Axis I Disorders (25). See Table 1 for further sample descriptions.

Our primary clinical measure of interest was the validated Spanish version of the DY-BOCS (23,26), which was used to rate the severity of six major obsessive-compulsive symptom dimensions: 1) contamination obsessions and cleaning compulsions; 2) obsessions about harm due to aggression, injury, violence, natural disasters, and/or related compulsions; 3) obsessions concerning sexual, moral, and/or religious issues and related compulsions; 4) obsessions about symmetry and/or just-right perceptions and compulsions to count and/or order-arrange; 5) obsessions and compulsions related to hoarding; and 6) miscellaneous obsessions and compulsions (Table 1). Due to concerns about the construct validity of the latter miscellaneous dimension (23), it was excluded from subsequent analyses. The DY-BOCS total global severity score was used to measure overall illness severity. Patients also completed the original Yale-Brown Obsessive-Compulsive Scale (24) to facilitate a comparison with past findings.

Obsessive-compulsive disorder patients were appropriately statistically matched for age, gender, and education level to 74 control subjects (Table 1). Each control subject underwent the Structured Clinical Interview for DSM-IV nonpatient version to exclude any Axis I or II psychiatric disorders. None had a personal history of neurologic or psychiatric illness. Comorbid depression and anxiety symptoms were measured using Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale with missing data existing for one control subject and one OCD patient. Mean (SD) scores on both scales were significantly more pronounced in OCD patients [HDRS, $F(1,145) = 178.7$, $p < .001$; Hamilton Anxiety Rating Scale, $F(1,145) = 161.9$, $p < .001$].

All the participants provided written informed consent to complete this study, after a complete description of its protocol, which was approved by the Institutional Review Board of the University Hospital of Bellvitge.

Image Acquisition and Preprocessing

A 1.5-T Signa Excite system (General Electric, Milwaukee, Wisconsin) equipped with an eight-channel phased-array head coil and single-shot echo-planar imaging software was used. The functional sequence consisted of gradient recalled acquisition in the steady state (repetition time, 2000 msec; echo time, 50 msec; and pulse angle, 90°) in a 24-cm field of view, with a 64 × 64 pixel matrix and a slice thickness of 4 mm (interslice gap, 1 mm). Twenty-two interleaved sections, parallel to the anterior-posterior commissure line, were acquired to generate 120 whole-brain volumes, excluding 4 initial dummy volumes. Participants were instructed to simply relax, stay awake, and to lie still without moving, while keeping their eyes closed throughout. We also acquired a high-resolution T1-weighted anatomical image for each subject using a three-dimensional fast spoiled gradient inversion-recovery prepared sequence with 130 contiguous slices (repetition time, 11.8 msec; echo time, 4.2 msec; flip angle, 15°) in a 30-cm field of view, with a 256 × 256 pixel matrix and a slice thickness of 1.2 mm.

Corticostriatal System Mapping

A validated resting-state functional connectivity mapping procedure was used to characterize ventral and dorsal corticostriatal systems via primary regions of interest (seeds) located in ventral and dorsal areas of the caudate nucleus and putamen (19–21,27–29). See Di Martino *et al.* (28) for a detailed rationale regarding the anatomical delineation of these regions. See Harrison *et al.* (19) for a full description of the identical methodology implemented herein. Figure S1 in Supplement 1 and text provide an overview of this procedure (including image preprocessing steps), which was used to generate participant-wise whole-brain striatal functional connectivity maps corresponding to each region of interest. In the current study, we elected to focus our remaining analyses on the ventral caudate (including nucleus accumbens) and dorsal caudate regions, taking into account our previous results (19), other recent studies (20,21), and the general interest in these ventral and dorsal corticostriatal systems in OCD.

Initial Group Analyses

For each striatal region, participants' connectivity maps were included in group-wise random-effects analyses adopting a 2 × 2 mixed design factorial model (group [control, patient] by hemisphere [right, left]). To control for the potential confounding influence of comorbid depression symptoms on group results (30), participants' HDRS scores were covaried for in each model. Spatial extent thresholds for all statistical comparisons were determined by 1000 Monte Carlo simulations using AlphaSim (31) as implemented in the SPM REST toolbox (32).

For within-group effects, the input parameters to AlphaSim included an individual voxel threshold probability of .001 and