Biological Psychiatry: Celebrating 50 Years

Commentary

Will Deep Brain Stimulation Help Move Precision Medicine to the Clinic in Psychiatry?

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In this issue of *Biological Psychiatry*, Tyagi *et al.* (1) present the results of a small study (n = 6) in which two deep brain stimulation (DBS) surgical targets for the treatment of intractable obsessive-compulsive disorder (OCD) are compared in an intraindividual trial design. Specifically, patients had DBS electrodes implanted bilaterally in the ventral capsule/ventral striatum (VC/VS) and anteromedial subthalamic nucleus (amSTN). They then entered a 12-week double-blind counterbalanced phase of either VC/VS or amSTN stimulation. This was followed by a 12-week open-label phase during which both targets were stimulated simultaneously, and cognitive behavioral therapy was added. In addition to OCD symptoms, mood and cognitive flexibility were assessed throughout the trial. Lastly, magnetic resonance imaging tractography data were collected from each patient. While the small sample size is a major limitation, during the initial 12-week double-blind phase both targets resulted in a roughly equivalent reduction of OCD symptoms. However, in addition to improvement of OCD symptoms, amSTN stimulation improved cognitive flexibility, whereas VC/VS stimulation had greater mood effects, and these effects were dissociable (i.e., considerably more prominent with one target but not the other). Further symptom improvement during the 12-week open-label phase with stimulation of both targets and the addition of cognitive behavioral therapy were minimal. Not surprisingly, each target was associated with connections with separate and distinct networks as measured by diffusion tractography with VC/VS connectivity to the medial orbitofrontal cortex and amSTN connectivity to the lateral orbitofrontal cortex, the dorsal anterior cingulate cortex, and the dorsolateral prefrontal cortex.

These results highlight two important features of circuit-based therapies: 1) brain-based disorders diagnosed via the presence of a constellation of disparate symptoms do not demonstrate consistent circuitry abnormalities across individuals diagnosed with a disorder, and 2) treatment based on impacting specific circuits likely impacts underlying symptomatology rather than the disorder as a whole. Take Parkinson's disease as an example. While the primary symptoms of Parkinson's disease are various manifestations of motor system dysfunction, the illness is also often associated with insomnia, autonomic dysfunction, memory difficulties, depression, and anxiety. The DBS targets (the STN and the globus pallidus interna) are effective in most patients for motor symptoms, such as tremor, but have minimal effects on other symptoms that are associated with the illness. In fact, a common side effect of STN DBS is increased impulsivity owing to the effect on the limbic system fibers within the STN. Our experience with DBS for Parkinson's disease and other movement disorders is much larger than our experience with DBS for psychiatric illness and shows us that DBS affects underlying symptoms (for better or worse) of disorders rather than the disorder as a whole.

DBS for psychiatric illness began in 1999 when Nuttin *et al.* (2) implanted DBS electrodes in the anterior limb of the internal capsule in four patients with severe, treatment-refractory OCD. The anterior limb of the internal capsule was chosen based on data suggesting that ablation of this region (i.e., anterior capsulotomy) was effective for intractable OCD. Published in *The Lancet* in 1999, Nuttin *et al.* (2) found that three of four patients experienced clinical benefit. Since then, this DBS target has moved posteriorly to the VC/VS and efficacy has been demonstrated in larger sample sizes (3). In addition, subsequent studies have also demonstrated benefit using the STN target for intractable OCD (4). In sum, both targets have been associated with efficacy for intractable OCD in previously published trials, and the VC/VS target was approved for the treatment of intractable OCD by the U.S. Food and Drug Administration (FDA) in 2009 and is still the only indication for DBS for a psychiatric illness that is approved by the FDA. Despite FDA approval of the VC/VS DBS target for intractable OCD, there are limited published controlled data for both targets.

Initial studies of DBS for treatment-resistant depression (TRD) were published more than half a decade later by Mayberg *et al.* (5), who published encouraging open-label data for DBS in the subcallosal cingulate cortex (a target based on neuroimaging studies of the circuitry abnormalities underlying the pathophysiology of major depressive disorder). In addition, because many patients with intractable OCD who received VC/VS DBS also experienced significant improvements in mood, open-label studies of the VC/VS target for TRD were conducted and also revealed positive results (6). Unfortunately, controlled trials of DBS at each target conducted for possible FDA approval of DBS for TRD were both negative (7,8). While possible reasons for the failures of these clinical trials have been discussed extensively elsewhere (9), investigators are exploring new approaches to mitigate factors that may have contributed to the trial failures, including individually based targeting based on tractography (rather than a standard target across all subjects), alternative targets, and alternative trial designs.

Tyagi *et al.* (1) suggest a different approach. Because different DBS targets affect separate networks and symptoms associated with these networks (e.g., cognitive

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flexibility and mood), perhaps the goal of DBS, at least in heterogenous psychiatric disorders, should be to target these underlying symptoms rather than the disorder as a whole (10). First, this approach addresses heterogeneity. Because the diagnosis of depression requires the presence of at least five of nine neurovegetative symptoms, in theory two patients with depression could share only one symptom but still be diagnosed with depression and have their DBS treatment targeted identically. Given this heterogeneity, perhaps we should not be surprised that our "one target fits all" approach has not yet proven effective for TRD. Second, if we can identify targets that affect circuits associated with underlying symptomatology (e.g., fear, reward, or approach-avoidance) and demonstrate that DBS at these targets positively affects said symptoms, then the DBS target could be used to treat these symptoms across diagnoses rather than within a single categorical diagnosis. Third, this approach brings us closer to precision medicine in psychiatry. Treaters could access which symptoms are present in an individual via deep phenotyping (e.g., not just interviews and psychometric scales, but perhaps even objective task-based assessments) and identify which symptoms most affect the patient. Next, we could possibly identify individual targets within the underlying circuitry to affect these symptoms via neuroimaging and/or electrophysiological measures. While we understand the basic nodes within fear and reward circuitry, for example, we also realize that there are individual differences in circuit function and dysfunction. Lastly, treaters could choose which symptoms and anatomical regions to target in a personalized medicine approach.

The types of studies described by Tyagi *et al.* (1), although difficult to conduct, will be essential for guiding future targeting, both anatomically and symptomatically, for DBS and likely for noninvasive neurostimulation approaches as well. While larger sample sizes will also be needed, this mapping of brain targets with effects on whole-disorder symptom improvement along with effects on specific symptoms will allow for more granular individual treatment targeting as the field of psychiatry moves more toward precision medicine and, hopefully, the improved clinical outcomes that come with it.

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