

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 $2 \times 2 \times 2$ 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

their interaction as well as pairwise contrasts. We applied parametric inference and report findings that were identified on group contrast maps with a corrected p value $< .05$. On the basis of a Monte Carlo simulation with 10,000 iterations implemented in AlphaSim (<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>), we selected for our a priori hypothesis test a height threshold of uncorrected $p \leq .005$ combined with a cluster filter of at least 61 adjacent voxels ($3 \times 3 \times 3$ mm each). The combined application of a statistical threshold and cluster filter minimizes the false-positive identification of activated regions at any given threshold (42), because clustering can distinguish between true regions of activation that tend to occur over adjacent voxels and noise that has less tendency to cluster.

Hypothesis Testing

We tested whether participants with or without OCD differed in brain activity in fronto-striatal regions during correct responses on incongruent trials compared with correct responses on congruent trials that were preceded by congruent trials (cl-cC contrast representing postcongruent conflict). Other contrasts were used in exploratory analyses to determine whether observed group differences were associated with the resolution of conflict on a current trial or with effects of trial sequence (Figure S2 in Supplement 1). We also explored group differences in task-related functional connectivity within fronto-striatal circuits and whether the functioning of and functional connectivity within fronto-striatal circuits differed across symptom dimensions (Supplement 1).

Results

Participants

Twenty-two OCD and 22 healthy control participants were scanned. The groups were matched on demographic characteristics (Table 1). Most participants in both groups were right-handed. All OCD participants were free of psychotropic medications (14 treatment-naïve and the other 8 had been off an SRI regimen for a mean of 94 [SD = 63] weeks) and free of any current comorbid Axis I disorder; 5 had a lifetime history of a depressive episode. As in prior studies (43), this was achieved by recruiting OCD subjects from the community (e.g., instead of relying solely upon psychiatrist referral). The target symptoms of the OCD participants were distributed across the five symptom dimensions (39). The two groups did not differ in movement within the scanner, defined by the total ($p = .63$) and cumulative ($p = .63$) displacement in each translational and rotational axis.

Behavioral Performance

No significant main effects of group or interaction of group \times congruence was detected in either model ($p > .45$), indicating that there were no group differences specific to stimulus type. As shown in Table 2, RTs and accuracy scores were similar on congruent and incongruent trials, and neither group made many errors. Both groups demonstrated a conflict effect (mean RT incongruent $>$ mean RT congruent) that was greater after congruent than after incongruent trials (congruence \times sequence interactions, OCD: $p = .02$; Control: $p = .05$) (Figure S3 in Supplement 1), and this postcongruent conflict effect did not differ across groups ($p = .37$). Both groups also demonstrated a sequence effect (mean RT alternation [trials in which the congruence alternated relative to the preceding trial] $>$ mean RT repetition [trials in which congruence repeated]) (Table S1 in

Table 1. Demographic and Clinical Characteristics of Participants

Characteristic	Participants				Analysis		
	OCD (n = 22)		Healthy Control (n = 22)				
	Mean	SD	Mean	SD	t	df	p
Age, yrs	30.00	9.09	30.14	9.35	-.05	42	.96
WASI IQ Score (Full-4)	12.73	14.06	17.05	14.22	-.99	40	.33
Duration of Illness, yrs	13.95	9.28	—	—	—	—	—
Age of OCD Onset, yrs	16.05	7.33	—	—	—	—	—
HAM-D Scores	4.81	3.65	—	—	—	—	—
Y-BOCS Total	25.91	4.20	—	—	—	—	—
Obsessions	12.50	2.18	—	—	—	—	—
Compulsions	13.41	2.36	—	—	—	—	—
	n	%	n	%			
Target Symptoms ^a							
Symmetry/ordering	5	22.72					
Doubt/checking	3	13.63					
Contamination/cleaning	6	27.27					
Taboo thoughts	7	31.81					
Hoarding	1	4.54					
Sex							
Male	11	50.00	11	50.00			
Female	11	50.00	11	50.00			
Handedness							
Right	18	81.82	19	86.36			
Left	4	18.18	3	13.64			
Ethnicity							
Asian	—	—	1	4.54			
African-American	4	18.18	4	18.18			
Caucasian	15	68.18	14	63.64			
Hispanic	3	13.64	3	13.64			

HAM-D, Hamilton Depression Scale; OCD, obsessive-compulsive disorder; WASI, Wechsler Abbreviated Scale of Intelligence; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

^aCurrent primary target symptoms from Y-BOCS checklist organized by the 5 symptom dimensions (38,39).

Supplement 1). Accuracy correlated inversely with scores on the doubt/checking symptom dimension, indicating that the OCD participants who endorsed the most pathological doubt and checking compulsions performed least accurately ($r = -.48$; $p = .02$). The conflict and sequence effects correlated positively with doubt/checking symptoms, indicating that the OCD participants who endorsed more of these symptoms took the longest to respond to incongruent versus congruent trials (conflict effect: $r = .59$; $p < .003$) and to alternating versus repeating trials (sequence effect: $r = .51$; $p = .01$).

A Priori Hypothesis Testing

Group Differences in Neural Activity Associated with Postcongruent Conflict. Significant group differences associated with postcongruent conflict were detected in right fronto-striatal regions, including a contiguous cluster encompassing the inferior frontal gyrus (IFG) (Brodmann area [BA] 46), insula (BA 13), and putamen (peak location $x, y, z = 33, -4, 16$) (Figure 1A). These differences derived from greater activation of this cluster in the OCD participants in response to cl versus cC.

Exploratory Analyses

Conflict Effects. With a less stringent threshold ($p = .05$, uncorrected), we explored neural activity associated with conflict

Table 2. Group Differences in Brain Activity Associated with Postcongruent Conflict

Region	Side	Cluster-Level		Peak-Level				
		K_e	p_{corr}	t	p_{uncorr}	x	y	z
Fronto-striatal Cluster	R	120	.045	3.72	.000	33	-4	16

corr, corrected; R, right; uncorr, uncorrected.

effects in both groups. Both the OCD and healthy participants activated fronto-striatal regions in response to postcongruent conflict (Figure 1B,C). In response to all conflict, regardless of the preceding stimulus (congruent or incongruent), both groups activated the pre supplementary motor area (BA 6), but healthy participants activated larger expanses of frontal regions, including ACC (BA 32), bilateral superior frontal gyri (BA 9), and middle frontal gyrus (BA 8) (Figure S4C in Supplement 1). These group differences associated with all conflict were significant at the more stringent threshold ($p < .05$, corrected).

Sequence Effects. To determine whether activation of the right fronto-striatal cluster in OCD was associated with the resolution of postcongruent conflict or with trial sequence (i.e., the alternation or repetition of congruence between current and preceding stimuli), we entered β estimates from the cluster into a repeated-measures factorial analysis of variance in SPSS (SPSS, Chicago, Illinois) (Supplement 1). A significant group \times sequence interaction ($p = .005$) derived from the different effects of trial sequence across groups (OCD, $p = .04$; Control, $p = .01$). Specifically, in OCD participants, activation of the right fronto-striatal cluster was greater during trials in which congruence alternated relative to the previous trial (i.e., cl and iC) than during trials in which congruence repeated (i.e., il and cC), whereas activation was greater during repeated compared with alternating trials in the control participants (Figure S5 in Supplement 1). No significant group \times current congruence interaction ($p = .70$) or main effect of current congruence was detected in either group (p values $> .1$), suggesting that greater fronto-striatal activity in the OCD compared with control participants represented sequence rather than conflict-related activity and was associated with their processing of the stimulus context.

Stimulus-Feature Effects. To exclude the possibility that group differences in fronto-striatal activations were driven by differences in the processing of stimulus features within the sequence (e.g., the repetition or alternation of the position and/or direction of arrow stimuli across trials), we ran an extended model with additional regressors (position repetition, position alternation, direction repetition, direction alternation) (Supplement 1). Neither the within-group effects nor the between-group differences in fronto-striatal activations were driven by the sequence of single stimulus features (all $p > .05$, uncorrected).

Functional Connectivity. To explore whether greater activation of the right fronto-striatal cluster could reflect greater connectivity within fronto-striatal circuits in OCD participants, we used the putamen (sphere centered at Montreal Neurological Institute coordinates $x, y, z = 33, -4, 16$ mm with a 1-mm radius) as the seed region in a connectivity analysis. These coordinates corresponded to those of the peak-level of significance of the right hemisphere cluster associated with postcongruent conflict in our a priori hypothesis test (Table 2). This analysis was a variant of a psychophysiological interaction analysis (44) in SPM8 that allowed assessment of group differences in condition-dependent and condition-independent functional connectivity during

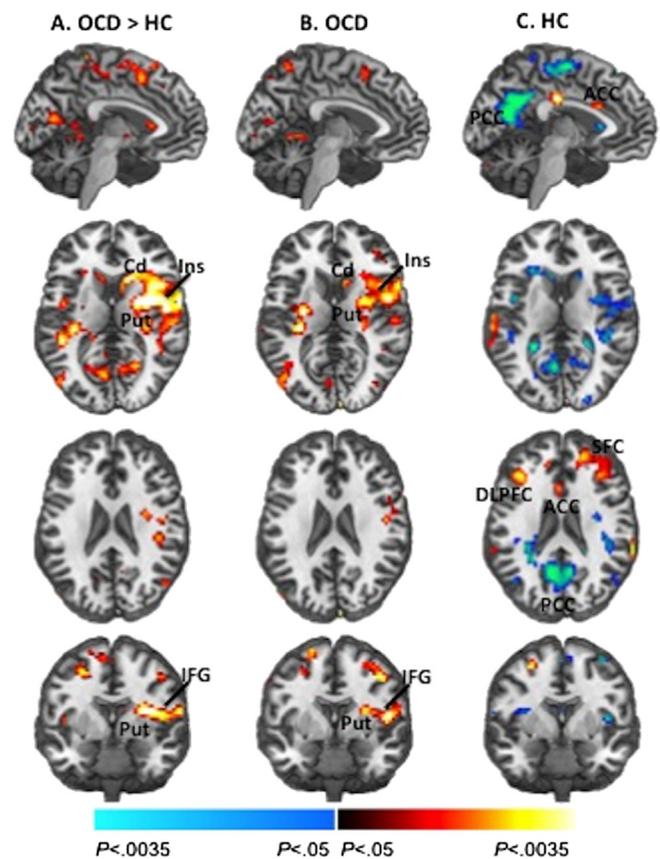


Figure 1. Group average brain activations associated with postcongruent conflict. (A) Group differences in brain activations associated with the processing and resolution of cognitive conflict preceded by congruent trials (postcongruent conflict, cl-cC) were detected in fronto-striatal (red) and default mode network (blue) regions. Group average brain activations are shown for the obsessive-compulsive disorder (OCD) (B) and healthy (HC) (C) participants. Increases in signal during correct responses to cl relative to cC trials are shown in red, and decreases are shown in blue. For display purposes, these maps (generated with MRIcroN; McCausland Center for Brain Imaging, Columbia, South Carolina) are thresholded at $p = .025$, uncorrected, with a cluster filter of 25. The within-group effects did not survive our a priori significance threshold ($p = .005$, cluster filter of 61). The between-group effects remained after controlling for age of onset in the OCD group. ACC, anterior cingulate cortex; Cd, caudate; DLPCF, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; Ins, insula; PCC, posterior cingulate cortex; Put, putamen; SFC, superior frontal cortex.

performance of the task (also see Supplement 1). There was significantly greater connectivity in the OCD compared with control participants between the putamen and large expanses of fronto-striatal and parietal areas (Figure 2; Table S2 in Supplement 1), including right superior frontal gyrus (BA 10), inferior parietal lobule (BA 7) and caudate, left cingulate gyrus (BA 31) and thalamus, and the bilateral precuneus (BA 7/19). Putamen connectivity did not interact with task conditions (i.e., the psychophysiological interaction analysis) either between or within groups (Supplement 1).

Symptom Severity Correlates. In the right fronto-striatal cluster, activity associated with postcongruent conflict and trial sequence correlated positively with doubt/checking symptoms (conflict: $r = .4$; $p = .06$, sequence: $r = .56$; $p = .006$), suggesting that the OCD participants who endorsed more of these

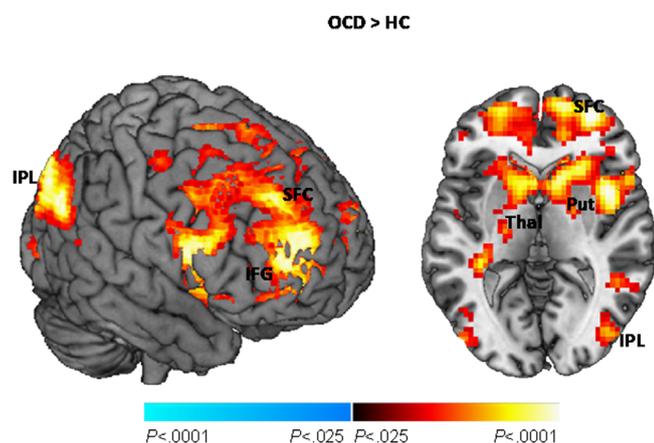


Figure 2. Functional connectivity. Group differences in seed connectivity from the Put. This map is thresholded at $p = .025$, uncorrected, with a cluster filter of 25. Also shown are the cluster- and peak-level statistics corresponding to these group differences in connectivity. CG, cingulate gyrus; Pcu, precuneus; IPL, inferior parietal lobule; Tha, thalamus; other abbreviations as in Figure 1.

symptoms also activated fronto-striatal regions more in response to postcongruent conflict and especially in response to the alternation of stimuli (i.e., during trial sequences in which the congruence of stimuli alternated). An outlier test (45) revealed that this positive correlation was not driven by the three OCD participants with the greatest number of doubt/checking symptoms. No significant correlations of brain activation with other symptom dimensions or overall symptom severity (Y-BOCS scores) were detected (p values $> .2$). In addition, no significant correlations of functional connectivity with symptom dimensions were detected (p values $> .05$) (Figure 3).

Discussion

Unmedicated OCD participants performed similarly to control subjects on a Simon task with low cognitive demand. Nevertheless, activation of a large right hemisphere cluster of fronto-striatal regions in response to postcongruent conflict was significantly greater in the OCD participants. These regions included the IFG, insula, and putamen. Greater activation of this right fronto-striatal cluster in OCD participants was driven by their response to the alternation of congruence across trials rather than current trial conflict. Functional connectivity between the putamen and large expanses of fronto-striatal regions was also greater in the OCD compared with control participants, suggesting that increased connectivity might contribute to increased activation within fronto-striatal circuits in OCD.

Previous fMRI studies of cognitive control and conflict processing also suggest excessive activation within fronto-striatal circuits in OCD patients compared with control subjects (8,13,14,46). Those studies report greater activation of the OFC (14,46) and ACC (8,13,16) with different tasks, including Go/No-go (11,14), continuous performance (13), multisource interference (8), and Stroop-like (10,16) tasks. Prior studies in healthy individuals indicate that the Simon task does not measure OFC functioning (22,23,30); thus it is unsurprising that this region was not implicated in our between- or within-group findings, but that healthy individuals activate the ACC in response to errors (47) and conflict (48) on the Simon task. We did not assess

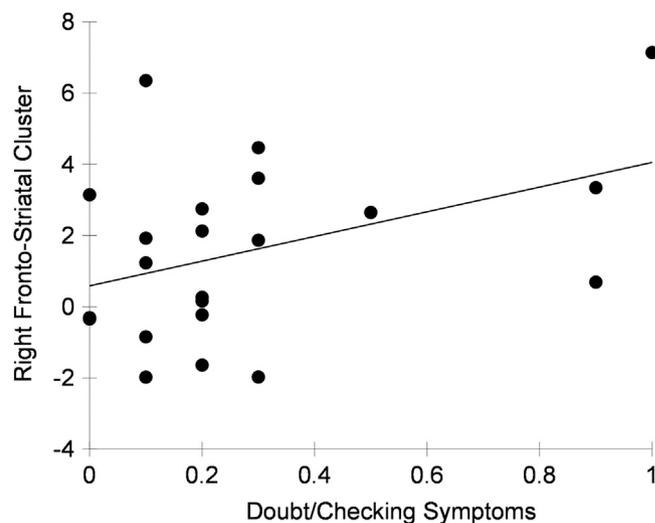


Figure 3. Main effects of symptom severity in the obsessive-compulsive disorder participants. A scatterplot of the association of sequence-related neural activity in the right fronto-striatal cluster with scores on the doubt/checking symptom dimension of the Yale-Brown Obsessive Compulsive Scale.

activation associated with errors, because our low cognitive demand task did not generate many errors in either group. The healthy but not our unmedicated OCD participants activated the ACC in response to postcongruent conflict (Figure 1C) and all conflict (Figure S4C in Supplement 1), consistent with prior findings from healthy individuals (22–24). Importantly, most prior fMRI studies of cognitive control and conflict processing in OCD recruited medicated patients (8,13,16), complicating comparison with our data, because SSRIs can alter activation of fronto-striatal circuits on various fMRI tasks (49). In addition, prior fMRI studies included OCD patients with comorbid depression and anxiety (11,14), whereas such participants were excluded from our study.

Our findings implicate instead a right fronto-striatal circuit involving the IFG, insula, and putamen in OCD. Right lateral prefrontal regions, particularly the right inferior frontal cortex, typically activate during successful response inhibition in healthy individuals (50–52). Activation of the right inferior frontal cortex has been associated with correctly rejected high conflict trials on Go/No-go tasks in OCD (11,14), with one study reporting increased (14) and the other reporting decreased activation compared with control subjects with a different task design with medicated patients (11). Altered resting-state connectivity from the insula to fronto-parietal and other brain areas (53), reduced serotonin transporter binding in the insula (54), and increased gray matter in the putamen has been reported in OCD compared with control participants (5,55). However, neither the insula nor the putamen has been implicated in prior fMRI studies of cognitive control or conflict processing in OCD. We speculate that differences between our Simon task and the tasks used previously, and our inclusion of only unmedicated OCD participants, contributed to our detection of increased activation of the right inferior frontal cortex, insula, and putamen.

Activation of this right fronto-striatal circuit was driven by the neural responses of OCD participants to the alternation of congruence across trials. This activation was driven neither by conflict per se nor by their differential responses to the alternation or repetition of lower-order stimulus features, such

as the position and direction of the arrow stimuli, but rather to their differential responses to sequential changes in conflict. Perhaps the OCD participants needed to engage these fronto-striatal regions more to compensate for their difficulty processing the alternating stimulus context, consistent with their phenomenological difficulty processing changing environmental contingencies and their overall cognitive inflexibility (1). These ideas are consistent with a neurocomputational model (56) used to explain the neural basis of cognitive inflexibility in OCD (57). The model quickly learns and actively maintains new sequences, flexibly shifting between them but can get “stuck,” becoming unable to shift from certain sequences so that it exhibits repetitive patterns of activity that are similar to the repetitive thoughts and behaviors of OCD. The model highlights the importance of the balance between direct (disinhibitory) and indirect (inhibitory) fronto-striatal pathways in OCD (57). Thus, the differential processing of alternating stimulus sequences and excessive activity within fronto-striatal circuits in OCD participants during Simon task performance might also be due to this imbalance between the direct and indirect pathways. These pathways are implicated in sequence learning, the acquisition and maintenance repetitive behaviors, and in OCD pathophysiology (58).

The pattern of functional connectivity from the putamen that we detected in both groups is consistent with prior functional connectivity studies of healthy individuals (59). Our finding of greater connectivity of the putamen with frontal and parietal brain areas in OCD is consistent with findings of greater resting-state connectivity within these circuits in OCD (53). Evidence from fMRI and animal lesion studies suggests that the putamen plays a key role in switching between stimuli on tasks of cognitive flexibility (60,61). Furthermore, frontal stimulation by transcranial magnetic stimulation disrupts fMRI signal associated with stimulus switching in the putamen and reduces fronto-putamen functional connectivity in healthy individuals (62). These findings suggest that greater functional connectivity of the putamen with frontal and parietal areas in OCD participants might contribute to their greater activation of the putamen in response to the alternation (or switching) of stimuli on the Simon task. By analogy, greater connectivity within these circuits in persons with OCD might also contribute to their overall cognitive inflexibility. Alternatively, the greater connectivity might be a compensatory strategy, allowing them to perform as well as control participants, despite their difficulty processing the alternating stimuli on the Simon task and possibly allowing them to function in a world of changing environmental contingencies despite their general cognitive inflexibility.

Prior neuroimaging studies report distinct neural correlates of different symptom dimensions (63–66). We found that OCD participants who endorsed the most doubt/checking symptoms experienced the most cognitive conflict (i.e., greatest conflict effect: mean RT incongruent > mean RT congruent) and performed least accurately on the task. Activation of the right hemisphere fronto-striatal cluster was also greatest in these participants, especially in response to the alternation of stimulus congruence (Figure S5 in Supplement 1). Pathological doubt and checking compulsions are associated with a high degree of intolerance for uncertainty (67). Thus, participants who endorse more of these symptoms possibly had to engage fronto-striatal circuits the most to compensate for their difficulty processing the uncertainty of the stimulus context (the alternating stimuli). The right fronto-striatal cluster included the insula, a region that activates in association with the

intolerance of uncertainty in healthy individuals (68). Recent findings suggest that morphometric alterations within the right insula (enlarged anterior and reduced posterior insular volumes compared with healthy individuals) are most pronounced in OCD patients with predominant checking symptoms (69). Thus, both functional and structural characteristics of the insula might differentiate doubt/checking from other dimensions.

Although one of the largest studies of inhibitory control and conflict resolution in unmedicated adults with OCD, this study is still limited by its modest sample size, inclusion of OCD subjects (8 of 22) with past exposure to psychotropic medication, and the absence of general anxiety measures. However, general anxiety was likely to be very low, because we excluded OCD participants with current comorbid Axis I disorders, including anxiety and depressive disorders.

Our findings suggest important avenues for future research. For example, the inclusion of additional tasks of response inhibition and conflict resolution in future studies would confirm that our findings generalize to other measures of these processes. Future studies should also investigate other capacities that rely on these circuits, such as stimulus-response (habit) learning that relies on the dorsolateral putamen (70). Perhaps an over-reliance on a right hemisphere fronto-striatal circuit involving the putamen allows the compulsive behaviors of individuals with OCD to crystalize into maladaptive habits, consistent with current theories suggesting that an abnormal reliance on habits might contribute, in part, to compulsions in OCD (71).

In summary, when engaging the control processes necessary to resolve conflict and process the alternating stimulus context, OCD participants displayed excessive activation in the putamen, insula, and IFG. This dysfunction was associated with the processing of changes in contextual information, and we speculate this might be related to the cognitive inflexibility that is typical of persons with OCD.

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1. Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ (2005): The neuropsychology of obsessive compulsive disorder: The importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci Biobehav Rev* 29: 399–419.
2. Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, *et al.* (2004): Mapping structural brain alterations in obsessive-compulsive disorder. *Arch Gen Psychiatry* 61:720–730.
3. Rosenberg DR, Keshavan MS (1998): A.E. Bennett Research Award. Toward a neurodevelopmental model of obsessive-compulsive disorder. *Biol Psychiatry* 43:623–640.

4. Atmaca M, Yildirim H, Ozdemir H, Tezcan E, Poyraz AK (2007): Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 31: 46–52.
5. Rotge JY, Guehl D, Dilharreguy B, Tignol J, Bioulac B, Allard M, *et al.* (2009): Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biol Psychiatry* 65:75–83.
6. Sumitani S, Harada M, Kubo H, Ohmori T (2007): Proton magnetic resonance spectroscopy reveals an abnormality in the anterior cingulate of a subgroup of obsessive-compulsive disorder patients. *Psychiatry Res* 154:85–92.
7. Bartha R, Stein MB, Williamson PC, Drost DJ, Neufeld RW, Carr TJ, *et al.* (1998): A short echo 1H spectroscopy and volumetric MRI study of the corpus striatum in patients with obsessive-compulsive disorder and comparison subjects. *Am J Psychiatry* 155:1584–1591.
8. Yucel M, Harrison BJ, Wood SJ, Fornito A, Wellard RM, Pujol J, *et al.* (2007): Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. *Arch Gen Psychiatry* 64: 946–955.
9. Maia TV, Cooney RE, Peterson BS (2008): The neural bases of obsessive-compulsive disorder in children and adults. *Dev Psychopathol* 20:1251–1283.
10. Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, *et al.* (2005): A functional MRI comparison of patients with obsessive-compulsive disorder and normal controls during a Chinese character Stroop task. *Psychiatry Res* 139:101–114.
11. Roth RM, Saykin AJ, Flashman LA, Pixley HS, West JD, Mamourian AC (2007): Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. *Biol Psychiatry* 62:901–909.
12. Gehring WJ, Himle J, Nisenson LG (2000): Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychol Sci* 11:1–6.
13. Ursu S, Stenger VA, Shear MK, Jones MR, Carter CS (2003): Overactive action monitoring in obsessive-compulsive disorder: Evidence from functional magnetic resonance imaging. *Psychol Sci* 14:347–353.
14. Maltby N, Tolin DF, Worhunsky P, O'Keefe TM, Kiehl KA (2005): Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: An event-related fMRI study. *Neuroimage* 24:495–503.
15. Page LA, Rubia K, Deeley Q, Daly E, Toal F, Mataix-Cols D, *et al.* (2009): A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Res* 174: 202–209.
16. 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.
17. van den Heuvel OA, Veltman DJ, Groenewegen HJ, Witter MP, Merkelbach J, Cath DC, *et al.* (2005): Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Arch Gen Psychiatry* 62:922–933.
18. Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr (2003): Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *Am J Psychiatry* 160:522–532.
19. Wagner G, Koch K, Schachtzabel C, Sobanski T, Reichenbach JR, Sauer H, *et al.* (2010): Differential effects of serotonergic and noradrenergic antidepressants on brain activity during a cognitive control task and neurofunctional prediction of treatment outcome in patients with depression. *J Psychiatry Neurosci* 35:247–257.
20. 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.
21. Simon JR (1969): Reactions toward the source of stimulation. *J Exp Psychol* 81:174–176.
22. Peterson BS, Kane MJ, Alexander GM, Lacadie C, Skudlarski P, Leung HC, *et al.* (2002): An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. *Brain Res Cogn Brain Res* 13:427–440.
23. Liu X, Banich MT, Jacobson BL, Tanabe JL (2004): Common and distinct neural substrates of attentional control in an integrated Simon and spatial Stroop task as assessed by event-related fMRI. *Neuroimage* 22:1097–1106.
24. Rubia K, Smith AB, Woolley J, Nosarti C, Heyman I, Taylor E, *et al.* (2006): Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. *Hum Brain Mapp* 27:973–993.
25. Wuhr P, Ansorge U (2005): Exploring trial-by-trial modulations of the Simon effect. *Q J Exp Psychol A* 58:705–731.
26. Sturmer B, Leuthold H, Soetens E, Schroter H, Sommer W (2002): Control over location-based response activation in the Simon task: Behavioral and electrophysiological evidence. *J Exp Psychol Hum Percept Perform* 28:1345–1363.
27. Mansouri FA, Buckley MJ, Tanaka K (2007): Mnemonic function of the dorsolateral prefrontal cortex in conflict-induced behavioral adjustment. *Science* 318:987–990.
28. Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999): Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402:179–181.
29. Ullsperger M, Bylsma LM, Botvinick MM (2005): The conflict adaptation effect: It's not just priming. *Cogn Affect Behav Neurosci* 5:467–472.
30. Horga G, Maia TV, Wang P, Wang Z, Marsh R, Peterson BS (2011): Adaptation to conflict via context-driven anticipatory signals in the dorsomedial prefrontal cortex. *J Neurosci* 31:16208–16216.
31. Kerns JG (2006): Anterior cingulate and prefrontal cortex activity in an fMRI study of trial-to-trial adjustments on the Simon task. *Neuroimage* 33:399–405.
32. Marsh R, Steinglass JE, Gerber AJ, O'Leary KG, Walsh BT, Peterson BS (2009): Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Arch Gen Psychiatry* 66:1–13.
33. Wilkinson D, Halligan P (2004): The relevance of behavioural measures for functional-imaging studies of cognition. *Nat Rev Neurosci* 5:67–73.
34. First MB, Spitzer RL, Gibbon M, Williams JBW (2002): *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition (SCID-I/NP)*. New York: Biometrics Research, New York State Psychiatric Institute.
35. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Henninger GR, *et al.* (1989): The Yale-Brown Obsessive Compulsive Scale: I. Development, use, and reliability. *Arch Gen Psychiatry* 46: 1006–1011.
36. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Henninger GR, *et al.* (1989): Yale-Brown Obsessive Compulsive Scale: II. Validity. *Arch Gen Psychiatry* 46:1012–1018.
37. Hamilton MAX (1967): Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278–296.
38. Pinto A, Eisen JL, Mancebo MC, Greenberg BD, Stout RL, Rasmussen SA (2007): Taboo thoughts and doubt/checking: A refinement of the factor structure for obsessive-compulsive disorder symptoms. *Psychiatry Res* 151:255–258.
39. Pinto A, Greenberg BD, Grados MA, Bienvenu OJ 3rd, Samuels JF, Murphy DL, *et al.* (2008): Further development of YBOCS dimensions in the OCD Collaborative Genetics study: Symptoms vs. categories. *Psychiatry Res* 160:83–93.
40. Wechsler D (1981): *WAIS-R Manual. Wechsler Adult Intelligence Scale-Revised*. San Antonio, Texas: The Psychological Corporation.
41. Henson RN, Price CJ, Rugg MD, Turner R, Friston KJ (2002): Detecting latency differences in event-related BOLD responses: Application to words versus nonwords and initial versus repeated face presentations. *Neuroimage* 15:83–97.
42. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magn Reson Med* 33:636–647.
43. Simpson HB, Shungu DC, Bender J Jr, Mao X, Xu X, Slifstein M, Kegeles LS (2012): Investigation of cortical glutamate-glutamine and γ -aminobutyric acid in obsessive-compulsive disorder by proton magnetic resonance spectroscopy. *Neuropsychopharmacology* 37:2684–2692.
44. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997): Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6:218–229.
45. Grubbs FE (1969): Procedures for detecting outlying observations in samples. *Technometrics* 11:1–21.
46. Ursu S, Carter CS (2009): An initial investigation of the orbitofrontal cortex hyperactivity in obsessive-compulsive disorder: Exaggerated

- representations of anticipated aversive events? *Neuropsychologia* 47: 2145–2148.
47. Menon V, Adleman NE, White CD, Glover GH, Reiss AL (2001): Error-related brain activation during a Go/NoGo response inhibition task. *Hum Brain Mapp* 12:131–143.
 48. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.
 49. Del-Ben CM, Deakin JF, McKie S, Delvai NA, Williams SR, Elliott R, *et al.* (2005): The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: An fMRI study. *Neuropsychopharmacology* 30:1724–1734.
 50. Rubia K, Smith AB, Brammer MJ, Taylor E (2003): Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* 20: 351–358.
 51. Marsh R, Zhu H, Schultz RT, Quackenbush G, Royal J, Skudlarski P, *et al.* (2006): A developmental fMRI study of self-regulatory control. *Hum Brain Mapp* 27:848–863.
 52. Chambers CD, Garavan H, Bellgrove MA (2009): Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev* 33:631–646.
 53. 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.
 54. Matsumoto R, Ichise M, Ito H, Ando T, Takahashi H, Ikoma Y, *et al.* (2010): Reduced serotonin transporter binding in the insular cortex in patients with obsessive-compulsive disorder: A [¹¹C]DASB PET study. *Neuroimage* 49:121–126.
 55. Valente AA Jr, Miguel EC, Castro CC, Amaro E Jr, Duran FL, Buchpiguel CA, *et al.* (2005): Regional gray matter abnormalities in obsessive-compulsive disorder: A voxel-based morphometry study. *Biol Psychiatry* 58:479–487.
 56. Verduzco-Flores S, Ermentrout B, Bodner M (2012): Modeling neuro-pathologies as disruption of normal sequence generation in working memory networks. *Neural Netw* 27:21–31.
 57. Maia TV, McClelland JL (2012): A neurocomputational approach to obsessive-compulsive disorder. *Trends Cogn Sci* 16:14–15.
 58. Graybiel AM (2008): Habits, rituals, and the evaluative brain. *Annu Rev Neurosci* 31:359–387.
 59. Postuma RB, Dagher A (2006): Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cereb Cortex* 16:1508–1521.
 60. Cools R, Ivry RB, D'Esposito M (2006): The human striatum is necessary for responding to changes in stimulus relevance. *J Cogn Neurosci* 18: 1973–1983.
 61. Cools R, Clark L, Robbins TW (2004): Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. *J Neurosci* 24:1129–1135.
 62. van Schouwenburg MR, O'Shea J, Mars RB, Rushworth MF, Cools R (2012): Controlling Human Striatal Cognitive Function via the Frontal Cortex. *J Neurosci* 32:5631–5637.
 63. Rauch SL, Wedig MM, Wright CI, Martis B, McMullin KG, Shin LM, *et al.* (2007): Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. *Biol Psychiatry* 61:330–336.
 64. van den Heuvel OA, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, *et al.* (2009): The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain* 132:853–868.
 65. Jang JH, Kim JH, Jung WH, Choi JS, Jung MH, Lee JM, *et al.* (2010): Functional connectivity in fronto-subcortical circuitry during the resting state in obsessive-compulsive disorder. *Neurosci Lett* 474:158–162.
 66. Gilbert AR, Akkal D, Almeida JR, Mataix-Cols D, Kalas C, Devlin B, *et al.* (2009): Neural correlates of symptom dimensions in pediatric obsessive-compulsive disorder: A functional magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 48:936–944.
 67. Tolin DF, Abramowitz JS, Brigidi BD, Foa EB (2003): Intolerance of uncertainty in obsessive-compulsive disorder. *J Anxiety Disord* 17:233–242.
 68. Simmons A, Matthews SC, Paulus MP, Stein MB (2008): Intolerance of uncertainty correlates with insula activation during affective ambiguity. *Neurosci Lett* 430:92–97.
 69. Song A, Jung WH, Jang JH, Kim E, Shim G, Park HY, *et al.* (2011): Disproportionate alterations in the anterior and posterior insular cortices in obsessive-compulsive disorder. *PLoS One* 6:e22361.
 70. Packard MG, Knowlton BJ (2002): Learning and memory functions of the basal ganglia. *Annu Rev Neurosci* 25:563–593.
 71. Gillan CM, Pappmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW, *et al.* (2011): Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry* 168:718–726.