How Does Deep Brain Stimulation Work?

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Deep brain stimulation (DBS) presents the promise of effective treatment for central nervous system disorders that are resistant to other available treatments. Deep brain stimulation has been reported to be effective in Parkinson's disease, essential tremor, pain syndromes, and medication resistant obsessive-compulsive disorder (OCD). Deep brain stimulation has also been reported to exert a remarkably large antidepressant effect in open-label, single blind lead-in, and long-term follow-up studies, even in patients in whom aggressive medication strategies and electroconvulsive therapy have failed (1). This is notable, given the expected low placebo response in such refractory patients. However, expectancy of benefit from invasive procedures such as DBS can be high, and the results of a sham-controlled randomized trial have yet to be published, although a large-scale trial is presently underway. Amidst the excitement about this exciting treatment that permits the translation of knowledge with regard to pathological circuits into a focal therapeutic circuit modulation, there looms a vexing and as yet unanswered question: How does it work?

If indeed DBS for depression is more effective than other available treatments and is able to achieve remission when all else has failed, then answering this question of mechanism is of great importance to advancing understanding of the causes of severe neuropsychiatric disorders and could shed light on their effective treatment and, hopefully, ultimately their cure. Historical explanatory models for the mechanism of action of DBS for depression as a virtual lesion have since been replaced with a more nuanced understanding of the impact of patterned electrical stimulation on neurocircuit functioning. For example, computational modeling of the impact of electric fields on subcompartments of neurons suggests that, dependent upon neuronal orientation relative to the field and intensity of stimulation, soma might be hyperpolarized whereas axons might be depolarized, resulting in a decoupling of cell body and axonal effects (2). This might in part explain observations of local inhibition coupled with increased axonal firing in response to DBS.

Mechanisms of action of DBS can be approached from multiple levels of analysis (molecular, cellular, and circuit), each of which can be expected to be important to a comprehensive understanding of how DBS exerts its clinical effects. At the cellular level, attention has been mostly focused on neuronal effects (local neurons, afferent inputs, and fibers of passage), but recent reports suggest that glia might also play a role. At the circuit level, consideration has been paid mostly to the topography of effects on connected brain regions within distributed mood regulatory networks, as revealed via diffusion tensor tractography (3). Recent work in Parkinson's disease DBS mechanisms has emphasized not just the spatial topography of circuit effects but also the temporal components of circuit behavior. Normalizing pathological oscillations in a network is one of the leading theories in Parkinson's disease literature (4), but this hypothesis has been relatively less-examined in the depression literature. There might be other as yet unexamined possibilities worth exploring beyond these, such as a potential impact of DBS on the blood brain barrier (5), which is relevant, given anecdotal reports that DBS might work better in patients while taking antidepressant medications.

Perhaps the greatest challenge to understanding the mechanism of action of DBS in depression is that DBS antidepressant action is typically delayed by weeks to months. Although some reports of acute interoperative effects have been described, it is not clear how long-lasting and replicable such effects will turn out to be. This suggests that the acute effects of DBS are, in and of themselves, insufficient to correct pathophysiological processes in the depressed brain; however, it is these immediate effects that are measured in most preclinical models. Delayed action in depression also makes the availability of biomarkers of therapeutic action, such as the recent report of short latency cortical activation correlating with clinical benefit of thalamic stimulation in tremor (6), more difficult to come by.

Hamani and Nobrega (7) present a comprehensive review summarizing work from their group and others with regard to the use of DBS in rodent models of depression. They highlight replicable evidence for antidepressant-like activity of DBS at particular dosages and stimulation targets. Summarizing existing literature specifically on mechanisms of ventromedial prefrontal cortex stimulation in several depression models, Hamani and Nobrega comment on some of the leading hypothesized mechanisms, including functional inactivation of local neurons at the site of stimulation and modulation of distant structures via activation of fibers of passage leading presumably to neurotransmitter release (with a hypothesized role for serotonin) and neuroplastic effects via brain-derived neurotrophic factor. They highlight that the effects of DBS are contingent upon myriad factors, including brain target, stimulation parameters, study design, and the behavioral paradigm. That the effects of DBS are contingent upon such factors is not surprising. Nonetheless, their review highlights the challenges faced by the field in seeking to synthesize the disparate literature and generate testable hypotheses with regard to mechanisms of antidepressant action.

Preclinical models provide a powerful tool for exploring how DBS works. These models allow for examination of DBS behavioral effects across a range of brain regions, stimulation parameters, and behavioral models, permitting high-throughput dose-finding studies as well as step-wise examination of mechanisms of action once a reliable behavioral effect is identified. This is a critical contribution, given the high dimensionality of the parameter space for DBS dosimetry, as shown in Figure 1. Unanswered dosimetry questions abound, such as whether it is critical for stimulation to be unilateral or bilateral, and if bilateral, do the pulses need to be synchronized across the two hemispheres.

As needed as these preclinical models are, there are, however, significant barriers to their clinical translation. First, modeling depression in rodents is no easy task. Although it is unlikely that the tasks widely used to model depression in rodents (i.e., the forced swim task and tail suspensions test) exhibit construct or face validity with human depression, there is increasing debate as to whether

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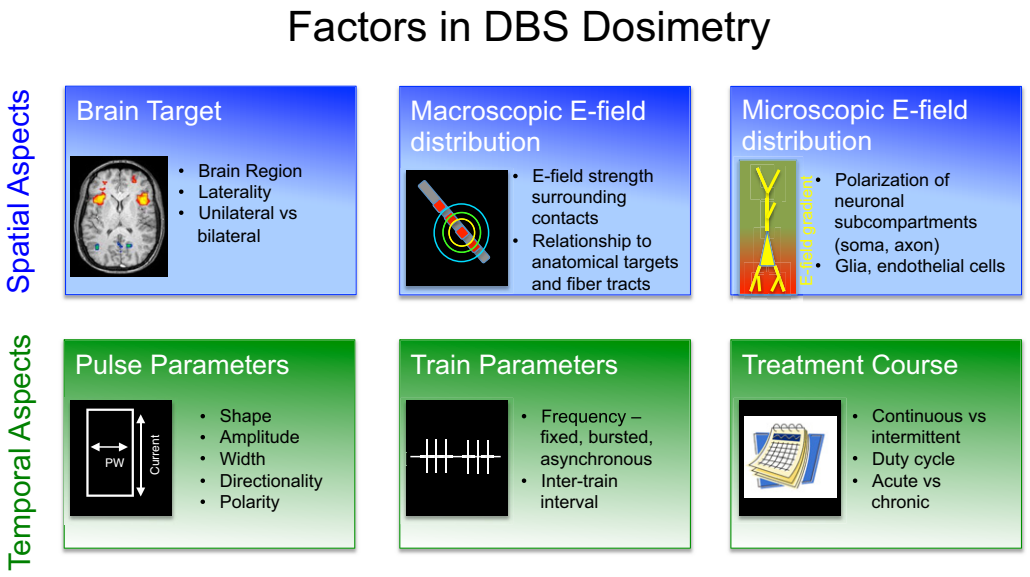

Figure 1. Summary of factors related to dosimetry of deep brain stimulation (DBS), grouped by spatial factors describing electric field distribution and temporal factors describing pulse, train, and duty cycle parameters. PW, pulse width.

these tests even exhibit predictive validity (8,9). Furthermore, the majority of preclinical studies of depression tend to be performed in animals with a normal brain as opposed to a "depressed" brain, not to mention a "treatment-resistant depressed" brain. Even in instances where preclinical studies attempt to examine the effect of various experimental manipulations on a "depressed" brain, the depressed brain state is typically modeled within a given animal on the basis of dysfunction across a single behavioral domain. This is of course a serious limitation, because depression by definition yields dysfunction across multiple distinct behavioral domains in the same patient. For example, although loss of appetite occurs in depression, isolated anorexia represents a distinct biological phenomenon, and it is likely suboptimal to consider a rodent model of isolated anorexia as a valid model of depression. Several rodent models of depression that exhibit construct, face (behavioral dysfunction across multiple distinct domains in the same animal), and/or predictive validity—including both genetic-risk models and stress-based models—have been reviewed in the literature (8,9); and there is no doubt that investigation of the effect of DBS on these preclinical models of a "depressed" brain would increase the translational value of current preclinical approaches. Second, acute DBS is insufficient to reverse depressive symptoms in humans. Thus, DBS likely lies "upstream" of the pathophysiological mechanisms that underlie depression. Furthermore, DBS might be expected to have accessory effects on the brain that do not contribute to its antidepressant-like properties. Because depression-related behavioral changes during DBS in preclinical models of depression might simply reflect the accessory modulation of these circuits, caution must be applied when interpreting the findings of these studies.

Emerging approaches such as chronic multi-circuit neurophysiological recordings create the potential for the effects of acute DBS to be monitored concurrently across entire brain circuits in freely behaving rodents (10). Moreover, widely distributed circuits can be measured in the same animal across weeks–months to determine the effect of chronic DBS on brain circuits and neural dynamics. Most importantly, this approach can be used concurrently with novel cell type/circuit-specific neuromodulatory approaches (i.e., optogenetics and designer receptors exclusively activated by designer drugs [DREADDs]) to selectively enhance or suppress the multiple downstream effects of DBS independently or to selectively activate downstream pathways in the absence of upstream DBS stimulation.

Ultimately the integration of the DBS approaches reviewed by Hamani and Nobrega—with improved animal models of major depressive disorder (and treatment-resistant depression), multi-circuit recording techniques that allow for activity to be chronically monitored across entire depression-related circuits during DBS—and these novel neuromodulatory approaches will enhance the translational utility of even the best preclinical studies described to date. Although the clinical role of DBS in depression remains to be clarified, the need for a safe and effective treatment for medication- and electroconvulsive therapy-resistant depression is indisputable. Further work into the mechanisms of action of DBS should shed light on how best to develop therapeutic focal neuromodulation for resistant depression and might ultimately lead to the development of novel therapeutics that directly target the dysfunctional circuit that underlie the full spectrum of depression-related disorders.

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