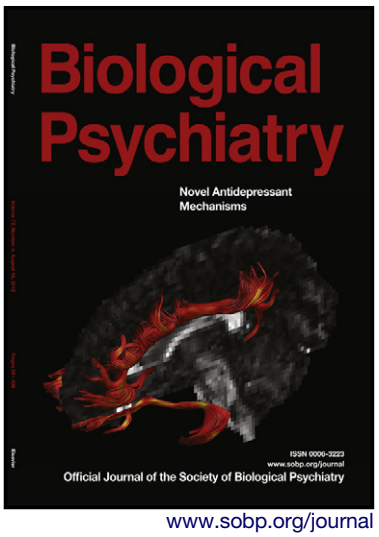

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Deep Brain Stimulation for Treatment-Resistant Psychiatric Illnesses: What Has Gone Wrong and What Should We Do Next?

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Abstract
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Invasive brain stimulation, particularly deep brain stimulation (DBS) has been heralded as a step forward for psychiatry. Despite great promise, recent well-controlled studies for psychiatric illness have failed. We hypothesize that the root of these difficulties is our inability to carefully choose the patients to whom we offer DBS. Based on emerging results in neurobiology, we suggest a way forward, through clinical studies that focus more closely on the underlying disturbances.

Roughly a decade ago, the literature blossomed with successes for DBS in refractory psychiatric illnesses. DBS showed open-label efficacy at multiple anatomic targets in major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) (1–3). Since then, despite careful design, two large randomized trials of DBS for MDD have failed (4). The lone survivor in the United States is DBS for treatment-refractory OCD. This is available under a Humanitarian Device Exemption (HDE), which does not require controlled data because few OCD patients qualify for implantation each year. Non-invasive neuromodulatory technologies have reached wider clinical use, but with a roughly 50% response rate in treatment resistant depression(5), there is a long way to go.

What went wrong? And how can we fix it? We cannot simply blame large placebo effects. Designing shams for neuromodulation is difficult, but recent trials have verified effective blinding(4). We submit that the solution is simpler and well-known to most investigators: clinical rating scales and the checklist-based diagnostic approach do not measure what DBS actually does.

The MDD trial failures illustrate this. None of the targets in those trials covers the full range of depression symptoms. The subcallosal cingulate (Cg25) target was selected for its role in negative mood (2). VC/VS' effects were first demonstrated for OCD, suggesting an effect on perseverative thinking (1). Medial forebrain bundle (MFB), the newest target with open-label results in MDD, was proposed for anhedonia (6). Each target has a different hypothesized mechanism of action and addresses a different MDD phenotype. Put another way, initiatives such as the NIMH Research Domain Criteria (RDoC) project reflect a growing understanding that each DSM diagnosis contains multiple phenotypic clusters, and each cluster may represent a different neuro-phenotype. DBS is an intervention on a circuit, which we would expect to only affect a subset of symptoms, not the full checklist of criteria. Trialing DBS for all-comers MDD, without first ensuring that patients have an appropriate circuit deficit or its corresponding clinical phenotype, biased our trials towards failure. Unless the investigator is lucky and recruits exactly the right patient sample, DBS has no substrate with which to work. By contrast, conventional treatments have begun to show that they are effective when targeted to specific functional deficits. A single cognitive-behavioral therapy, focused on emotion regulation, has proven efficacious across mood and anxiety disorders (7). The iSPOT-D trial recently indicated that MDD patients who show a specific cognitive-impairment phenotype also have a different pattern of medication response (8).

Building on the above, we propose a new direction: DBS trials should select patients based on measureable trans-diagnostic behaviors embedded within clinical diagnoses,

and should emphasize change in those behaviors as their primary outcomes. From a regulatory perspective, it will still be necessary to target DBS to disorders, not to the behaviors directly. In the United States, at least, the Food & Drug Administration labels devices for diagnoses. We cannot readily test a DBS equivalent of psychotherapy's Unified Protocol. However, we **can** select patients based on a biomarker within a disorder. This is the foundation of NIMH's "experimental medicine" approach to clinical trials. It enables the construction of more reliable models of mental illness at multiple levels (9). It also comports with what we now know. DBS, at any target, modulates the activity of a distinct circuit (although targets may access overlapping circuits). Each circuit can be mapped to a functional domain, whether an RDoC Construct or a broader notion such as obsessional thinking. That domain level is also what we can measure with psychophysical tasks. This implies that most of the human neuroscience literature tells us about domains and circuits, not disorders. We propose to adapt those neuroscience schemas to the realm of clinical trials, developing a more rational basis for DBS targeting. No one would be surprised if a trial of an antibiotic for "fever" failed; we would expect efficacy against a specific bacterium type. The next generation of DBS trials should aim for similar precision.

That cross-diagnostic approach also offers a "silver lining" for recent failed trials. Investigators now have patient cohorts with functional implants and varying degrees of clinical response. Studying them through fMRI, EEG and/or MEG could reveal biomarkers and circuit-specific phenomena that could then refine patient selection or define a new trial target. As an example, in our recent trial of VC/VS DBS for

depression, improvement on the Montgomery-Asberg Depression Rating Scale (MADRS) correlated with DBS-induced change in a psychophysical task. DBS reduced reaction times in an Affective Interference Task, which combines emotional distractors with Stroop-like cognitive interference. That reduction correlated with the absolute decline in MADRS ($r=0.56$, $p<0.03$) (10). This matches a similar finding from the iSPOT-D investigators(8). To exploit this in a clinical trial, we could screen patients with treatment-resistant depression using the same task. Entry to the trial would then depend on impaired performance and/or abnormal patterns of brain activation, e.g. recruitment of additional brain areas to compensate for a deficit. This would identify a cohort of patients with specific impairments in a circuit linked to VC/VS, who in turn might be more likely to benefit from VC/VS DBS. The same approach could apply across disorders/targets, e.g. an emotion-regulation task to screen for patients with Cg25-relevant impairment, or a reward valuation task to screen for anhedonic MFB DBS candidates.

The inventor R. Buckminster Fuller reportedly said "There is no such thing as a failed experiment, only experiments with unexpected outcomes." DBS' recent tribulations were unexpected, but in retrospect, not surprising. From those apparent failures, we now have an opportunity to enhance both the basic science and the clinical toolkit of psychiatry.

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Footnotes and Table/Figure Legends

None.