Probing Striatal Function in Obsessive-Compulsive Disorder: A PET Study of Implicit Sequence Learning

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Positron emission tomography was employed to contrast the brain activation pattern in patients with obsessive-compulsive disorder (OCD) to that of matched control subjects while they performed an implicit learning task. Although patients and control subjects evidenced comparable learning, imaging data from control subjects indicated bilateral inferior striatal activation, whereas OCD patients did not activate right or left inferior striatum and instead showed bilateral medial temporal activation. The findings further implicate corticostriatal dysfunction in obsessive-compulsive disorder. Furthermore, when OCD patients are confronted with stimuli that call for recruitment of corticostriatal systems, they instead appear to access brain regions normally associated with explicit (conscious) information processing.

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Obsessive-compulsive disorder (OCD) is a common psychiatric disease, affecting more than 1% of the population worldwide.[1] It is characterized as an anxiety disorder.[2] The hallmark symptoms of OCD include intrusive thoughts (obsessions) as well as ritualistic behaviors (compulsions). Substantial evidence has accrued implicating corticostriatal dysfunction in the pathophysiology of OCD.[3–6] Neuroimaging studies[7] have demonstrated volumetric abnormalities involving the caudate nucleus.[7,8] Imaging studies have also revealed resting hypermetabolism in the orbitofrontal cortex and caudate nucleus[7,9,10] (attenuated following successful medication or behavioral therapy[9–12]), as well as increased activation of these same areas when OCD symptoms are provoked.[13] Furthermore, cases have been reported of patients with acquired striatal lesions in which the initial clinical presentations are phenocopies of OCD.[14]

Corticostriatal systems are thought to mediate a variety of normal functions, including a nonconscious form of learning called *implicit* (or more specifically, *procedural*) learning.[15] Implicit learning and memory refer to the acquisition and expression of information not accompanied by awareness of its content or influence on behavior. Explicit learning and memory refer to the acquisition and retrieval of information that is accompanied by awareness of the learned information and its

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influence on behavior. Neurologic patients with known striatal pathology (such as Huntington's disease) have been shown to exhibit performance deficits on implicit learning tasks.[16,17] Recent studies of implicit sequence learning using positron emission tomography (PET) have consistently demonstrated activation of corticostriatal systems.[15,18,19] In contrast, data from a variety of sources,[20] including functional imaging studies,[21,22] suggest that explicit (conscious) learning and memory are mediated by lateral prefrontal cortex and medial temporal structures (the hippocampal/parahippocampal region).

OCD entails conscious cognitive intrusions in the context of purported corticostriatal dysfunction; we therefore theorized that patients with OCD might recruit systems typically reserved for explicit processing to compensate for dysfunctional implicit processing systems. In the current study, we sought to test this hypothesis by comparing PET brain activation patterns in OCD patients with patterns in matched normal control subjects via an implicit sequence learning paradigm. We predicted that patients with OCD would show impaired striatal activation and inappropriate activation of other brain systems while performing an implicit sequence learning task. We also sought to determine whether patients with OCD would show impaired implicit learning by behavioral measures of reaction time.

METHODS

All procedures were conducted in accordance with requirements of the Subcommittee on Human Studies of the Massachusetts General Hospital. Written informed consent was obtained from all subjects prior to participation. Nine females with OCD and 9 female normal control subjects, matched for years of age (mean ± SD, control: 32.3 ± 11.1; OCD: 31.7 ± 11.1; $t = 0.13$, $df = 16$, $P = 0.90$), and education (control: 15.7 ± 3.6; OCD: 14.1 ± 2.4; $t = 1.07$, $df = 16$, $P = 0.30$) were studied as described in Figure 1. Although we routinely attempt to achieve an ethnic and racial representation that accurately reflects the regional clinical population, the vast majority of these subjects were white (control subjects: 8 white, 1 black; OCD: all white). Subjects with OCD were outpatients recruited from the Obsessive Compulsive Disorders Clinic and Research Unit at Massachusetts General Hospital; normal control subjects were recruited via local advertisements. All subjects were right-handed.[23] OCD was diagnosed by psychiatric examination and confirmed by structured clinical interview.[24] Normal control subjects had no history of any Axis I psychiatric disorder; OCD subjects had no history of psychosis, substance dependence, bipolar disorder, current major depression, or substance abuse. All subjects were medically healthy by report and had no history of significant head injury, seizure, neurologic condition, or current major medical condition. No subject had taken any psychotropic medication, or other medicine that would interfere with the study procedures, during the 4 weeks prior to testing.

FIGURE 1. Experimental design: summary of the sequence of conditions, as well as the corresponding scanner status and timing. The PET implicit sequence learning paradigm has been fully described elsewhere.[15]

EXPERIMENTAL DESIGN			
Condition	**Stimuli**	**Scanning Status**	**Delay Before Next Block**
Baseline	Random	Transmission scan	5 minutes
Baseline	Random	PET scan 1	2 minutes
Baseline	Random	Offline	2 minutes
Implicit	Sequence	Offline	2 minutes
Implicit	Sequence	PET scan 2	10 minutes
Implicit	Sequence	PET scan 3	10 minutes
Baseline	Random	PET scan 4	1 minute
Debriefing		Offline	

The PET implicit sequence learning paradigm has been fully described elsewhere[15] (see Figure 1), as have the general methods for PET data acquisition and analysis.[13,25] The serial reaction time task[26] provides a measure of implicit sequence learning. As previously described,[15] the paradigm entails presentation of asterisks at one of four spatial locations displayed on a computer monitor. Subjects were instructed to press one of four keys; each key corresponded to one stimulus position, and each key press was performed with the corresponding finger (first two fingers on each hand). Stimuli were presented in blocks of 144 trials, and mean median reaction times were calculated. For the Baseline condition, the order of the stimulus locations was random; for the Implicit Learning condition, unbeknownst to the subjects, a 12-item repeating sequence was introduced. Quantification of implicit learning is based on the reaction time advantage associated with blocks of repeating sequence versus random presentation of stimuli. Each subject performed 3 blocks of Baseline trials, then 3 blocks of Implicit Learning trials, then another block of Baseline trials. Debriefing was performed as previously described.[15] In order to quantify subjects' explicit recall for the sequence

as an index of explicit contamination, subjects were instructed to generate the sequence of key presses without visual cues.

PET data were acquired during two blocks of each condition via a Scanditronix PC4096 PET camera (General Electric, Milwaukee, WI) while subjects inhaled oxygen-15–labeled CO_2 for 1 minute. Movement-corrected, whole brain–normalized images reflecting relative regional cerebral blood flow (rCBF) were transformed to Talairach space.[27] Then, for each cohort, a statistical parametric map corresponding to the Implicit Learning minus Baseline contrast was generated, with units in z-score. The statistical maps were inspected to identify foci of significant activation within the striatum (z scores ≥ 2.58, corresponding to $P \leq 0.005$ uncorrected for multiple comparisons, or approximately $P \leq 0.05$ corrected for multiple comparisons in the context of *a priori* hypotheses), as well as other locations ($z \geq 3.09$, corresponding to $P \leq 0.001$ uncorrected for multiple comparisons). The boundaries of the striatal search volume were defined stereotactically, as were the nominal locations of all activation foci. A planned secondary analysis was performed to directly compare inferior striatal rCBF values between groups. This analysis entailed the stereotactic placement of circular regions of interest (5 pixels in diameter) about the centroids of activation determined via the Implicit Learning minus Baseline contrast in the control group. Then a three-factor repeated-measures analysis of variance (ANOVA; group, region, condition) was performed, using mean rCBF values from each region of interest.

RESULTS

Behavioral data demonstrated significant learning for both groups, evidenced by reaction time advantages for the Implicit Learning versus Baseline contrast, with no significant between-group difference (Table 1). Debriefing data were available on 8 subjects in each group and indicated nonsignificant explicit knowledge for both groups (control: $t = 0.58$, df = 15, $P = 0.50$; OCD: $t = 1.26$, df = 15, $P = 0.20$), and nonsignificant between-group differences in explicit knowledge ($t = 0.81$, df = 15, $P = 0.43$). These recall results suggest that the measures of implicit learning were not significantly contaminated by explicit knowledge of the sequence.

Imaging results are presented in Table 2 and Figure 2. The control group showed significant activation in the bilateral inferior striatum. The OCD cohort did not show significant activation in any inferior striatal territory; they showed no significant activation in the right striatum, and left striatal activation was confined to an extreme dorsolateral locus. Furthermore, the OCD group showed significant activation in bilateral parahippocampal/hippocampal regions, not seen in normal control subjects. Other disparities between the groups,

TABLE 1. Behavioral results on the serial reaction time task[a]

Condition	Normal Control	OCD	*t*-values (df = 16)
Baseline	467.40 ± 175.80	428.11 ± 98.61	0.58, $P = 0.57$
Implicit	432.94 ± 193.89	370.45 ± 84.96	0.89, $P = 0.39$
Difference (learning)	34.46 ± 45.06[b]	57.65 ± 34.92[b]	1.22, $P = 0.24$

Note: OCD = obsessive-compulsive disorder.

[a]Behavioral results are given as mean median reaction times in milliseconds (±SD). Behavioral measures were taken from the same test blocks used for the analysis of imaging data.

[b]Within-group analyses comparing reaction times for the Implicit versus Baseline conditions found significant learning effects for both groups; Normal Control: $t = 2.29$, df = 8, $P = 0.05$; OCD: $t = 4.95$, df = 8, $P = 0.001$. No significant between-group differences in reaction times were found.

TABLE 2. Brain regions exhibiting significantly increased activation associated with Implicit Learning versus Baseline

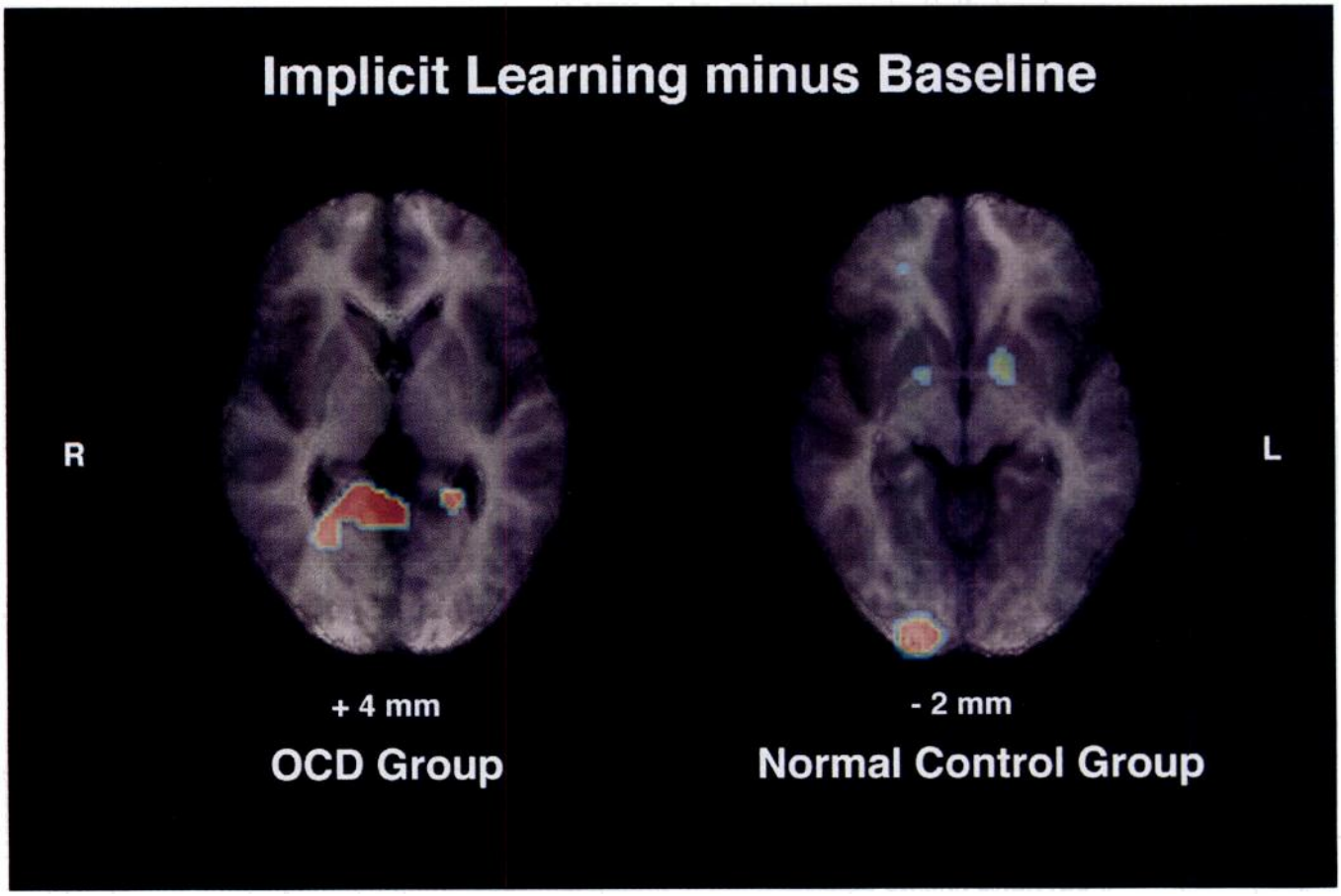
Group/Brain Region	z score, Max Pixel Value[a]	Max Pixel Coordinates[b]
Normal control		
Left striatum (caudate)	2.64	−12, 11, −8
Left striatum (lenticulate)	2.65	−13, 6, −4
Right striatum (lenticulate)	2.61	15, 3, 0
Left brainstem	3.54	−6, −34, −8
Right visual cortex (~BA 18)	3.09	6, −91, −4
Right visual cortex (~BA 17)	3.53	12, −95, 4
Obsessive-compulsive disorder		
Left hippocampal/parahippocampal	3.25	−21, 44, 4
Right hippocampal/parahippocampal	3.72	13, −42, 4
Left striatum (lenticulate)	3.13	−22, 2, 12
Right premotor cortex (~BA 6)	4.57	57, 7, 16

Note: BA = Brodmann area.

[a]Values represent the actual maximum pixel value (in z-score units) within the brain region from the statistical parametric map. All loci within the striatum with $z \geq 2.58$, as well as all loci within the entire data set with $z \geq 3.09$, are listed. Regional activations with z scores ≥ 2.58 correspond to $P \leq 0.005$ uncorrected for multiple comparisons, or approximately $P \leq 0.05$ corrected for multiple comparisons, in the context of *a priori* hypotheses regarding the striatum. The threshold of $z \geq 3.09$, corresponds to $P \leq 0.001$ uncorrected for multiple comparisons. More stringent thresholds would be $z \geq 3.50$ or 4.20, corresponding to approximately $P \leq 0.05$ corrected for multiple comparisons in the absence of any specific *a priori* hypotheses, based on the number of pixels in the largest brain slice or in the entire image volume, respectively.

[b]Coordinates defining the location of the maximum pixel values within each brain region from the statistical parametric maps in Talairach space (27) are expressed as "x, y, z"; $x > 0$ is right of the midsagittal plane, $y > 0$ is anterior to the anterior commissure, and $z > 0$ is superior to the intercommissural plane.

FIGURE 2. PET results: slices from PET statistical maps that reflect composite data across all subjects (n = 9) per group. Thresholds for significance were $z \geq 2.58$ for the striatum ($P \leq 0.005$ uncorrected, and approximately $P \leq 0.05$ corrected for multiple comparisons in the context of *a priori* hypotheses), and $z \geq 3.09$ for all other territories (corresponding to $P \leq 0.001$, uncorrected). PET data are superimposed over nominally normal averaged structural magnetic resonance images (n = 8) transformed to Talairach space[27] for anatomical reference. All images are transverse sections parallel to the intercommissural plane, shown in conventional neuroimaging orientation (top = anterior; bottom = posterior; right = left; left = right). Each transverse section is labeled with its z coordinate, denoting its position with respect to the intercommissural plane (superior > 0). The group with obsessive-compulsive disorder (OCD) shows bilateral activation of the hippocampal/parahippocampal region (left panel), not present in the Normal Control group. At a different horizontal level, the Normal Control group shows bilateral activation within an inferior territory of striatum (right panel), not present in the OCD group.



although not predicted, included the failure of the OCD cohort to significantly activate visual cortex.

In the secondary analysis of imaging data, a direct comparison was performed between OCD and normal control subjects for rCBF values within inferior striatal regions of interest, in accordance with *a priori* hypotheses. A three-factor repeated-measures ANOVA (group, region, condition) yielded a significant group × condition interaction (F = 7.34, df = 1,16, P = 0.02), with no significant main effect of group (F = 2.66, df = 1,16, P = 0.12). Post hoc t-tests confirmed that the two groups differed in terms of inferior striatal rCBF during the Implicit Learning condition (t = 2.57, df = 16, P = 0.02) and not during the Baseline condition (t = 0.54, df = 16, P = 0.60).

DISCUSSION

These initial findings should be interpreted cautiously pending replication. As is typical in functional imaging research, this study was conducted with a modest number of subjects; consequently, the results are potentially vulnerable to statistical errors of both types. Other limitations of the current work include those that are intrinsic to the imaging methods employed.[15,25] In particular, localization of activation foci is constrained by the spatial resolution of PET as well as spatial normalization to Talairach space. These concerns are underscored for experiments that seek to compare cohorts for which regional brain volumetric differences are presumed to exist.[8] Specifically, in the case of OCD, there is

evidence to suggest reduced caudate volume in comparison with normal control subjects.[8] Decreased caudate volume, on this spatial scale, could cause lower caudate rCBF values, although the results of the secondary analysis speak against this possibility. Furthermore, morphometric abnormalities involving the caudate or other structures could adversely influence the precision and accuracy of Talairach transformation, resulting in greater within-group variability or mislocalization of structures for the OCD cohort. However, the comparability of the rCBF variance within the striatum in our OCD and control groups, as well as quality control steps in our transformation scheme, likewise militate against these factors as major confounds in this case. Finally, the contrasting of brain activation patterns between groups should ideally be performed via direct comparison. Although we did perform such a direct comparison for a circumscribed subterritory of inferior striatum, data collection from a larger number of subjects is required to provide sufficient statistical power to optimally assess between-group differences over the entire brain.

On the other hand, noteworthy strengths of this study include well-characterized and well-matched cohorts, with a relatively homogeneous population of right-handed, female OCD patients, off medications and without major comorbid psychopathology. Similarly, the PET paradigm employed has yielded reproducible inferior striatal activation, as evidenced by the replication of our prior findings,[15] and provides the benefits of online behavioral measures of performance. These features of the study militate against error risks due to inadequate matching, confounding comorbidity, or heterogeneity of study populations, while ensuring reliable PET findings in the normal cohort, a means for confirming that all subjects performed the task in earnest, and data that simultaneously provide information about performance and graphically illustrate the brain systems recruited.

Despite purported corticostriatal dysfunction in OCD and the role of corticostriatal systems in normally mediating implicit sequence learning, OCD patients showed no performance decrement on the implicit sequence learning task. Findings of inferior striatal activation in control subjects are consistent with previous results employing the same[15] and similar PET paradigms.[19] Disparate striatal activations in the OCD group, namely the absence of activation in right-sided and inferior territories of the striatum, may reflect corticostriatal dysfunction or at least a failure to normally recruit this system. Failure of the OCD group to activate the visual cortex, which participates in the corticostriatal circuit purported to mediate the visuospatial learning aspects of the task,[15] lends additional support to this interpretation. Furthermore, the presence of significant bilateral medial temporal activation in OCD patients, not present in the normal subjects, is consistent with the hypothesis that OCD involves abnormal activation of limbic or paralimbic networks[12,13] in contexts where normal individuals use corticostriatal systems. It remains to be confirmed that the disparate striatal activation pattern in the OCD cohort does not represent a type II error and that this cohort's apparent activation of bilateral medial temporal regions does not reflect a type I error.

These preliminary findings lend support to a new heuristic model of OCD: we hypothesized that in the face of dysfunctional corticostriatal systems, patients with OCD would adapt by accessing explicit networks[20] in order to process material that normal individuals "put to rest" implicitly (that is, automatically and without conscious awareness). Such a conceptualization not only helps to explain the phenomenology of intrusive thoughts in OCD, but may also shed light on the neuropsychology and pathophysiology of this common disorder. Still, the finding that patients with OCD showed no decrement in performance suggests that, if indeed their corticostriatal systems are dysfunctional, the alternative processing systems being employed are sufficient, at least in the context of this particular simple task. Moreover, the fact that the OCD group did not exhibit significant explicit knowledge indicates that mere recruitment of medial temporal structures is not synonymous with conscious awareness, conscious processing, or explicit knowledge. Nonetheless, it remains plausible—though as yet unproven—that information processed via medial temporal structures might have preferential access to the conscious and/or affective domains.

Future research will seek to replicate and expand on these findings by studying implicit and explicit learning paradigms with additional subjects, including an analogous male cohort. Subsequent projects should also involve subjects with purportedly related disorders (such as Tourette's syndrome[4,6,28]) as well as other psychiatric comparison populations. Finally, considering that functional brain abnormalities in OCD have previously been primarily associated with a symptomatic state,[4,6,7,9–13] it could be of great interest to explore the influence of treatment on the above observed phenomena.

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