Altered Activation in Fronto-Striatal Circuits During Sequential Processing of Conflict in Unmedicated Adults with Obsessive-Compulsive Disorder

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Background: The aim of this study was to examine the functioning of fronto-striatal brain circuits that support self-regulatory capacities including conflict resolution and sequential processing in unmedicated adults with obsessive-compulsive disorder (OCD).

Methods: We compared functional magnetic resonance imaging blood oxygen level–dependent response in 22 adults with OCD with 22 healthy, age-matched control subjects during performance of a Simon Spatial Incompatibility task. We used general linear modeling to compare groups in their patterns of brain activation during correct responses to conflict-laden stimuli and explore the effects of trial sequence on group differences.

Results: Behavioral performance on the Simon task did not differ between groups. In response to conflict-laden stimuli, OCD participants activated fronto-striatal regions significantly more than control subjects, specifically a right hemisphere cluster encompassing the putamen, insula, and inferior frontal gyrus. Their activation of this cluster was driven not by conflict on a current trial but by their response to the alternation of stimulus congruence (incongruent or congruent) across trial sequences (i.e., current and preceding trials) and was most accentuated in participants with more severe symptoms in the doubt/checking dimension. Functional connectivity from the putamen to other fronto-striatal regions was also greater in the OCD compared with control participants.

Conclusions: When engaging the self-regulatory control necessary to resolve conflict and process alternating stimuli, OCD participants displayed excessive activation in a fronto-striatal circuit that differs from the orbitofrontal cortex–anterior cingulate cortex–caudate circuit typically implicated in OCD. Dysfunction in this circuit was associated with processing changes in the stimulus context. We speculate that this dysfunction might be related to the cognitive inflexibility typical of persons with OCD.

Key Words: Cognitive conflict, fMRI, fronto-striatal systems, obsessive-compulsive disorder, self-regulation, Simon task

Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts, images, or impulses (i.e., obsessions) and repetitive acts that are performed to prevent or reduce distress (i.e., compulsions). Obsessions and compulsions are hypothesized to result from a failure to inhibit or control thoughts and behaviors, respectively (1). Indeed, neuroimaging evidence suggests that the fronto-striatal circuits supporting inhibitory control processes are structurally (2–5), metabolically (6–8), and functionally (9) abnormal in OCD. Most findings implicate the orbitofrontal (OFC) and anterior cingulate (ACC) cortices and caudate nucleus in the pathophysiology of OCD. However, inhibitory control processes involve additional fronto-striatal brain areas that might also be dysfunctional in OCD.

Previous functional magnetic resonance imaging (fMRI) studies have examined the functioning of fronto-striatal circuits in adults with OCD during performance of inhibitory control and conflict tasks requiring the inhibition of irrelevant or conflicting information (10–17). Discrepant findings across studies of increased and decreased activation of OFC and ACC relative to control subjects are likely due to differences in the tasks used (e.g., Stroop, Go/No-go), task designs (e.g., block, event-related), and performance variables (e.g., errors, correct responses). Moreover, most samples were small (<15), with patients taking medication. Positron emission tomography findings suggest that selective serotonin reuptake inhibitors (SSRIs) attenuate metabolic activity in fronto-striatal regions in OCD participants (18), and fMRI findings suggest that SSRIs attenuate fronto-striatal activations associated with inhibitory control in other disorders (19). Only one prior fMRI study of adult OCD patients assessed brain function during an inhibitory control task before and after symptom improvement with SSRI ($n = 4$), reporting no changes in fronto-striatal activations compared with baseline (20). Thus, the effect of SSRIs on fronto-striatal activations in OCD remains unclear, and the functioning of these circuits in unmedicated adults warrants further investigation.

The Simon Spatial Incompatibility task (21) requires ignoring a task-irrelevant feature of a stimulus (the side of the screen on which an arrow appears) when it conflicts with a more task-relevant one (the direction the arrow points). When responding correctly on incongruent (i.e., conflict-laden) trials, healthy individuals activate fronto-striatal regions including dorsolateral/dorsomedial prefrontal cortices and ACC, supplementary motor areas, caudate, and putamen (22–24). Behaviorally, healthy individuals respond more slowly to incongruent stimuli that are preceded by congruent stimuli than to incongruent stimuli preceded by incongruent stimuli, because conflict on a preceding incongruent trial enhances inhibitory control and facilitates processing on a current incongruent trial (25,26). Fronto-striatal activations also depend on trial sequence (27–29). For example,

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we measured brain activation in healthy individuals during their performance of a Simon task variant that included congruent and incongruent appearing equally often, thereby allowing us to distinguish neural activity associated with the conflict resolution on a current trial from activity associated with effects of trial sequence (i.e., the alternation or repetition of congruence between current and preceding stimuli). Activation of frontal regions increased with increasing levels of conflict, with the greatest magnitude in response to postcongruent stimuli (i.e., incongruent preceded by congruent stimuli) (30). This task variant eliminates potential oddball effects associated with the infrequent presentation of incongruent stimuli, reduces priming effects associated with long repeated trials of congruent stimuli, and is easier than other Simon task versions (22,23,31,32), allowing for group comparisons of brain activity that are not confounded by performance differences (33).

We report an event-related fMRI study in which we used this Simon task to investigate the neural substrates of inhibitory control and conflict resolution in unmedicated adults with OCD. We hypothesized that, despite their normal performance on the task, OCD participants would activate fronto-striatal regions to a greater extent than control subjects when responding correctly to incongruent stimuli, reflecting their greater reliance on this circuit. Our analyses focused on the postcongruent conflict effect (incongruent compared with congruent stimuli preceded by congruent stimuli), because this contrast is associated with the most conflict and greatest magnitude of activation in fronto-striatal regions in healthy individuals. Given their cognitive inflexibility and tendency to "get stuck" in the face of changing environmental contingencies, we suspected that OCD participants would demonstrate greater reliance on and hence greater activation of fronto-striatal circuits than control subjects in response to postcongruent conflict. We also explored general conflict effects, trial sequence effects, group differences in task-related functional connectivity within fronto-striatal circuits, and associations of fronto-striatal activations with OCD symptom dimensions.

Methods and Materials

Participants

Unmedicated adults with OCD and healthy control participants (group-matched by age, sex, and ethno-racial groups) were recruited through flyers, internet advertisements, and word-of-mouth. Participants with a history of neurological illness, past seizures, head trauma with loss of consciousness, mental retardation, pervasive developmental disorder, or current Axis I disorders (other than OCD for the OCD participants) were excluded. Control subjects had no lifetime Axis I disorders. Formal diagnoses of OCD and the presence of comorbid Axis I diagnoses were established by a psychiatric evaluation and confirmed with the Structured Clinical Interview for DSM-IV (34). On the day of the MRI scan, a trained rater assessed OCD severity with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (35,36) and depressive severity with the Hamilton Depression Scale (37). The Y-BOCS Symptom Checklist was used to ascertain the presence and severity of five different symptom dimensions (38,39). Full-scale IQs were estimated with the Wechsler Abbreviated Scale of Intelligence (40). Movement within the scanner was assessed for each participant by calculating the average displacement in each translational and rotational axis. The totals of those averages were then compared across groups. The Institutional Review Board of the New York State Psychiatric Institute approved this study. Participants provided written informed consent.

fMRI Paradigm

Stimuli were presented through nonmagnetic goggles (Resonance Technologies, Inc., Salem, Massachusetts) with EPRIME software (Psychology Software Tools, Inc., Sharpsburg, Pennsylvania). A series of white arrows pointing left or right were displayed against a black background to the left or right of a white gaze fixation cross-hair positioned at midline. Stimuli subtended 1 vertical and 3.92 horizontal degrees of the visual field. Stimuli were "congruent" (pointing in the same direction as their position on the screen), "incongruent" (pointing opposite their position on the screen), or "blank" (a cross-hair positioned at midline).

Participants were instructed to respond quickly to the direction of the arrow by pressing a button on a response box, with the index finger of their right hand for a left-pointing arrow and the middle finger of that hand for a right-pointing arrow. The button press recorded responses and reaction times (RTs) for each trial containing congruent or incongruent stimuli. Stimulus duration was 1300 msec, with a jittered interstimulus interval (mean = 5352 msec, SD = 842 msec, range = 4009–6857 msec). Each run contained 55 stimuli (5 min, 7 sec), with 22 congruent stimuli (11 left-pointing arrows presented to the left of midline; 11 right-pointing arrows presented to the right of midline), 22 incongruent stimuli (11 left-pointing arrows presented to the right of midline; 11 right-pointing arrows presented to the left of midline) and 11 blank stimuli (longer periods of fixation) (Figure S1 in Supplement 1). These stimuli were arranged and presented in a pseudorandom order. Each experiment contained 3 runs, totaling 66 congruent and 66 incongruent stimuli. Details of the MRI pulse sequence, image processing, and behavioral and exploratory image analyses are described in Supplement 1.

Image Analysis

First-level parametric analyses were performed individually for each participant with a modified version of the general linear model function in SPM8 with a weighted least-squares algorithm (Wellcome Department of Imaging Neuroscience, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/). Preprocessed blood oxygen level–dependent time series data at each voxel, concatenated from all three runs of the task (420 volumes), were modeled with a general linear model with the following predictors corresponding to each trial type: 1) congruent preceded by congruent (cC); 2) congruent preceded by incongruent (iC); 3) incongruent preceded by congruent (cI); 4) incongruent preceded by incongruent (iI); 5) blank trials; 6) fixation trials; 7) all incorrect; and 8) correct trials (either congruent or incongruent). These events were then convolved with the canonical hemodynamic response function (41). A first-order autoregression with restricted maximum likelihood algorithm was used to estimate parameters for each independent variable and remove serial correlations in the fMRI time series. The parameter estimates for the three runs were averaged to produce β maps for each trial type for each participant.

The resulting β maps were entered into a second-level mixed model analysis in SPM8: a 2 × 2 × 2 repeated-measures factorial analysis of variance with within-subjects factors: 1) current congruence (congruent, incongruent); and 2) trial sequence (congruence repeated or alternating between the preceding and current trial). The between-subjects factor was diagnosis (OCD, Control). We assessed the main effects of these factors and