Biological Psychiatry: Celebrating 50 Years

Commentary

Toward Precision Medicine: Prediction of Deep Brain Stimulation Targets of the Ventral Internal Capsule for Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is common and can be profoundly debilitating. Deep brain stimulation (DBS)—the delivery of high-frequency stimulation via electrodes to neural targets—is safe and effective for the treatment of refractory OCD (1,2). DBS has been approved by the United States Food and Drug Administration for treatment of Parkinson's disease since 2002 and OCD since 2009. Although this treatment is effective on a group level, why specific patients respond but others less so remains an open question. In this issue of *Biological Psychiatry*, Baldermann *et al.* (3) address this question in an elegant study describing the prediction of treatment outcome of DBS targeting the ventral internal capsule (VIC) for OCD, highlighting frontothalamic tracts involving the right dorsolateral prefrontal cortex (DLPFC) and the left dorsal anterior cingulate cortex (3).

The study has several notable strengths and important implications. Baldermann *et al.* (3) use the individual's own preoperative diffusion magnetic resonance imaging (MRI) scan in 10 patients with OCD to define the volume of tissue activation (VTA) surrounding the optimal stimulation contacts using Lead-DBS and weighted tract fibers coursing through the VTA based on the E-field gradient strength. Connectivity strength was defined as weighted numbers of fiber tracts between the stimulation site and each voxel. Each voxel on the connectivity map was then correlated with obsessive-compulsive clinical improvement, resulting in correlation coefficients within an R-map, or an "optimal connectivity map." The higher the R-value, the greater the relationship between connectivity strength and good clinical outcome. To demonstrate predictive validity, a separate R-map was then created, critically using normative MRI data from the Human Connectome Project in a second population of 12 patients with OCD. The R-map created from individual MRI data from the 10 OCD patients was then used to cross-predict outcome of the 12 OCD patients with normative MRI data and vice versa. Finally, Baldermann *et al.* (3) repeated the analysis with normative MRI data applied across all subjects and validated using leave-one-out cross-validation. These findings converge, highlighting optimal VIC stimulation in which tracts with the highest connectivity strength, namely tracts to the right DLPFC and left dorsal anterior cingulate, were correlated with improved symptoms of OCD. The findings explained approximately 40% of the variance of clinical outcome. The study shows both reproducibility and generalizability, highlighting the potential of normative MRI data in predicting individual outcomes, which may be particularly relevant for subjects without a preoperative MRI. Using a region of interest analysis, Baldermann *et al*. (3) emphasized that connectivity of stimulation sites to the right DLPFC (right middle frontal gyrus) but not to the left dorsal anterior cingulate cortex correlated with OCD outcome.

Focusing on subcortical streamlines predictive of outcome using fiber tracts connected to VTAs across all patients and normative data, the authors confirmed the anterior frontothalamic tracts as being positively predictive but the medial forebrain bundle carrying dopaminergic fibers to the prefrontal cortex as being negatively predictive of OCD outcome. A separate secondary analysis of 18 subjects preliminarily suggested that tracts to the ventromedial prefrontal cortex and cingulum bundle were associated with improvement in depressive symptoms, thus dissociating OCD and mood outcomes and emphasizing the relevance of careful clinical assessment and symptom targeting. These findings also argue against targeting the medial forebrain bundle for compulsive symptoms either within the VIC or closer to its output from the ventral tegmental area. In the VTA-based analysis, optimal improvement was associated with more apical and posterior white matter area of the VIC, consistent with the evolution of OCD VIC DBS clinical practice, with a move from anterior toward more posterior targeting demonstrating greater clinical efficacy and efficiency (4), and also consistent with their dorsal prefrontal tract findings.

These findings contrast with several recent studies from differing centers using preoperative scan data. One study, using seeds in the ventral tegmental area and mediodorsal thalamus to define tracts, highlighted that the most clinically effective contacts for 12 patients with OCD VIC DBS were more closely aligned with the medial forebrain bundle than with anterior thalamic tracts (5). A recent tractographic analysis in a dual-stimulation DBS study in 6 patients with OCD highlighted dissociable fiber bundle stimulation from two different stimulation targets within the same individual (6). The optimal and most dorsal VIC contact was associated with more ventral tracts involving the medial orbitofrontal cortex, mediodorsal thalamus, the amygdalofugal pathway, and the habenula tracts. In contrast, the anterior subthalamic contact, another target with known efficacy in OCD, was associated with tracts to a different network involving the lateral orbitofrontal cortex, dorsal cingulate cortex, and DLPFC. Although tractography did not correlate with clinical outcome, the fact that VIC DBS was associated with mood improvement led Tyagi *et al.* (6) to suggest that VIC DBS and its associated ventrally stimulated tracts implicated improvement of mood states whereas subthalamic DBS improved extradimensional set shifting, suggesting greater specificity for compulsive symptoms. Finally,

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an OCD DBS study targeting the caudate and ventral striatum gray matter rather than VIC white matter highlighted the role of predictive OCD symptom–specific functional imaging and tractography. In six of seven responders, a preoperative MRI index (composed of the probability that tracts from the approximate VTA of the optimal contact reached functionally identified task-based MRI regions based on OCD symptom–specific triggers, such as contamination or ordering imagery) could differentiate between effective contacts located within either caudate or ventral striatum (7).

These inconsistencies in the literature suggest that additional work is required to investigate the role of methodological differences or interindividual heterogeneity. Clinical and analytic methodological differences may account for some of these tractographic differences within the same VIC target. Prefrontal tracts follow a dorsal–ventral and posterior–dorsal to anterior–ventral organization through the VIC in primates (8) and humans (9); that the optimal and most dorsal contact in one VIC target implicates the medial orbitofrontal cortex (6) whereas optimal VIC targeting in the current study implicates dorsal frontothalamic fibers (3) might suggest subtle differences in neurosurgical targeting between clinical centers on an anterior–posterior or ventral–dorsal extent. Differences in clinical stimulation optimization might exist between differing clinical centers, including symptom target (e.g., targeting obsessive-compulsive–specific, mood, anxiety, or an interaction of symptoms), stimulation parameters (e.g., differences in pulse width or frequency may have differing mechanistic effects), and duration of symptom optimization [e.g., 3-month optimization during the randomized controlled trial (6) vs. clinical optimization over an extended duration (3)]. Differences in tractographic analytic methods may also contribute, depending on how seeds are defined [e.g., VTA-based (3,6) or ventral tegmental area– and mediodorsal thalamus–based (5)].

Other relevant unanswered issues include heterogeneity in disease or anatomical substrates. Substantial interindividual differences in prefrontal tract organization through the VIC have been demonstrated in primate tract tracing and normative human tractography studies that may be relevant for individualized targeting (8,9). Whether this interindividual variability is necessarily clinically relevant, though—given the extent of VTA during stimulation or with the use of tractography from larger normative data sets averaged across individuals, which this article appears to suggest—remains an open question. Differences in OCD presentation associated with different cognitive impairment profiles may also be highly relevant. Baldermann *et al.*'s findings (3) are consistent with observations of OCD cognitive impairments in monitoring, control, and executive processes, such as hyperactive error monitoring and conflict, uncertainty, goal-directed control, planning, working memory, reflection impulsivity (10), and possibly extradimensional set shifting (6), which implicates the ventrolateral PFC and to a lesser extent the DLPFC. In contrast, stimulation of ventral prefrontal regions may play more of a role in anxiety, mood states, negative biases, or fear extinction and also associative learning and outcome tracking for behavioral flexibility. Stimulation targeting differing fiber bundles or neural targets may indeed improve OCD, possibly via differing cognitive processes. Whether the addition of functional connectomics from resting-state data or cognitive or functionally based neural imaging substrates (6,7,10) might further enhance stimulation prediction remains to be established. For instance, a study focusing on the anterior limbic–cognitive subthalamic nucleus showed convergence between a large normative multiecho resting-state data set and coordinates from the optimal contacts in DBS targeting the subthalamic nucleus in patients with OCD (10). In this study, the subthalamic nucleus was functionally dissociated into anterior limbic–cognitive and posterior motor regions using resting-state functional connectivity from prefrontal seeds in normative data and was consistent with the location of optimal coordinates from the OCD DBS patients clustering in the anterior subthalamic nucleus. Furthermore, which targets might be most effective—including subregions of the VIC, the subthalamic nucleus, and possibly the caudate, ventral striatum, inferior thalamic peduncle, or medial forebrain bundle—might differ between target regions as a function of disease and individual heterogeneity.

These studies highlight the maturation of DBS treatment for OCD, pushing the field forward toward more precise individualized target prediction for OCD DBS and enhancing clinical efficacy and efficiency and, more critically, raising additional compelling questions that should be addressed. The findings extend beyond the realm of DBS, providing insight into more precise targeting for lesion surgeries and noninvasive stimulation. The careful parcellation of symptom dimensions with specific tracts may also be clinically relevant for DBS dimensionally across a range of psychiatric disorders, including disorders of mood, addiction, and anxiety.

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