Neuroanatomical Characteristics Associated With Response to Dorsal Anterior Cingulotomy for Obsessive-Compulsive Disorder

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IMPORTANCE Approximately 10% of patients with obsessive-compulsive disorder (OCD) have symptoms that are refractory to pharmacologic and cognitive-behavioral therapies. Neurosurgical interventions can be effective therapeutic options in these patients, but not all individuals respond. The mechanisms underlying this response variability are poorly understood.

OBJECTIVE To identify neuroanatomical characteristics on preoperative imaging that differentiate responders from nonresponders to dorsal anterior cingulotomy, a neurosurgical lesion procedure used to treat refractory OCD.

DESIGN, SETTING, AND PARTICIPANTS We retrospectively analyzed preoperative T1 and diffusion magnetic resonance imaging sequences from 15 patients (9 men and 6 women) who underwent dorsal anterior cingulotomy. Eight of the 15 patients (53%) responded to the procedure.

MAIN OUTCOMES AND MEASURES We used voxel-based morphometry (VBM) and diffusion tensor imaging to identify structural and connectivity variations that could differentiate eventual responders from nonresponders. The VBM and probabilistic tractography metrics were correlated with clinical response to the cingulotomy procedure as measured by changes in the Yale-Brown Obsessive Compulsive Scale score.

RESULTS Voxel-based morphometry analysis revealed a gray matter cluster in the right anterior cingulate cortex, anterior to the eventual lesion, for which signal strength correlated with poor response ($P = .017$). Decreased gray matter in this region of the dorsal anterior cingulate cortex predicted improved response (mean [SD] gray matter partial volume for responders vs nonresponders, 0.47 [0.03] vs 0.66 [0.03]; corresponding to mean Yale-Brown Obsessive Compulsive Scale score change, −60% [19] vs −11% [9], respectively). Hemispheric asymmetry in connectivity between the eventual lesion and the caudate (for responders vs nonresponders, mean [SD] group laterality for individual lesion seeds, −0.79 [0.18] vs −0.08 [0.65]; $P = .04$), putamen (−0.55 [0.35] vs 0.50 [0.33]; $P = .001$), thalamus (−0.82 [0.19] vs 0.41 [0.24]; $P = .001$), pallidum (−0.78 [0.18] vs 0.43 [0.48]; $P = .001$), and hippocampus (−0.66 [0.33] vs 0.33 [0.18]; $P = .001$) also correlated significantly with clinical response, with increased right-sided connectivity predicting greater response.

CONCLUSIONS AND RELEVANCE We identified features of anterior cingulate cortex structure and connectivity that predict clinical response to dorsal anterior cingulotomy for refractory OCD. These results suggest that the variability seen in individual responses to a highly consistent, stereotyped procedure may be due to neuroanatomical variation in the patients. Furthermore, these variations may allow us to predict which patients are most likely to respond to cingulotomy, thereby refining our ability to individualize this treatment for refractory psychiatric disorders.
Obsessive-compulsive disorder (OCD) is a debilitating and chronic disorder with a lifetime prevalence of 2% to 3%. The disorder is characterized by intrusive thoughts and repetitive intentional behaviors that persist despite a desire to suppress them, often accompanied by marked anxiety. Although most patients attain adequate symptomatic relief with medication and cognitive-behavioral therapy, it is estimated that OCD may be refractory to these treatments in 10% to 20% of patients. Unfortunately, alternative treatment options are limited.

A subset of patients with refractory OCD may be candidates for surgical treatment. Given the risk of morbidity with surgery, candidate patients must be carefully evaluated by a multidisciplinary team consisting of psychiatrists, neurosurgeons, psychologists, and neurologists in consultation with ethicists. Typical inclusion criteria for surgical consideration are a diagnosis of persistent severe OCD that is refractory to several adequate pharmacologic trials and cognitive-behavioral therapy, the ability to follow instructions and provide consent, and demonstration of realistic expectations. Typical exclusion criteria are severe medical comorbidities, imminent suicidal intent, comorbid severe psychiatric disorders, and evidence of neurocognitive disorders. Given these necessarily stringent requirements for surgical consideration, the number of appropriate surgical candidates is relatively small.

Stereotactic surgical lesions, originally developed in the mid-20th century, have been successfully used for decades to treat severe refractory OCD and other psychiatric disorders. The necessity for safe, accurate, and reproducible surgical treatment options for psychiatric conditions was a major motivation for the development of stereotactic neurosurgery in the late 1940s. The dorsal anterior cingulotomy, one such stereotactic procedure, involves lesioning the dorsal anterior cingulate cortex (dACC), a region believed to play a role in the pathogenesis of the neural network that causes OCD. Clinical series with long-term follow-up have demonstrated a durable response rate of 45% to 70% following cingulotomy. This response rate is significant considering that these patients had been refractory to conventional therapy for years or even decades. Response rates of an alternative lesion procedure, the anterior capsulotomy, were fairly similar in open-label series but data from controlled blinded trials are limited. Nevertheless, these are invasive procedures with a complication rate of 5% to 10%. Improving our ability to predict which patients will respond to surgical treatment would represent a major advance in our management of OCD.

Whereas our understanding of the role of the dACC in both normal cognitive processes and OCD is steadily improving, few studies have investigated features that predict outcome after cingulotomy or other neuropsychiatric surgical procedures. Structural differences have been described between patients with OCD and individuals serving as controls in components of the limbic circuitoscal gangliothalamo-cortical (CBTC) network, including the orbitofrontal, parahippocampal, and cingulate cortices; the striatum; and the medial thalamus. Voxel-based morphometry (VBM) studies have reported gray matter volume differences in these structures, and diffusion tensor imaging (DTI) studies have demonstrated hemispheric asymmetries in white matter bundles connecting limbic structures, including the anterior limb of the internal capsule and cingulum. Significant heterogeneities in these metrics exist across studies, and the population of patients with intractable OCD who are surgical candidates could have different organizational patterns from those reported in the previous studies. Nevertheless, existing data suggest that these metrics are reasonable candidate predictors of response.

We therefore hypothesized that preoperative structural or connectivity variations in and between these regions may underlie the variability in patients’ response to cingulotomy. We tested this hypothesis by applying VBM and DTI analyses to preoperative imaging data in patients who received this stereotyped surgical lesion to determine whether neuroanatomical factors can predict response.

### Methods

#### Ethics Statement

All study procedures were approved by the Columbia University Medical Center and Massachusetts General Hospital institutional review boards. The requirement for informed consent was waived by both institutions.

#### Participants

We retrospectively reviewed the records of all patients receiving cingulotomy for severe, intractable OCD between January 1, 2000, and December 31, 2010, at Massachusetts General Hospital. Patients who received preoperative magnetic resonance imaging (MRI) with either a high-resolution T1 or DTI sequence were included in the study. Patients with prior neurosurgical interventions to treat OCD were excluded. Details regarding the clinical outcome of these patients have been described. Surgical technique is described in the eAppendix in the Supplement.

#### Patient Evaluation

Surgical candidacy was determined by a multidisciplinary team as described previously. Patients underwent a psychiatric evaluation prior to cingulotomy and during follow-up visits. The severity of OCD was assessed by the treating psychiatrist using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The Y-BOCS score obtained during the follow-up visit closest to 1 year after intervention was used as the postoperative score. For patients who underwent another neurosurgical procedure within the first 12 months, the score obtained immediately before the second procedure was used. Patients with a 35% or greater reduction in the Y-BOCS score were considered responders.

High-resolution (in-plane resolution, ≤1 mm; out-of-plane spacing, ≤2.5 mm) T1-weighted and diffusion (6 or 25 directions) sequences were acquired on a 1.5T scanner (Signa HDxt; GE Healthcare). Mann-Whitney analyses were performed to assess for scan parameter biases between responders and nonresponders (eTable 1 in the Supplement).
Gray Matter Analysis
Analyses were performed at Columbia University Medical Center. All patients with a preoperative high-resolution T1 MRI sequence were included. We used VBM to identify differences in gray matter between the brains of responders and nonresponders, along with a model-free algorithm to avoid preconceived biases regarding regions of interest. Strict statistical thresholding was used to account for multiple comparisons.

An optimized VBM protocol was performed using the FMRIB Software Library, version 5.0 (FMRIB; University of Oxford), which included brain extraction, segmentation, and linear/nonlinear transformation. A left-right, symmetric, study-specific gray matter template was designed from native-space T1 images after affine transformation to the gray matter ICBM 152, version 2009c (McConnell Brain Imaging Center) 2-mm standard template. Native-space gray matter volumes were nonlinearly normalized to the study-specific template. A modulation algorithm, part of the FMRIB Software Library protocol, was used to compensate for distortion from nonlinear transformation. Resultant gray matter volumes were smoothed with an isotropic gaussian kernel of sigma 3.5.

The FMRIB Software Library randomize function was used to perform permutation-based nonparametric inference using a generalized linear model to compare responders and nonresponders. In addition to changes in the Y-BOCS score, the generalized linear model included age and sex as nuisance variables. A threshold-free cluster enhancement analysis was used to compare modulated gray matter maps between groups on a voxelwise basis (5000 permutations). The results were subjected to a voxelwise Bonferroni correction to account for familywise errors. An after-correction value of $P < .05$ was considered significant.

A spherical region-of-interest diameter of 10 mm was constructed using FSLView in standard space, centered on the voxel with the smallest postcorrection $P$ value. For each patient’s modulated gray matter volume map, the mean gray matter fraction in the area of the spherical region of interest was calculated using fslstats and regressed against patient-specific Y-BOCS score changes.

White Matter Analysis
All patients who underwent preoperative DTI were included. We used DTI data to estimate the connectivity between the eventual lesion site and predefined target structures. To delineate the lesioned area, we created patient-specific lesion masks using postoperative T2-weighted images. This delineation was performed by 2 investigators (B.H. and D.H.) blinded to patient information. We assessed interrater reliability using the Cohen $k$ test. The lesion masks were determined for patients individually and then transformed to the diffusion space defined by each patient’s preoperative DTI scan. These lesion masks were the seeds for the subsequent DTI analysis.

To objectively define the target structures, we used the 2-mm cortical and subcortical Harvard-Oxford structural probability atlases, with a threshold set a priori at 25% probability. By using these atlases, there were 56 possible seed-target pairs. The atlases were transformed to patient diffusion space using linear/nonlinear transformation.

The tractography analysis was performed in patient diffusion space using the Diffusion Toolbox of the FMRIB Software Library. For each patient we sought to estimate the strength of connectivity between the origin seed (lesion mask) and the atlas-defined target structures. To do so, we calculated probability distributions based on 2 fiber directions using a previously described multiple fiber extension algorithm. We used these calculated streamline distributions to estimate fiber tracts from the origin seeds to ipsilateral target regions. The strength of connectivity from an origin seed to any other area in the brain correlates with the number of seed-originating streamline traces passing through the target. To suppress spuriously generated tracts passing through areas unlikely to support white matter connectivity, a patient-specific cerebrospinal fluid termination mask was designed by thresholding the nondirectionally weighted diffusion image. Streamline tracking originated in the seed and stopped after leaving brain space or encountering the cerebrospinal fluid mask. To quantify connections from the origin seed to ipsilateral targets, we calculated the percentage of seed-originating streamlines reaching the targets. Left- and right-hemisphere connections were calculated separately. For the primary analysis, we only considered ipsilateral tracts, ignoring any hemisphere-crossing streamlines. An analysis allowing hemispheric crossings through the corpus callosum is included in eTable 2 in the Supplement.

To select appropriate seed-target pairs, only pairs wherein at least 1 streamline connecting the origin seed to the ipsilateral target in all patients were used. This requirement prevented unnecessary analysis on spurious seed-target pairs that had no anatomical basis. In addition, dorsal cingulate and para-cingulate targets were excluded because they partially overlapped with the origin seed in standard space, and tracts would therefore automatically connect to their target and create spurious results. Target pairs meeting the above criteria were considered in network and were included in the analysis.

We quantified hemispheric asymmetry in seed-target connectivity by calculating a laterality metric (LM). For each seed-target pair, we subtracted the right-sided streamline percentage from the left-sided streamline percentage and divided by the sum. The LM is thus a ratio between −1 and 1 that describes whether the right- or left-sided target was more highly connected to the seed area, with negative values indicating greater right-sided connectivity. A Mann-Whitney test was performed to compare the LM between responders and nonresponders for in-network targets. All results were subjected to a Benjamini-Hochberg false discovery rate correction to account for multiple comparisons.

The primary analysis used each patient’s lesion mask as the seed. As a secondary analysis, we created a standard lesion mask by aggregating the individual lesion masks. All individual lesions were transformed to standard space, and the threshold for the resultant lesion probability distribution was set at $P < .05$ after threshold-free cluster enhancement and familywise error correction to create the standard lesion mask. This standard lesion mask was transformed linearly and nonlinearly to patient-specific diffusion space and used as the seed for this secondary analysis. In-network targets were determined separately for the standard lesion mask analysis.
Results

Patients
Fifteen patients (9 men [60%]; mean age, 37 years) met the study inclusion criteria. Of these, 14 individuals (93%) had preoperative high-resolution MRI T1 sequences and 13 (87%) had preoperative DTI sequences. Eight of the 14 patients (57%) with high-resolution T1 and 7 of the 13 patients (54%) with DTI data were responders (Table 1). There were no significant differences between responders and nonresponders in sex, age, surgical year, or preoperative Y-BOCS score as determined by a Mann-Whitney test.

Imaging Parameters
We found no significant differences between responders and nonresponders in voxel volume on T1 images, slice spacing on T1 images, or DTI gradient direction number (eTable 1 in the Supplement). Nonetheless, to address the possible effect of heterogeneity in acquisition parameters, several additional analyses were performed (eTables 3-5 and eFigures 1-3 in the Supplement). No analysis suggested that the distinction between responders and nonresponders was driven by this heterogeneity. Representative images of the postoperative T2 sequences along with the segmented lesions are shown in eFigure 4 in the Supplement.

Gray Matter Results
The VBM analysis of whole-brain gray matter topography demonstrated a gray matter cluster associated with the outcome. The cluster, centered in the right anterior cingulate cortex (x = 2, y = 42, and z = 20) several millimeters anterior to the standard lesion area, demonstrated greater gray matter volume in nonresponders (Figure 1A). Postcorrection significance of the cluster was P = .017. No clusters of gray matter surviving familywise error correction correlated with age or sex. Given the heterogeneity of the scans, the scan parameters were included as nuisance repressors in the generalized linear model;

Table 1. Demographic Information and Clinical Severity Scores of Participants

<table>
<thead>
<tr>
<th>Patient Sex/Age, y</th>
<th>Postoperative Interval, mo&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Y-BOCS Score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Preoperative&lt;sup&gt;b&lt;/sup&gt;</th>
<th>1 Year&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Delta&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Delta (%)</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/30</td>
<td>2001</td>
<td>12</td>
<td>32</td>
<td>2</td>
<td>−30</td>
<td>−93.8</td>
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</tr>
<tr>
<td>F/56</td>
<td>2009</td>
<td>12</td>
<td>40</td>
<td>11</td>
<td>−29</td>
<td>−72.5</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>F/28</td>
<td>2008</td>
<td>13</td>
<td>35</td>
<td>10</td>
<td>−25</td>
<td>−71.4</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>M/29</td>
<td>2003</td>
<td>7</td>
<td>34</td>
<td>15</td>
<td>−19</td>
<td>−55.9</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>M/27</td>
<td>2003</td>
<td>12</td>
<td>36</td>
<td>16</td>
<td>−20</td>
<td>−55.6</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>F/43</td>
<td>2007</td>
<td>7</td>
<td>40</td>
<td>22</td>
<td>−18</td>
<td>−45.0</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>F/49</td>
<td>2008</td>
<td>12</td>
<td>38</td>
<td>21</td>
<td>−17</td>
<td>−44.7</td>
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<tr>
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<td>10</td>
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<td>21</td>
<td>−13</td>
<td>−38.2</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>Nonresponders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/22</td>
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<td>13</td>
<td>34</td>
<td>27</td>
<td>−7</td>
<td>−20.6</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>M/44</td>
<td>2000</td>
<td>9</td>
<td>35</td>
<td>29</td>
<td>−6</td>
<td>−17.1</td>
<td>T1</td>
</tr>
<tr>
<td>F/49</td>
<td>2003</td>
<td>14</td>
<td>38</td>
<td>32</td>
<td>−6</td>
<td>−15.8</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>M/33</td>
<td>2007</td>
<td>14</td>
<td>39</td>
<td>35</td>
<td>−4</td>
<td>−10.3</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>F/38</td>
<td>2003</td>
<td>7</td>
<td>28</td>
<td>27</td>
<td>−1</td>
<td>−3.6</td>
<td>T1, DTI</td>
</tr>
<tr>
<td>M/29</td>
<td>2006</td>
<td>11</td>
<td>35</td>
<td>36</td>
<td>+1</td>
<td>+2.9</td>
<td>DTI</td>
</tr>
<tr>
<td>M/33</td>
<td>2007</td>
<td>13</td>
<td>35</td>
<td>36</td>
<td>+1</td>
<td>+2.9</td>
<td>T1, DTI</td>
</tr>
</tbody>
</table>

Group comparison, mean (SD)

| All patients        | NA/37.1 (10.1) | 2005.4 (2.9) | 11.1 (2.6) | 35.5 (3.18) | 22.7 (10.4) | −15 (9.7) | −35.9 (30.0) | NA |
| Responders          | NA/38.5 (11.3) | 2005.9 (3.0) | 10.6 (2.4) | 36.1 (2.9)  | 14.8 (6.9)  | −21.4 (6.0) | −59.6 (18.5) | NA |
| Nonresponders       | NA/35.4 (9.1)  | 2004.9 (2.9) | 11.6 (2.7) | 34.9 (3.5)  | 31.7 (4.1)  | −3.1 (3.4)  | −8.8 (9.7)  | NA |

P Value<sup>f</sup>

| .75/.84 | .34 | .33 | .54 | <.001 | <.001 | <.001 |

Abbreviations: DTI, diffusion tensor imaging; NA, not applicable; Y-BOCS, Yale-Brown Obsessive Compulsive scale.

<sup>a</sup> The Y-BOCS score was calculated by a staff psychiatrist at the preoperative and follow-up visits.

<sup>b</sup> Number of months after the operation that the 1-year postoperative evaluation was performed.

<sup>c</sup> The preoperative Y-BOCS score was obtained as part of psychiatric evaluation during the month prior to the operation.

<sup>d</sup> The postoperative Y-BOCS score was obtained as part of psychiatric evaluation during the follow-up visit closest to 1 year after surgery but before additional neurosurgical procedures.

<sup>e</sup> Delta value was calculated by subtracting the preoperative Y-BOCS score from the Y-BOCS score at 1 year.

<sup>f</sup> P value was calculated using a Mann-Whitney test.
subsequently, correlations in the same area remained statistically significant (eFigure 1 in the Supplement).

We quantified the relationship for illustrative purposes by placing a 10-mm diameter seed in the right dACC at the cluster center and plotting gray matter volume against the Y-BOCS score change (Figure 1B). Decreased gray matter in this region of the dACC predicted improved response (mean [SD] gray matter partial volume for responders vs nonresponders, 0.47 [0.03] vs 0.66 [0.03]; corresponding to mean Y-BOCS score change, −60% [19] vs −11% [9], respectively).

**White Matter Analysis**

Two investigators (B.H. and D.H.) blinded to response status delineated the lesions on postoperative T2 MRIs of individual patients. The Cohen interrater κ statistic was 0.92, indicating a consistent segmentation.

Of the 56 potential seed-target pairs, 18 pairs (32%) were considered in network for the lesion study and included in the analysis (Table 2). After false discovery rate correction, the LM for 4 of the 18 structures (22%) differed significantly between the groups. Connectivity to the thalamus, putamen, pallidum, and hippocampus readily distinguished responders from nonresponders (Table 2). The LMs of these 4 targets were plotted against patient-specific Y-BOCS score changes (Figure 2).

Greater right-sided connectivity between the lesioned areas in the dACC and these 4 target areas correlated with better response to cingulotomy.

To permit preoperative evaluation of patients in whom the lesion was not yet created, the analysis was repeated using a standardized lesion area (eFigure 5 in the Supplement). In this analysis, 23 structures were considered in network (Table 2). Again, 4 seed-target LM pairs differed significantly between responders and nonresponders. However, in this standardized analysis, the caudate nucleus instead of the putamen LM was significant. Targets of the significant pairs included the thalamus, pallidum, hippocampus, and caudate nucleus. Anatomical targets and tracts are described in eFigures 6 and 7, respectively, in the Supplement. Significant LMs for the standard areas were plotted against Y-BOCS score changes for illustrative purposes (Figure 3), and greater right-sided connectivity predicted better response. Right-sided dominance of at least 2 of the 3 consistent structures (thalamus, pallidum, and hippocampus) had strong positive and negative predictive values for treatment response in this small cohort (eAppendix in the Supplement). Allowing for streamline crossing through the corpus callosum did not significantly alter the results (eTable 2 in the Supplement).

**Discussion**

We identified several neuroanatomical features associated with clinical outcome following a stereotactic surgical lesion procedure for severe intractable OCD. We observed differences in gray matter signal in the anterior cingulate gyrus as well as in connectivity between the dorsal cingulate, caudate, putamen, pallidum, thalamus, and hippocampus that readily distinguished responders from nonresponders to cingulotomy.

These structures are part of the limbic CBTC loop implicated in the neural network dysfunction thought to be responsible for OCD. Other than defining the DTI seed based on the location of the lesion, our analysis was agnostic to candidate brain structures. Even without an a priori region of interest definition, limbic CBTC structures were the only areas to survive stringent significance testing. Previous studies25,37,38 have identified structural differences in components of this circuit between patients with OCD and matched controls. Our results extend these findings by demonstrating that anatomical characteristics of these structures also predict which patients are likely to respond to cingulotomy.

Our findings were strongly lateralized: less gray matter in the right dACC and greater right-sided connectivity in the limbic CBTC circuit predicted improved response. This notion of lateralized anatomical differences in OCD is consistent with the findings of previous studies demonstrating unilateral differences between patients and healthy controls throughout the CBTC circuit.29,40 Although bilateral differences have also been identified,25,37 Several pharmacologic and cognitive-behavioral therapy trials have demonstrated unilateral right-sided imaging changes across metabolic45-47 and perfusion45-47 domains, all of which correlated with response to treatment. Fewer
lesions and have reported similar outcomes.12-14,54 However, capsule. Again, most capsulotomy studies use bilateral lapped in the right, but not left, anterior limb of the internal capsule, a region very close to the DBS target. In a study by Lippitz et al53 including 29 patients, all 16 patients with a good outcome had lesions that over-
ated functions, the planning, decisionmaking, and response correlations. Targeted surgical interventions provide further support for the laterality hypothesis. Although most clinical series and trials of deep brain stimulation (DBS) for OCD have used bilateral stimulation,50 2 reports2,51 described results with unilateral right-sided stimulation of the ventral striatum, with similar response to bilateral stimulation.52 A similar possibilitythat, just as language and verbal memory are heavily lateralized functions, the planning, decision making, and reward circuitry dysfunction that underlies OCD could also be significantly lateralized. Further work in this area is necessary to explore this possibility.

An important implication of our results pertains to the presurgical evaluation of patients with severe refractory OCD who are being considered for neurosurgical treatment. Although the complication rate of these procedures is relatively low, the procedures are nonetheless invasive and

### Table 2. Statistical Comparison of LM Between Responders and Nonresponders

<table>
<thead>
<tr>
<th>Network Target</th>
<th>LM Values for Individual Lesion Seeds</th>
<th>LM Values for Standardized Lesion Seeds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group LATERALITY, Mean (SD)</td>
<td>Uncorrected P Valueb</td>
</tr>
<tr>
<td>Anterior frontal pole</td>
<td>0.21 (0.37) 0.01 (0.53) .84</td>
<td>0.19 (0.43) 0.21 (0.34) &gt;.99</td>
</tr>
<tr>
<td>Insula</td>
<td>0.27 (0.64) 0.58 (0.44) .05</td>
<td>0.09 (0.63) 0.57 (0.42) .14</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>0.05 (0.25) 0.18 (0.38) .63</td>
<td>0.01 (0.16) 0.18 (0.23) .37</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>-0.35 (0.58) 0.02 (0.61) .37</td>
<td>-0.04 (0.16) 0.07 (0.49) .73</td>
</tr>
<tr>
<td>Pars opercularis</td>
<td>0.41 (0.62) 0.40 (0.79) .84</td>
<td>0.59 (0.48) 0.42 (0.67) &gt;.99</td>
</tr>
<tr>
<td>Pars triangularis</td>
<td>NA NA</td>
<td>-0.16 (0.56) 0.35 (0.49) .18</td>
</tr>
<tr>
<td>Primary motor cortex</td>
<td>-0.08 (0.62) 0.05 (0.60) .63</td>
<td>-0.20 (0.55) 0.07 (0.57) .37</td>
</tr>
<tr>
<td>Primary sensory cortex</td>
<td>-0.28 (0.73) -0.13 (0.68) .73</td>
<td>-0.24 (0.79) -0.10 (0.56) .45</td>
</tr>
<tr>
<td>Lateral occipital cortex</td>
<td>0.09 (0.78) 0.24 (0.51) .73</td>
<td>-0.32 (0.66) 0.20 (0.53) .23</td>
</tr>
<tr>
<td>Ventromedial PFC</td>
<td>NA NA</td>
<td>-0.24 (0.81) 0.41 (0.31) .23</td>
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<tr>
<td>Supplementary motor area</td>
<td>0.48 (0.32) 0.18 (0.26) .23</td>
<td>0.54 (0.30) 0.36 (0.28) .37</td>
</tr>
<tr>
<td>Subgenual PFC</td>
<td>NA NA</td>
<td>-0.10 (0.53) -0.02 (0.48) .84</td>
</tr>
<tr>
<td>Precuneus</td>
<td>NA NA</td>
<td>0.02 (0.69) 0.06 (0.61) &gt;.99</td>
</tr>
<tr>
<td>Lateral orbital frontal</td>
<td>-0.01 (0.73) 0.35 (0.68) .30</td>
<td>0.33 (0.64) 0.36 (0.58) .95</td>
</tr>
<tr>
<td>Anterior parahippocampal</td>
<td>NA NA</td>
<td>-0.54 (0.42) 0.11 (0.64) .10</td>
</tr>
<tr>
<td>Posterior parahippocampal</td>
<td>-0.72 (0.22) 0.07 (0.62) .01</td>
<td>-0.59 (0.27) 0.18 (0.60) .02</td>
</tr>
<tr>
<td>Frontal operculum</td>
<td>-0.31 (0.73) 0.46 (0.56) .07</td>
<td>-0.59 (0.68) 0.29 (0.43) .04</td>
</tr>
<tr>
<td>Parietal operculum</td>
<td>NA NA</td>
<td>-0.59 (0.68) 0.29 (0.43) .04</td>
</tr>
<tr>
<td>Thalamus</td>
<td>-0.82 (0.19) 0.41 (0.24) .001</td>
<td>-0.73 (0.35) 0.37 (0.24) .001</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>-0.79 (0.18) -0.08 (0.65) .04</td>
<td>-0.70 (0.27) 0.08 (0.45) .008</td>
</tr>
<tr>
<td>Putamen</td>
<td>-0.55 (0.35) 0.50 (0.33) .001</td>
<td>-0.29 (0.57) 0.50 (0.36) .01</td>
</tr>
<tr>
<td>Pallidum</td>
<td>-0.78 (0.18) 0.43 (0.48) .001</td>
<td>-0.64 (0.28) 0.42 (0.50) .002</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-0.66 (0.33) 0.33 (0.18) .001</td>
<td>-0.64 (0.27) 0.33 (0.34) .002</td>
</tr>
<tr>
<td>Amygdala</td>
<td>-0.67 (0.23) -0.10 (0.69) .34</td>
<td>-0.61 (0.51) 0.05 (0.63) .05</td>
</tr>
</tbody>
</table>

Abbreviations: LM, lateriality metric; NA, not applicable (not in network); PFC, prefrontal cortex.

* The top portion of the table compares the responder and nonresponder groups.

b P values were determined by a Mann-Whitney test.

c P values determined using Benjamini-Hochberg false discovery rate correction were .02 for individual lesion seeds and .03 for standardized lesion seeds.

d P value determined using Benjamini-Hochberg false discovery rate correction was .046 for standardized lesion seeds.

e P value determined using Benjamini-Hochberg false discovery rate correction was .02 for individual lesion seeds.

Examples exist of left-sided47 and bilateral48,49 imaging-response correlations. Targeted surgical interventions provide further support for the laterality hypothesis. Although most clinical series and trials of deep brain stimulation (DBS) for OCD have used bilateral stimulation,34 2 reports39,44 described results with unilateral right-sided stimulation of the ventral striatum, with similar response to bilateral stimulation.35 A similar situation holds for the results from ventral capsulotomy, a stereotactic lesion targeting the ventral portion of the anterior limb of the internal capsule, a region very close to the DBS target. In a study by Lippitz et al31 including 29 patients, all 16 patients with a good outcome had lesions that overlapped in the right, but not left, anterior limb of the internal capsule. Again, most capsulotomy studies use bilateral lesions and have reported similar outcomes. However, image evaluators in the Lippitz et al study were not blinded to response, and those findings were not reproduced in a later capsulotomy study55 in patients with non-OCD anxiety disorders from the same group. Finally, a recent DBS study56 found that blood oxygen level-dependent functional MRI sig-
should be offered only to appropriately selected patients. Previous studies\textsuperscript{57} of cingulotomy lesions suggest that lesion size is not a strong predictor of response. Given this finding as well as the reproducibility of stereotactic lesion procedures, it may be that response variability is more dependent on patients’ neuroanatomical variation\textsuperscript{58-60} than on lesion heterogeneity.\textsuperscript{9,57} The ability to preoperatively, noninvasively identify patients who are more likely to respond to specific neurosurgical interventions would therefore represent a significant advance in our treatment algorithm. The imaging metrics we identified could be applied prospectively to patients undergoing targeted interventions, such as stereotactic lesions or DBS.

Better preoperative evaluation techniques should ideally lead to a more individualized view of each patient’s disorder. Improved understanding of the neuroanatomical basis of OCD will inevitably lead to more refined and individualized targeting for stereotactic neurosurgical procedures. A more comprehensive appreciation of the underlying circuit will not only help predict which patients are likely to respond but also which aspects of their disorder are likely to improve.

Important limitations of our study are its retrospective design and consequent scan parameter heterogeneity. However, because there were no significant differences between responders and nonresponders when imaging parameters were compared, we believe this limitation was unlikely to have significantly affected the results of our study. Moreover, our tractography analysis used only within-subject comparisons to avoid the difficulty of intersubject comparisons with differing scan parameters. Although the sample size was not large, these procedures are rare, and this study represents, to our knowledge, the largest investigating preoperative imaging predictors of response to a stereotactic lesion.

Conclusions

In this group of patients undergoing dorsal anterior cingulotomy for severe intractable OCD, we found structural and connectivity differences in the limbic CBTC circuit that distinguished responders from nonresponders. Decreasing right anterior cingulate gray matter volume and increasing connectivity between the right cingulate and caudate, putamen, pallidum, thalamus, and hippocampus correlated with improved clinical outcomes. These results emphasize the importance of hemispheric asymmetry in the pathophysiol-
Figure 3. Regression of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) Score Changes Against Laterality Metric Values for Each of the Significant Target Pairs in the Standard Area Study

A Standard area to pallidum connectivity

B Standard area to hippocampus connectivity

C Standard area to caudate connectivity

D Standard area to thalamus connectivity

Standard area connectivity to the pallidum (A), hippocampus (B), caudate nucleus (C), and thalamus (D).

...ogy of OCD as well as the possibility of using neuroanatomical markers to inform treatment decisions and predict outcomes in an individualized manner. Prospective work will help determine the generalizability of these results as well as whether these findings should be considered for clinical decision making.

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Study concept and design: Banks, Mikell, Eskandar, Sheth.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Banks, Mikell, Henriques, Kelly, Herrera, Dougherty, Sheth.

Critical revision of the manuscript for important intellectual content: Banks, Mikell, Youngerman, Chan, Eskandar, Sheth.

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Administrative, technical, or material support: Banks, Mikell, Youngerman, Chan, Eskandar, Sheth.

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