It takes time to tune

Brandon S. Bentzley[1], Jaspreet Pannu[1], Bashar W. Badran[2], Casey H. Halpern[3], Nolan R. Williams[1]

[1]Department of Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, USA; [2]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA; [3]Department of Neurosurgery, Stanford University, Stanford, CA, USA

Correspondence to: Nolan R. Williams, MD. Department of Psychiatry & Behavioral Sciences, 401 Quarry Road, Stanford, CA 94305, USA.
Email: nolanw@stanford.edu.

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In a recent issue of *JAMA Psychiatry*, Bergfeld *et al.*, report the results of an investigator-initiated trial of bilateral deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule (vALIC) for treatment of treatment-resistant depression (TRD) (1). The results of this trial indicate that DBS of vALIC produces an antidepressant response that slowly accumulates over the course of a year and rapidly dissipates when stimulation is discontinued. This is encouraging and brings hope to patients with a debilitating depression who have exhausted most currently available treatment options. Indeed, the patients selected for this trial were particularly refractory, having failed electroconvulsive therapy (ECT) as well as numerous pharmacotherapeutic approaches, including two selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and lithium augmentation. Despite reports of recently failed industry-sponsored trials of DBS for treatment of TRD (2,3), the medical field has an obligation to continue to investigate potential treatments for this group of severely afflicted patients. Although the results of this trial inspire some hope for an effective treatment for TRD, this hope comes with a caveat of caution driven by two recently failed trials (2,3) as well as several unique aspects of this trial that raise questions of how to move the field of invasive neuromodulation for TRD forward.

Perhaps the most striking aspect of this study is the clinical trial design (4). Aside from one notable exception (5), the process of discovering the optimal settings for a new invasive neuromodulation approach in a psychiatric condition can take months to years to mature (3). This latency is likely due to the still cryptogenic mechanism of action of DBS as well as its guess-and-check approach to programing (6). There is no immediate symptom-based feedback parameter currently available for TRD as exists for movement disorders (7), that can be used to determine if the programming changes are likely to be beneficial; thus, each new set of DBS parameters must be tested for several days to weeks before its effect can be determined. In our own experience with determining the optimal programming parameters for treating TRD with epidural prefrontal cortical stimulators (EpCS), a similar implantable technology to DBS stimulators, this onerous and methodical process took years to discover the appropriate stimulation settings that ultimately resulted in remission in 80% of patients (8,9). In the absence of an immediate symptom-based feedback parameter, a randomized clinical trial requires a yearlong (or longer) period during which the comparison between active and sham parallel groups is made. Alternatively, a yearlong open-label lead-in period transitioning to a short sham-controlled cross-over phase, was employed by Bergfeld *et al.*, a design similar to that used in a trial of DBS for treatment of obsessive-compulsive disorder (10). There are several advantages to this later approach. It is more patient-centered, as a potentially life-saving treatment is withheld for the shortest duration possible to demonstrate efficacy, and the maximal efficacy of the DBS can be optimized through iterative programing, especially as compared to trials that use constant, unified

DBS parameters across patients. However, there are also drawbacks to this approach. During the open-label lead-in phase, non-responders will tend to drop out of the study at higher rates than responders, biasing the sample used for the double-blinded crossover phase of the trial with a higher proportion of responders. Indeed, eight of the nine participants who withdrew during the open-label phase of the trial were non-responders. Although the authors show that this did not likely alter the conclusions, the true effect cannot be known. Further, the ability to demonstrate efficacy in this design depends on a rapid loss of efficacy when stimulation is discontinued, which occurred in this trial. This rapid loss of efficacy could indicate that the device was providing an anti-depressant response compared to sham, but it could also represent a pro-depressant rebound effect due to sudden discontinuation of stimulation, a confound not inherent in traditional parallel-group trials (11).

Another major concern that limits overall enthusiasm for this report and many similar reports, is the absence of relevant diagnostics to determine which neural or behavioral processes are being modulated by stimulation that mediate the antidepressant effect (11). Without a clear mechanistic intermediate target, or a more delineated structural target, it is difficult to explain why some patients were non-responders or to inform changes in approach to improve future trials, and improvements are needed, as the number needed to treat was approximately 2.5, a lower efficacy than that seen after DBS for the motor symptoms of Parkinson's disease. Further, the protracted latency to produce an anti-depressant response raises the question that long-term brain stimulation may be continuously changing the brain's response to stimulation or slowly accumulating changes in functional connectivity (12); however, without an hypothesis-driven approach with a mechanistic intermediate process, the possible mechanism of DBS efficacy remains unclear. Previously, we have suggested that the use of functional neuroimaging (such as an interleaved DBS-BOLD and/or a DBS-PET approach) may aid in the selection of treatment parameters and therefore greatly reduce the time to select appropriate parameters (13); this approach is safe (14) and could be used to serially track neural response to stimulation over time, allowing for an fMRI-based intermediate, functional target. Another possibility would be the use of closed loop devices, which have both a sense and stimulate capability, and are capable of providing an ongoing physiological readout of the neurophysiology of the system (15).

The positive results of this study are a contrast to a recent industry-sponsored trial of DBS of the ventral capsule/ventral striatum (VC/VS). Despite the relative proximity of the vALIC and VC/VS, the VC/VS trial did not demonstrate separation between sham and active stimulation (1). This could be due to the heterogeneity of the target and the differences in the lead used creating variability in the electric field produced (16). This is not surprising when dealing with three-dimensional targeting approaches (17). Furthermore, these findings could be in part due to differences in trial design; namely, the VC/VS trial did not utilize a long open-label lead-in period to optimize DBS programing, and the VC/VS trial did not report on the effects of sudden discontinuation of stimulation. However, the contrasting outcomes of these trials could also indicate the high degree of topological precision and accuracy that are required for DBS to be successful in treating depression. The importance of this nuance is highlighted by DBS studies of TRD targeting the subcallosal cingulate; responders and non-responders could be defined by recruitment of a particular white matter tract (18). Thus, it could be that the vALIC presents a more reliable target for treatment of TRD. Alternatively, the success of this trial could simply be a result of serendipitous alignment of the DBS leads (Medtronic 3389) with the relevant fiber tracts that run in proximity or as a part of the vALIC. Considering the high individual variability in white matter tract topology in ALIC (19), without immediate neurophysiological and/or neuroimaging verification of target engagement, it is difficult to compare the two studies (20).

Finally, it is prudent to consider the participants involved. Depression is a very heterogeneous diagnosis with 126 unique combinations of the nine core symptoms that can result in a diagnosis of major depression. It appears that major depression may be a term that encompasses at least four neural network abnormalities (21). Bergfeld *et al.* were very inclusive in their recruitment, including over half of patients screened; however, it remains unreported if there are specific core symptoms or neural network abnormalities that are treated better with DBS of particular brain regions (4). Certainly, when using transcranial magnetic stimulation (TMS) as a probe of endophenotypes, it appears that certain depression neural subtypes respond differentially (22). Only one invasive neuromodulation approach has accounted for the multiple endophenotypes issue by selecting cortical nodes involved in several of the neural network abnormalities (8,9). Similarly, it is unclear

if specific patients are more prone to developing adverse events. Intracranial hemorrhage is a major concern of devices implanted in brain parenchyma and occurred at a rate of 4% in this trial. Fortunately, the intracranial hemorrhage occurred in the supplementary motor area and did not cause any lasting neurological deficits. Other approaches such as epidural cortical stimulation and vagal nerve stimulation obviate this concern and may be considered before a patient is referred for DBS. TMS, a noninvasive alternative, removes the need for device implantation whatsoever and may be a preferred in less severely treatment-resistant patients who are at greater risk for surgical complications. TMS can also be used as a pre-surgical probe for determination of potential efficacy of an implanted device (23) and aggressive rTMS protocols may be a method for selecting potential responders based off of mechanistic intermediate targets (24). Nevertheless, all of these neuromodulation treatments suffer from the response latency seen with DBS. Although not reflective of the ultimate efficacy of implanted stimulators, latency allows for a vulnerable period of time during which patients may be more prone to adverse events including suicidal ideation. The development of a rapid onset antidepressant, such as ketamine and accelerated theta burst stimulation, is unlikely to immediately replace these longer term therapies for refractory patients; however, they may serve as useful "bridging" therapies between implantation and DBS effect onset, thereby minimizing adverse events during this time as demonstrated by the two deaths and four suicide attempts in non-responders. The concerns of adverse events need to be carefully balanced against the perhaps greater risk of treatment failure.

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Footnotes

Conflicts of Interest: The authors have no conflicts of interest to declare.

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