ORIGINAL ARTICLE

Frontal-Striatal Dysfunction During Planning in Obsessive-Compulsive Disorder

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Background: Dysfunction of frontal-striatal, particularly orbitofrontal-striatal, circuitry has been implicated in the pathophysiology of obsessive-compulsive disorder (OCD), characterized by obsessions, ritualistic behavior, anxiety, and specific cognitive impairments. In addition, neuropsychological studies in OCD have reported impairments in visuospatial tasks and executive functions, such as planning.

Objective: To determine whether dorsal prefrontal-striatal dysfunction mediates planning impairment in patients with OCD.

Design: A parametric self-paced pseudorandomized event-related functional magnetic resonance imaging version of the Tower of London task was used in 22 medication-free patients with OCD and 22 healthy control subjects. This paradigm, allowing flexible responding and post hoc classification of correct responses, was developed to compare groups likely to differ in performance.

Results: Behavioral results showed significant planning impairments in OCD patients compared with control subjects. During planning, decreased frontal-striatal responsiveness was found in OCD patients, mainly in dorsolateral prefrontal cortex and caudate nucleus. In addition, OCD patients showed increased, presumably compensatory, involvement of brain areas known to play a role in performance monitoring and short-term memory processing, such as anterior cingulate, ventrolateral prefrontal, and parahippocampal cortices.

Conclusions: These findings support the hypothesis that decreased dorsal prefrontal-striatal responsiveness is associated with impaired planning capacity in OCD patients. Because the described frontal-striatal dysfunction in OCD is independent of state anxiety and disease symptom severity, we conclude that executive impairment is a core feature in OCD.

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CLINICAL, NEUROSURGICAL, and functional neuroimaging studies have provided evidence that dysfunctional prefrontal cortex (PFC)–basal ganglia circuits are involved in the pathogenesis of obsessive-compulsive disorder (OCD). The high cooccurrence between OCD and other basal ganglia disorders strongly supports the so-called frontal-striatal hypothesis.[1,2] In addition, recent neuropsychological studies[3,4] have shown cognitive impairments in OCD, particularly with regard to visuospatial processing, executive functioning, and motor speed. Other cognitive domains appear to remain intact, indicating a specific, rather than a general, cognitive deficit.

Executive functioning implies different subdomains of higher-order cognitive functioning. Planning, that is, the ability to achieve a goal through a series of intermediate steps, is an essential component of higher-order cognitive processing, such as problem solving. Using a neuronal network model, Dehaene and Changeux[5] proposed multiple hierarchical levels coding for specialized subprocesses of planning, such as plan generation, working memory, and internal evaluation and reward. Some subprocesses seem to be relatively independent of task load, ie, increasing planning complexity, while other subprocesses are mainly involved at higher levels of planning behavior.

A frequently used test to probe planning processes is the Tower of London task (ToL), adapted from the Tower of Hanoi task.[6,7] The ToL has been used to investigate planning in healthy control subjects using positron emission tomography,[8-12] single-photon emission computed tomography,[13,14] and functional magnetic resonance imaging (fMRI).[12,15-20] The results of these imaging studies agree on the involvement of dorsolateral prefrontal cortex

Table 1. Demographic Characteristics*

Variable	Control Subjects (n = 22)	Patients With Obsessive-Compulsive Disorder (n = 22)
Age, y	29.9 ± 7.4	34.4 ± 8.6
Male/female ratio	11:11	7:15
Education (range, 1-8), y†	7.36	5.67‡
Yale-Brown Obsessive Compulsive Scale	0	22.2 ± 6.5§
Padua Inventory–Revised	9.9 ± 10.4	61.3 ± 21.9§

*Data are given as mean ± SD unless otherwise indicated.
†1 indicates primary school; 8, university.
‡$P<.01$.
§$P<.001$.

(DLPFC) and parietal-occipital regions during planning. However, activation of other brain regions, such as cingulate[9,10,12,16,17,19] and insular[9,10,17] cortices, striatum,[8,10,12,16,17,20] and rostral PFC,[9,10,17] has not been found across all mentioned studies. These inconsistencies are likely to be explained by methodological differences between these studies, such as group size, scanning modality, analysis technique (regions of interest vs whole-brain analysis), and details of task paradigms. For example, baseline conditions have not been uniform (low level vs matched for visual complexity and motor demands). Also, some paradigms require mental execution, whereas in others a touch screen is used. Keith Berg and Byrd[21] emphasized the potential effect of such modifications, providing recommendations for constructing, for example, computerized versions of the ToL to increase comparability across studies.

Neuropsychological studies of planning ability, as a measure of executive functioning, in patients with OCD have not provided wholly consistent results. Veale et al,[22] using a computerized version of the ToL, found no difference in accuracy between OCD patients and control subjects. However, when OCD patients made a mistake, they spent more time than controls in generating alternative solutions or in checking next responses. Normal accuracy in planning execution in OCD was also found by Schmidtke et al,[23] using the Tower of Hanoi task; however, in this study, no response time (RT) data were collected. Results of a study by Purcell et al,[24] comparing neuropsychological profiles of patients with OCD, panic disorder, and major depressive disorder (MDD), highlight the importance of task implementation. Although motor speed was decreased, OCD patients showed a normal ability to organize and execute a series of goal-directed moves on a planning task when using a touch screen, providing external validation of ongoing performance. In contrast, when the task had to be executed mentally, OCD patients were significantly impaired. Whether impaired executive functioning is a trait feature of OCD, that is, not secondary to present mood or anxiety symptoms, is not yet clear. Impaired performance relative to controls was found in a study[25] of subclinical obsessive-compulsive subjects. However, in this study, it was also found that performance was inversely correlated with symptom severity, particularly severity of checking behavior.

Although these neuropsychological studies, together with functional imaging studies in healthy subjects, suggest that the executive impairment found in OCD patients reflects dorsal prefrontal-striatal dysfunction, so far no imaging study has been published in which this hypothesis has been investigated. Functional imaging studies using executive tasks have been performed in schizophrenia[26] and MDD,[27] whereas in OCD most studies have used symptom provocation paradigms. However, evidence of striatal dysfunction in OCD has been provided in a positron emission tomography study using an implicit learning task.[28,29] In this study, OCD patients showed increased activity of posterior (temporal and parietal) cortical regions relative to controls, explained as compensatory mechanisms.

The aim of the present study was to investigate dorsal prefrontal-striatal function during performance of a planning task in OCD patients compared with controls. We used a parametric self-paced pseudorandomized event-related version of the ToL,[17] suitable for fMRI. A self-paced parametric design allows flexible responding, as well as comparisons between subjects or groups at each task level, resulting in increased comparability across groups with varying levels of performance. In addition, an event-related design enables post hoc classification of events based on subjects' responses, so that correct responses and errors can be analyzed separately. Based on previous studies, we expected task performance in OCD subjects to be impaired; in addition, we hypothesized this planning deficit to be reflected in decreased responsiveness of striatal and dorsal prefrontal regions as assessed using fMRI.

METHODS

SUBJECTS

Twenty-two OCD patients (mean age, 34.4 years [age range, 21-49 years]; 7 men and 15 women) and 22 healthy control subjects (mean age, 29.9 years [age range, 23-51 years]; 11 men and 11 women) performed the ToL while fMRI data were collected. All subjects were right-handed, as assessed during a medical interview. Exclusion criteria were the presence of major medical illness, co-occurrence of other major psychiatric disorders, and the use of psychotropic medication. Subjects had to be off medication for at least 4 weeks. Diagnoses were established using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[30] The Yale-Brown Obsessive Compulsive Scale[31] and the Padua Inventory–Revised[32,33] were used to assess symptom characteristics and severity scores (**Table 1**). Patients were recruited from the Outpatient Clinic for Anxiety Disorders and Dutch Foundation for Anxiety Disorders, Driebergen, the Netherlands. The ethical review board of the VU University Medical Center approved the study, and all participants provided written informed consent.

TASK PARADIGM

A pseudorandomized self-paced version of the ToL was used, discussed in detail previously.[17] This version consisted of 6 conditions, including a baseline condition and 5 planning conditions, ranging from 1 to 5 moves. In the planning conditions, subjects saw a starting configuration together with a target configuration, with the instruction to "count the number of steps." Two possible answers were shown, from which the correct one had to be selected (**Figure 1**A). In both configurations, 3 colored beads were placed on 3 vertical rods, which could accom-

modate 1, 2, and 3 beads each. One bead could be moved at a time and only when there was no other bead on top. Subjects were requested to determine the minimum number of moves necessary to reach the target configuration and to press the button corresponding to the side (left or right) of the screen where the correct answer was presented. In the baseline condition, subjects simply had to count the total number of yellow and blue beads (Figure 1B). A pseudorandomized design was adopted to control for any overflow effects (ie, perseverance of task-related cognitive processes after a difficult trial). Therefore, each trial of 3 or more moves was followed by a baseline trial. No feedback regarding the answers was provided during the task. A maximum RT of 30 seconds for each trial was applied. After performing the task, subjects were asked to rate subjective distress using 100-point analogue scales. To ensure that participants were familiar with the procedure, the test was explained and practiced outside the scanner before fMRI was performed.

DATA ACQUISITION

Imaging was performed on a 1.5-T Sonata system (Siemens Medical Solutions, Erlangen, Germany) with a standard circularly polarized head coil. Stimuli were generated by a Pentium personal computer (Dell Inc, Round Rock, Tex) and projected on a screen at the end of the scanner table, which was seen through a mirror mounted above the subject's head. Two magnet-compatible 4-key response boxes were used to record the subject's performance and RTs. To reduce motion artifacts, the subject's head was immobilized using foam pads.

Anatomic imaging included a coronal 3-dimensional gradient-echo T1-weighted sequence (matrix, 256×160 pixels; voxel size, 1×1×1.5 mm; 160 sections). For fMRI, an echoplanar imaging sequence (repetition time, 3.045 seconds; echo time, 45 milliseconds; matrix, 64×64 pixels; field of view, 192×192 mm; flip angle, 90°) was used, creating transversal whole-brain acquisitions (35 slices, 3×3-mm in-plane resolution, 2.5-mm slice thickness, 0.5-mm interslice gap). In total, 433 echoplanar imaging volumes per subject were scanned. The distribution frequency of event types was based on RT data of a pilot study, so that a similar number of scans (approximately 70 echoplanar imaging volumes) was acquired per subject for each of the 6 conditions.

DATA ANALYSIS

Demographic and behavioral data were analyzed using SPSS software (version 11.0; SPSS Inc, Chicago, Ill). Imaging data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, London, England). After discarding the first 4 volumes, time series were corrected for differences in slice acquisition times and realigned. Spatial normalization into approximate Talairach and Tournoux space was performed using a standard statistical parametric mapping echoplanar imaging template. Data were resliced to 2×2×2-mm voxels and spatially smoothed using a 6-mm gaussian kernel.

Next, data were analyzed in the context of the general linear model, using delta functions convolved with a canonical hemodynamic response function to model responses of varying lengths to each type of stimulus. In addition, error trials were modeled separately as a regressor of no interest. For each subject, weighted contrasts were computed for main effects, that is, all active conditions vs baseline. In addition, specific linear contrasts for task load were computed.[34] Contrast images containing parameter estimates for main effects and task load were entered into a second-level (random effects) analysis. Main effects for each group are reported at $P<.05$ corrected for multiple comparisons; group interaction effects (masked with the appropriate main effect) are reported at an uncorrected threshold of $P<.001$.

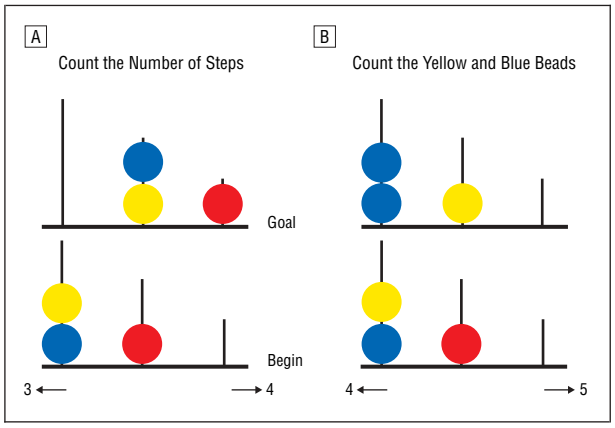

Figure 1. Display screen of Tower of London task as used in the present study. A, Planning condition. B, Baseline condition.

RESULTS

DEMOGRAPHIC AND BEHAVIORAL DATA

The groups did not differ significantly with respect to age and sex ratio. Education level, however, was higher in control subjects. The OCD symptom severity, as measured with the Yale-Brown Obsessive Compulsive Scale and Padua Inventory–Revised questionnaires, was significantly higher in patients (Table 1). Analysis of variance of behavioral data showed significant differences in performance between OCD patients and controls at all task levels, whereas RTs were longer in OCD patients compared with controls only in the 2 easiest planning conditions (**Table 2**). The mean ± SD subjective distress scores were significantly higher in the OCD group compared with the control group (42.1±25.5 vs 21.2±11.8, $F_{1,42}=12.4$; $P<.001$). Within groups, performance was not significantly correlated with trait or state measures ($P>.10$ for all).

IMAGING DATA

Main Effects of Task

In controls, regions showing increased blood oxygenation level–dependent signal during planning compared with baseline (**Table 3**) were found bilaterally in dorsolateral prefrontal (Brodmann areas [BAs] 9 and 46), motor and premotor (BAs 4, 6, and 8), inferior parietal (BA 40), and insular and superior occipital (BA 19) cortices, as well as in bilateral precuneus (BA 7), right caudate nucleus, and left globus pallidus. The OCD patients showed increased blood oxygenation level–dependent signal in most of these regions as well. However, in contrast to control subjects, no activation was found in the striatum during planning in OCD patients. In addition, activation was found in right cingulate cortex (BA 32). Group-by-task interaction analyses (**Table 4**) showed increased activation in controls compared with OCD patients in right DLPFC (BAs 9 and 46),

Table 2. Response Times and Performance Scores*

Condition	Control Subjects (n = 22)		Patients With Obsessive-Compulsive Disorder (n = 22)	
	Response Time, s	Performance Score, %	Response Time, s	Performance Score, %
Baseline	3.71 ± 0.88	94.2 ± 1.7	4.23 ± 1.07	88.3 ± 3.7†
1 Move	4.44 ± 1.10	97.6 ± 2.0	5.46 ± 1.39‡	78.5 ± 9.0†
2 Moves	5.79 ± 1.26	95.4 ± 4.0	6.66 ± 1.49§	79.3 ± 16.0†
3 Moves	7.40 ± 1.89	96.7 ± 3.6	8.51 ± 2.08	72.0 ± 15.7†
4 Moves	10.06 ± 2.48	89.9 ± 7.1	10.72 ± 3.41	68.1 ± 14.3†
5 Moves	14.99 ± 3.99	82.2 ± 12.6	14.99 ± 5.54	63.6 ± 21.3†

*Data are given as mean ± SD.
†$P<.001$.
‡$P<.01$.
§$P<.05$.

Table 3. Brain Regions Showing Significant Blood Oxygenation Level–Dependent Signal Increase During Planning Compared With Baseline*

Region	Side	Brodmann Area	Control Subjects (n = 22)				Patients With Obsessive-Compulsive Disorder (n = 22)			
			Talairach Coordinates				Talairach Coordinates			
			x	y	z	*z* Score	x	y	z	*z* Score
Dorsolateral prefrontal cortex	Left	9, 46	–40	30	28	4.46	. . .	. . .	. . .	. . .
	Left	9	. . .	. . .	. . .	. . .	–44	38	30	3.78
	Right	9	48	34	34	4.05	. . .	. . .	. . .	. . .
	Right	9, 46	. . .	. . .	. . .	. . .	48	38	30	3.63
Cingulate cortex	Right	32	. . .	. . .	. . .	. . .	10	24	42	3.78
Premotor cortex	Left	4, 6	–20	–6	50	4.50	. . .	. . .	. . .	. . .
	Right	4	24	–12	52	4.31	. . .	. . .	. . .	. . .
	Left	6	–22	10	58	4.67	–24	12	52	5.69
	Right	6	22	16	50	4.83	24	6	54	4.54
	Left	8	–22	20	48	3.48	. . .	. . .	. . .	. . .
	Right	8	8	24	48	3.67	. . .	. . .	. . .	. . .
Precuneus	Left	7	–6	–54	48	5.05	. . .	. . .	. . .	. . .
	Left	7	–12	–62	22	4.90	–2	–56	54	4.84
	Right	7	10	–58	48	5.59	8	–58	52	4.41
Inferior parietal cortex	Left	40	–26	–44	48	4.52	–30	–48	46	4.03
	Right	40	52	–40	46	3.82	38	–42	44	3.53
Insular cortex	Left		–28	18	–2	4.91	–32	22	–4	3.65
	Right		28	26	0	4.36	. . .	. . .	. . .	. . .
Caudate nucleus	Right		12	12	0	4.23	. . .	. . .	. . .	. . .
Globus pallidus	Left		–10	8	–2	4.04	. . .	. . .	. . .	. . .
Superior occipital cortex	Left	19	–42	–76	30	5.05	–38	–78	32	4.60
	Right	19	38	–78	32	3.95	. . .	. . .	. . .	. . .

*At $P<.05$ corrected.

right premotor cortex (BA 6), left cingulate cortex (BA 32), bilateral precuneus (BA 7), left inferior parietal cortex (BA 40), right caudate nucleus (**Figure 2**), and left putamen. No significant group-by-task interactions were found in OCD patients compared with controls.

Task Load

In controls, increased task load (**Table 5**) was correlated with increased blood oxygenation level–dependent signal bilaterally in anterior prefrontal (BA 10), dorsolateral prefrontal (BAs 9 and 46), cingulate (BA 32), premotor (BAs 6 and 8), and insular cortices and in the precuneus (BA 7). Furthermore, increases were observed in right inferior parietal cortex (BA 40), left superior occipital cortex (BA 19), and left caudate nucleus. The OCD patients, in contrast, did not show increased activity in the caudate nucleus correlating with task load. Instead, task load was correlated with increased activation bilaterally in supplementary motor area, as well as left posterior globus pallidus, left parahippocampal gyrus (PHG), thalamus and dorsal brainstem, and right ventrolateral prefrontal cortex (VLPFC) (BA 44). Group-by-task interaction analyses (**Table 6**, **Figure 3**, and **Figure 4**) showed increased activation in controls compared with OCD patients in left DLPFC (BA 46). In con-

Table 4. Brain Regions Showing Significant Blood Oxygenation Level–Dependent Signal Increase During Planning Compared With Baseline*

Region	Side	Brodmann Area	Talairach Coordinates			*z* Score
			x	Y	z	
Dorsolateral prefrontal cortex	Right	9, 46	32	42	14	3.37
Premotor cortex	Right	4, 6	24	–14	54	3.76
Cingulate cortex	Left	32	–14	20	34	3.73
Precuneus	Left	7	–10	–64	22	3.66
	Right	7	10	–78	44	3.30
Inferior parietal cortex	Left	40	–52	–28	32	3.21
Caudate nucleus	Right	. . .	8	16	6	3.73
Putamen	Left	. . .	–26	16	–6	3.74

*Control subjects vs patients with obsessive-compulsive disorder at $P<.001$ uncorrected. There were no significant regions in patients with obsessive-compulsive disorder vs control subjects.

trast, OCD patients, compared with controls, showed increased activation bilaterally in cingulate (BA 32), ventrolateral prefrontal (BAs 45 and 47), and parahippocampal cortices, as well as left anterior temporal cortex and dorsal brainstem.

Analysis of Covariance

In OCD subjects, neither main effects for task nor task load effects were associated with symptom severity scores (Yale-Brown Obsessive Compulsive Scale and Padua Inventory–Revised), except for a small region in left VLPFC (BA 44) ($z=3.24$). Additional analyses of covariance were performed to investigate whether the observed between-group differences could be explained by differences in demographic variables or levels of subjective distress. However, the already described group-by-task interaction effects in favor of control subjects persisted after controlling for differences in age, education level, sex ratio, and state anxiety.

COMMENT

In the present study, a parametric self-paced pseudorandomized event-related fMRI version of the ToL was used to investigate the neural substrate of planning in medication-free OCD patients compared with healthy control subjects. This paradigm allowed flexible responding and post hoc selection of correct trials, so that analyses of imaging data were not confounded by performance differences.[35] The present results not only confirm previous findings with regard to impaired planning capacity in OCD but also clearly demonstrate decreased responsiveness of dorsal prefrontal-striatal circuits in OCD patients.

Behavioral data showed increased RTs in OCD patients only during the 2 easiest task levels, whereas performance scores were significantly lower compared with those of control subjects across all levels. These behavioral findings are in agreement with some, but not all, previous findings with regard to planning performance in OCD. Although some studies have reported decreased response speed[24] or performance scores,[25] other studies[22,23] found unaffected planning capacity in OCD patients compared with controls. As discussed previously, these differences are likely to reflect methodological differences in task implementation, such as mental performance vs the use of a touch screen or providing feedback vs no feedback.[21,24]

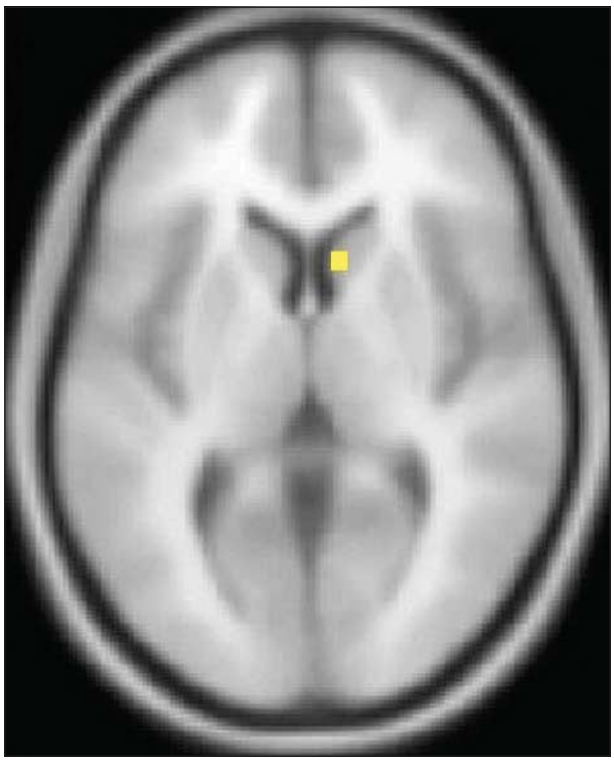

Figure 2. Increased blood oxygenation level–dependent signal in right caudate nucleus during planning compared with baseline, in control subjects compared with patients with obsessive-compulsive disorder.

Imaging results showed increased task-associated activation in controls compared with OCD patients in several regions previously found to be involved in planning, particularly DLPFC, basal ganglia, and parietal cortex. Task load–correlated activity was found in left DLPFC in control subjects compared with OCD patients. In contrast, OCD patients showed increased ac-

Table 5. Brain Regions Showing Significant Blood Oxygenation Level–Dependent Signal Increase Correlating With Increased Task Load*

			Control Subjects (n = 22)				Patients With Obsessive-Compulsive Disorder			
			Talairach Coordinates				Talairach Coordinates			
Region	Side	Brodmann Area	x	y	z	*z* Score	x	y	z	*z* Score
Anterior prefrontal cortex	Left	10	–24	52	2	3.29	–36	52	8	4.14
	Right	10	38	50	–4	3.66	. . .	. . .	. . .	. . .
	Right	10	34	62	4	3.69	. . .	. . .	. . .	. . .
	Right	10, 46	32	52	6	3.49	38	54	8	5.03
Dorsolateral prefrontal cortex	Left	9	. . .	. . .	. . .	. . .	–44	32	34	4.62
	Left	9, 46	–44	38	24	4.86	–42	32	28	4.51
	Left	46	–30	42	4	3.95	. . .	. . .	. . .	. . .
	Right	9	44	32	32	4.73	38	40	34	5.17
	Left	8	–40	28	44	3.91	–30	36	46	5.30
	Right	8	28	24	50	4.44	30	24	46	4.48
Ventrolateral prefrontal cortex	Right	44	. . .	. . .	. . .	. . .	58	16	6	4.63
Cingulate cortex	Left	32	–10	22	34	3.82	–6	34	28	4.50
	Right	32	6	22	40	4.01	6	34	24	3.88
Supplementary motor area	Left	6	. . .	. . .	. . .	. . .	–6	28	36	4.82
	Right	6	. . .	. . .	. . .	. . .	6	20	44	5.55
Premotor cortex	Right	4, 6	18	–10	58	4.46	26	–2	50	4.33
	Left	6	–22	6	58	5.55	–34	16	56	4.48
	Right	6	26	8	50	4.98	28	4	52	5.20
	Left	6, 8	. . .	. . .	. . .	. . .	–24	16	50	4.58
Precuneus	Left	7	–10	–54	48	4.98	–2	–62	52	4.40
	Right	7	8	–60	52	5.29	2	–54	52	4.52
Inferior parietal cortex	Left	40	. . .	. . .	. . .	. . .	–50	–42	40	4.74
	Right	40	50	–42	54	4.55	56	–40	40	4.66
Insular cortex	Left	. . .	–32	20	–4	4.08	–32	20	–4	5.00
	Right	. . .	34	22	–4	4.84	34	20	–6	4.33
Caudate nucleus	Left	. . .	–18	4	16	3.78	. . .	. . .	. . .	. . .
Globus pallidus posterior	Left	. . .	. . .	. . .	. . .	. . .	–16	–6	4	4.36
Parahippocampal gyrus	Left	. . .	. . .	. . .	. . .	. . .	–26	–24	–22	3.56
Thalamus	Left	. . .	. . .	. . .	. . .	. . .	–14	–4	–4	3.42
Brainstem	Left	. . .	. . .	. . .	. . .	. . .	–8	–22	–26	3.71
Occipital cortex	Left	19	–42	–70	36	3.71	–40	–72	38	4.50

*At $P<.05$ corrected.

tivation, correlated with increased task load, in bilateral cingulate, ventrolateral prefrontal, and parahippocampal cortices, in left anterior temporal cortex, and in dorsal brainstem. Our finding of decreased responsiveness of dorsal prefrontal-striatal circuits during planning in OCD patients is in accord with previous findings with regard to basal ganglia dysfunction in OCD in implicit learning.[28,29] However, in the study by Rauch et al,[28] OCD subjects showed impaired performance during motor skill acquisition, suggesting basal ganglia–motor cortical rather than dorsal prefrontal-striatal dysfunction, as found in the present study. In addition, several functional imaging studies[36-40] using symptom provocation designs have reported abnormalities in orbitofrontal-striatal function in OCD, thought to reflect its role in ritualistic behavior. Most of these studies,[36,37,40] however, lacked adequate control groups or failed to find significant group-by-task interactions in subcortical areas. Increased prefrontal-subcortical glucose uptake in OCD patients relative to controls, resolving after successful therapy, has also been reported in several resting-state imaging studies.[41-45] Although dorsal prefrontal abnormalities were apparently found in 1 study,[43] most of these studies reported increased orbitofrontal-striatal metabolism. Moreover, although dorsal PFC and ventral PFC are known to project to dorsal and ventral parts of the striatum, spatial resolution of positron emission tomography with [^{18}F]fluorodeoxyglucose may have been insufficient to detect differences based on topographical organization within the basal ganglia. Therefore, the evidence for pathologically increased baseline activity in dorsal prefrontal-striatal, as opposed to ventral prefrontal-striatal, loops in OCD is still inconclusive. However, although the present fMRI data do not allow baseline comparisons, our finding of decreased or absent prefrontal-striatal responsiveness is compatible with existing pathophysiological models of OCD hypothesizing basal ganglia disinhibition due to an altered balance between indirect, inhibitory, and direct excitatory cortico-striatal-thalamico-cortical circuits.[46,47] Whether the failure of OCD patients to recruit dorsal prefrontal-striatal regions compared with controls, as found in the present study, is specific for planning tasks is also not yet clear. In a recent fMRI study, van der Wee et al[48] found decreased perfor-

Table 6. Brain Regions Showing Significant Blood Oxygenation Level–Dependent Signal Increase Correlating With Increased Task Load*

Region	Side	Brodmann Area	Talairach Coordinates x	y	z	*z* Score
Control Subjects vs Patients With Obsessive-Compulsive Disorder						
Dorsolateral prefrontal cortex	Left	46	–32	40	4	3.38
Patients With Obsessive-Compulsive Disorder vs Control Subjects						
Cingulate cortex	Left	32	–2	18	32	3.40
	Right	32	9	26	26	3.49
Ventrolateral prefrontal cortex	Left	47	–50	24	–10	3.68
	Left	47	–46	24	0	3.51
	Right	47	50	24	–2	3.84
	Right	45	58	20	8	3.63
Anterior temporal cortex	Left	. . .	–44	0	–32	3.54
Parahippocampal gyrus	Left	. . .	–24	–24	–24	3.62
	Right	. . .	24	–18	–26	3.54
Brainstem	Left	. . .	–4	–26	–20	3.54

*At $P<.001$ uncorrected.

mance only at the highest task level in OCD patients compared with controls during performance of a spatial n-back task. Imaging results showed similar activity in bilateral DLPFC and parietal cortex in both groups, from which the authors concluded that (spatial) working memory in OCD was not abnormal. The findings of the present study provide support for this conclusion. Whereas it might be argued that in our paradigm not only planning complexity but also working memory load was (linearly) increased, our results reveal impaired planning at all levels, which is difficult to explain by differences in working memory capacity.

In the present study, OCD patients, compared with control subjects, showed increased activation, correlated with task load, in bilateral ventrolateral prefrontal, anterior cingulate, and parahippocampal cortices, in left temporal cortex, and in dorsal brainstem. These interaction effects may reflect compensatory processes and increased arousal. Functional neuroanatomical subdivisions of the lateral PFC (ie, VLPFC and DLPFC) have been proposed based on stimulus type (verbal vs object or spatial)[49,50] and process type (maintenance or manipulation), with recent evidence favoring the latter hypothesis.[51,52] Therefore, the VLPFC (BAs 44, 45, and 47) supports processes that transfer, maintain, and match information in working memory. In contrast, the DLPFC (BAs 9 and 46) supports complex processes operating on information (spatial and nonspatial) that is maintained in working memory, such as monitoring, manipulation, and higher-level planning. Beyond maintenance in VLPFC and manipulation in DLPFC, the anterior PFC (BAs 8 and 10) is associated with processes of a third level of executive control.[53] Increased VLPFC activity may reflect not only working memory load, that is, the number of items kept "online," but also retrieval and maintenance of abstract rules used for problem solving.[54] In addition, it has been shown that VLPFC activity is selectively increased during arithmetic computations, particularly when subjects attempt to resolve a conflict between externally presented answers and internally computed solutions.[55] Such a mechanism may explain the increased activity of bilateral VLPFC associated with task load in OCD patients compared with control subjects observed in the present study.

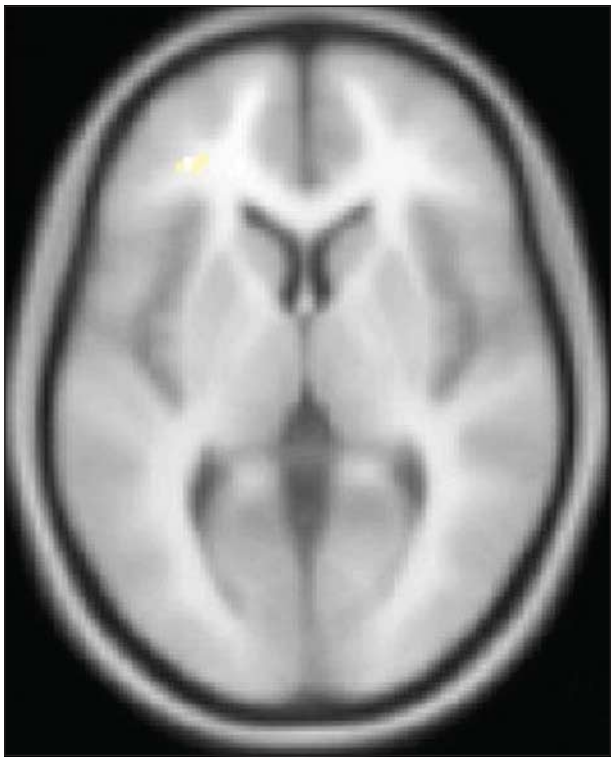

Figure 3. Increased blood oxygenation level–dependent signal in left dorsolateral prefrontal cortex (Brodmann area 46) correlating with task load, in control subjects compared with patients with obsessive-compulsive disorder.

Compared with controls, OCD patients also showed increased activity of anterior cingulate cortex (ACC) (BA 32) correlated with task load. Anterior cingulate cortex involvement in OCD has been observed at rest, during symptom provocation, and after having committed errors during cognitive tasks.[37,40] The ACC has been im-

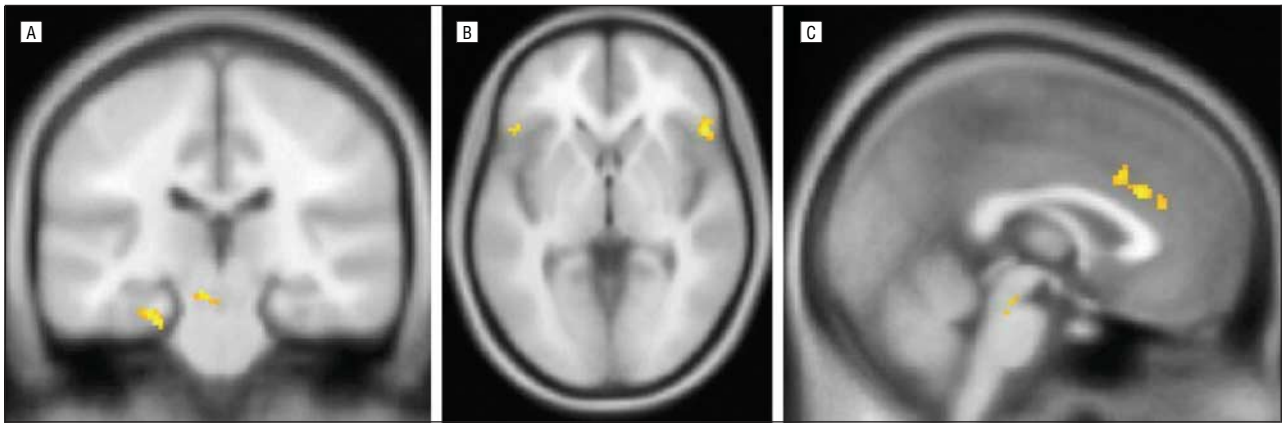

Figure 4. Increased blood oxygenation level–dependent signal correlating with task load, in patients with obsessive-compulsive disorder compared with control subjects. A, In parahippocampal gyrus and brainstem. B, In bilateral ventrolateral prefrontal cortex (Brodmann areas [BAs] 45 and 47). C, In cingulate cortex (BA 32).

plicated in performance monitoring, error detection, conflict monitoring, response selection, and reward expectation.[56] Anterior cingulate cortex activity has been found before a response during correct trials and immediately following error trials, reflecting its role in error prevention and detection.[57] Ursu et al[58] reported increased activation of ACC in OCD patients, compared with control subjects, during error and correct trials, indicative of an overactive performance monitoring system in OCD, independent of the actual occurrence of errors. These results were replicated in a subclinical group of obsessive-compulsive undergraduates.[59] In addition to ACC, supplementary motor area may have a role in performance monitoring.[60] Increased activity in ACC and supplementary motor area was also observed during performance of a spatial n-back task in OCD patients, thought to reflect increased effort to develop an efficient strategy or increased error monitoring.[48] A functional neuroanatomical dissociation between these areas has been proposed, with error processing associated with the ACC region and response competition with supplementary motor area.[61] Increased performance monitoring during correct task performance, as well as during errors, may be characteristic of the critical self-evaluation of performance in OCD, leading to inappropriate need for correction and, consequently, repetitive behavior.

Increased activity correlated with task load was also observed in bilateral PHG in OCD patients relative to controls. Similar results were obtained by Rauch et al[28] in OCD patients during a motor sequence learning paradigm. The authors hypothesized that dysfunction of corticostriatal systems in OCD resulted in compensatory recruitment of "explicit networks" to perform the task. However, data from their study showed that OCD patients did not differ from controls in explicit knowledge with regard to the task. In the present study, PHG involvement may reflect intermediate-term memory for spatial information, in addition to working memory, supported by parietal and lateral PFC as already discussed, and long-term memory (more than about 2 minutes) provided by the hippocampal formation.[62] Increased activity of PHG and VLPFC may therefore be secondary to OCD patients' failure to develop an adequate strategy, so that they need to rely on short- and intermediate-term memory capacity to perform tasks.[3] Connections exist between rostral ACC (BA 32) and PHG.[63] Faw[64] described this system of ACC and adjacent dorsomedial PFC, with extensions to the hippocampal stream, as a key player in spatiotemporal processing and attention, supporting executive functions located in DLPFC.

Finally, we found an area of increased activation in left dorsal brainstem associated with task load in OCD patients compared with control subjects. This region was located within the reticular formation, extending rostrally into the periaqueductal gray, and may therefore reflect increased arousal at higher task loads in our OCD group.[65,66] Arousal responses implicate activation of the hypothalamic-pituitary-adrenal axis and the reticular activating system. The reticular activating system is composed of cholinergic neurons from the pedunculopontine nucleus, stimulating the noradrenergic system of the locus ceruleus (LC), which in turn inhibits cholinergic output of the pedunculopontine nucleus.[65] Evidence from nonstress experiments suggests that phasic LC activity is associated with increased attention and task-related performance,[66-68] whereas increased tonic activity of the LC results in attentional instability, decreased performance, and increased emotional reactivity.[66,68] Chronic stress, on the other hand, may lead to LC damage, resulting in reduced output from the LC[69] and disinhibition of the pedunculopontine nucleus.[70] In the present study, our finding that increased dorsal brainstem activity in OCD was associated with task load suggests increased effort rather than increased subjective distress, although we cannot rule out the latter possibility.

To our knowledge, this study is the first to demonstrate impaired planning associated with decreased dorsal prefrontal-striatal responsiveness in OCD. Strengths of the study are the inclusion of medication-free subjects, the provision of a large group size permitting random-effects analyses, and the use of a parametric self-paced event-related design. The present study is not without limitations, however. First, education level was higher in control subjects, although we controlled for performance differences by selecting correct responses only. In addition, post hoc analyses of covariance with regard to education level, sex ratio, and age were performed. Moreover, it has been shown that planning performance (error rates and RTs) is not corre-

lated with intelligence measures.[71] Second, although in the present study, in accord with previous studies,[3,48] no clear correlations were found between symptom severity ratings and outcome measures, we did not specifically investigate OCD subgroups, for example, those with prominent washing or checking symptoms. Although little is known with regard to the generalizability of neuropsychological deficits across clinical subtypes, a dimensional model of OCD has been proposed, in which various symptom dimensions are associated with differential patterns of functional neuroanatomical abnormalities.[72,73] Recent data showed that activation of VLPFC and caudate nucleus correlated with washing characteristics and activation of dorsal regions (DLPFC, thalamus, putamen, and globus pallidus) correlated with checking symptoms.[73] Based on these subtype differences in provocation experiments, one might hypothesize that impaired planning and decreased responsiveness of dorsal prefrontal-striatal circuits as found in the present study mainly concern OCD patients with predominant checking symptoms. Another issue for future research is whether the dorsal prefrontal-striatal dysfunction observed in this study is specific for OCD or extends to other neuropsychiatric disorders. These include not only anxiety disorders but also basal ganglia disorders, such as Tourette syndrome and MDD. Major depressive disorder is characterized by impairments in various executive functions, such as verbal fluency and attentional set shifting.[74] However, in MDD, dorsal prefrontal baseline perfusion is decreased rather than increased.[75] Moreover, MDD is not associated with striatal pathologic conditions.[76] Whereas depressive symptoms frequently co-occur in OCD, cognitive deficits in OCD are not associated with comorbid depression,[3] suggesting different pathophysiological mechanisms in OCD compared with MDD. Future studies should also investigate whether the executive deficits in OCD are specific for the present paradigm or can be replicated during other "strategic" tasks, such as set-shifting tasks. Finally, to further elucidate the pathophysiology of OCD, the "state-trait" issue needs to be addressed by using pre-post treatment designs.

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