

# Deep Brain Stimulation in Psychiatry

## Mechanisms, Models, and Next-Generation Therapies



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### KEYWORDS

- Closed-loop DBS • Network-oriented DBS • DBS in psychiatry
- Mechanisms of DBS • Dimension-oriented psychiatry

### KEY POINTS

- The likely mechanism of deep brain stimulation is altered interneuronal communication, which may include alterations in neural firing patterns, oscillatory dynamics, or synaptic plasticity.
- Deep brain stimulation acts at the network level, not on single brain structures.
- Advanced technologies, including closed loop systems, are being deployed in movement disorders. Recent progress in novel applications suggests that they may soon be used in psychiatry.
- The optimal use of deep brain stimulation likely requires a dimensional approach to identify patients with treatment-amenable brain circuit impairment.

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Abbreviations	
CBF	Cerebral blood flow
LFP	Local field potential
MDD	Major depression
NAc	Nucleus accumbens
OCD	Obsessive-compulsive disorder
PR	Parkinson disease
STN	Subthalamic nucleus

## INTRODUCTION: THE PROMISE AND FRUSTRATIONS OF DEEP BRAIN STIMULATION IN PSYCHIATRY

As discussed in the companion article by Darin D. Dougherty, “[Deep Brain Stimulation—Clinical Applications](#),” in this issue, deep brain stimulation (DBS) has promise in intractable obsessive-compulsive disorder (OCD) and major depression (MDD), but has not fared well in traditional randomized trials. This contrasts with the success of DBS in Parkinson disease (PD), where it has become a part of standard care.<sup>1</sup> The difference in outcomes arises because PD and other movement disorders arise from well-explored neural circuitry, with well-understood, reliable measures of symptoms. Psychiatric conditions arise from multiple dysfunctional neural circuits, not all of which are known or well-described.<sup>2,3</sup> Our symptom measures are also less robust, diluting the clinical signal.<sup>4,5</sup> For example, a metaanalysis of depression questionnaires showed that general factors, such as mood, explain more variance than any specific MDD symptom.<sup>6</sup> In the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*, field trials, comorbidity was more common than “pure” diagnoses, suggesting that diagnostic criteria and rating scales do not measure separable entities.<sup>7</sup>

Studies in both psychiatric and PD patients have yielded proposed mechanisms of DBS, leading to new treatment strategies. Some of these proposals emphasize anatomy; others have both functional and anatomic components. We argue that DBS in psychiatry depends on both function and anatomy, viewed at the circuit/network level. Herein, we review the functional and network-oriented theories of psychiatric DBS. We begin each section with a review of what is known or strongly suspected, then highlight directions the field may soon take.

## NEUROPHYSIOLOGIC MECHANISMS OF DEEP BRAIN STIMULATION

### *Neural Inhibition*

DBS often mimics the clinical effect of a brain lesion at the target site. Most of the PD and MDD/OCD targets were chosen because a lesion at that target was known or expected to ameliorate disease.<sup>8,9</sup> Several studies reported decreased neural activity at the DBS site.<sup>10–12</sup> Yet, DBS-like stimulation can also increase neural activity, depending on how the electric field is oriented relative to individual cells.<sup>13,14</sup> DBS also seems to increase brain metabolism at structures connected to the target.<sup>15–17</sup> This finding casts doubt on the inhibition hypothesis.

### *Informational Lesion*

One possible explanation for these contradictions is that DBS may be inhibitory at the level of information flow. The high-frequency pulses (>100 Hz) used in DBS are above the firing frequency of most neurons, meaning that DBS effectively “takes over” the

stimulated axons and cell bodies. Normal brain activity is irregular and variable, and that irregularity conveys information. DBS changes this to regularized, less-variant activity,<sup>18</sup> decreasing the amount of information sent between network nodes in a mathematical sense.<sup>19</sup> This decrease might make the overall network function better. For instance, in a hemiparkinsonian rat model of PD, the amount of information (ie, neuronal entropy) in the globus pallidus and substantia nigra increased after the onset of Parkinsonism.<sup>20</sup> DBS of those regions decreased local information but increased the information transmission between these regions.<sup>20</sup> The informational lesion theory has only been evaluated in PD, but with good results. A human study showed that pulse sequences optimized for information blockade are as effective as high-frequency, DBS but require much less energy delivery to the brain.<sup>21</sup>

### ***Disruption of Pathologic Oscillations***

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Neural network communication requires coordination of activity within and between areas. When networks are functioning efficiently, coordinated oscillations appear in the local field potential (LFP)<sup>22</sup> and scalp electroencephalogram. Neural network dysfunction may be reflected in abnormal oscillatory activity, and rhythmic DBS might restore normal oscillations. For example, beta band (12–30 Hz) power normally decreases during movement.<sup>23</sup> In PD, however, corticobasal circuits remain in synchronized (ie, coherent) beta oscillation, which is believed to produce the core symptoms in PD of bradykinesia and rigidity.<sup>24,25</sup> Patients receiving DBS for the first time showed decreased beta-gamma synchrony (cross-frequency coupling) between the subthalamic nucleus (STN) and motor cortex.<sup>26</sup> Similarly, the extent to which the power of gamma band activity (>40 Hz) was nested within alpha/beta band activity decreased with DBS of ventral striatum/ventral capsule in patients with OCD,<sup>27</sup> although this effect did not replicate in an independent sample.<sup>28</sup> This touches a much broader difficulty with identifying oscillatory biomarkers of psychiatric illness, to which we return elsewhere in this article. The beta findings in PD, replicated by multiple groups, led to an important innovation: DBS systems that can record and store electrophysiologic information from human patients as they undergo treatment.<sup>29</sup> Those systems offer an unparalleled view into brain function.<sup>30</sup>

The effect of DBS on oscillations offers the potential for treatment innovation. Stimulation could be aligned to coincide with the phase of frequency of a band of interest, such as frontal theta in anxiety disorders<sup>31</sup> or beta band in PD.<sup>24,32</sup> This approach was taken in a PD DBS study, where phase dependent DBS (ie, DBS delivered in synchrony with beta band activity) was superior to consistent, high-frequency DBS.<sup>32</sup> In depression, a transcranial magnetic device operating on similar frequency-locked principles has evidence of possible efficacy.<sup>33</sup> The authors have launched a trial specifically designed to modify oscillations in corticostriatal loops of OCD (NCT03184454). As we learn to better identify the oscillatory features of dysfunctional networks, oscillation-based DBS may become useful in psychiatric disorders.

### ***Neuroplasticity***

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Neuroplasticity underlies the brain's long-term learning and reorganization capabilities.<sup>34</sup> Psychiatric DBS changes symptoms over a slow time course consistent with plasticity effects,<sup>16,25,35</sup> implying that DBS may work through neuroplasticity. This hypothesis is supported by animal studies.<sup>36–39</sup> Hamani and colleagues<sup>36</sup> found that a single DBS session increased stressed rats' performance on a working memory task, but only when measured 33 days after the DBS treatment. Chakravarty and colleagues<sup>37</sup> demonstrated that DBS of ventromedial prefrontal cortex, a putative rodent homologue of human subcallosal cingulate, increased synaptic density. Last, Creed

and colleagues<sup>39</sup> reversed cocaine-induced plasticity in the nucleus accumbens (NAc) of rodents with DBS. They found that DBS successfully suppressed sensitization responses caused by repeated exposure to cocaine, but only when administered with a D1R antagonist that altered local excitability. These findings demonstrate the potential of DBS to induce neuroplasticity and structural alterations of neural networks. This could be a critical mechanism to exploit, given the role of learning and plasticity impairments in psychiatric conditions.<sup>40,41</sup>

## NETWORK MECHANISMS AND TARGETS FOR DEEP BRAIN STIMULATION

Modern neuroscience focuses on networks as units of study.<sup>42</sup> Psychiatric dysfunctions are commonly believed to be dysfunctions of neural networks, and DBS likely acts at the network level. For example, STN and globus pallidus internus are both parts of the cortico-basal ganglia network,<sup>43</sup> and DBS at either site can be effective in PD. DBS of the STN is believed to reduce excitation from STN to globus pallidus, leading to higher firing rates in globus pallidus and a variety of downstream effects.<sup>44</sup> This process ultimately normalizes activity throughout the corticobasal loop, decreasing the motor signs of PD.<sup>45</sup> Similarly, dysfunctions of corticostriothalamocortical<sup>9,46,47</sup> circuits are associated with OCD, and nodes in these loops are targeted for OCD neurosurgery.<sup>46,48,49</sup> With the advent of modern imaging technologies, such as diffusion tensor imaging and functional connectivity MRI, researchers can better study structural and functional networks.<sup>50</sup> This methodology is enabling more rigorous empirical and computational studies of the mechanisms of DBS at a network level.<sup>51</sup>

### *Network Studies and Functional Mapping*

Network effects of DBS are readily observable in regions connected to a DBS target. In their study of the subgenual anterior cingulate (Cg25), Mayberg and colleagues<sup>12</sup> showed reduced cerebral blood flow (CBF) to Cg25 and the neighboring orbitofrontal cortex after DBS. However, long-term responders to DBS also demonstrated CBF changes in other regions involved in depression, such as increases in dorsolateral prefrontal cortex and decreases in hypothalamus.

Similar findings are also seen with acute stimulation. Rauch and colleagues<sup>15</sup> found increased CBF in right medial orbitofrontal cortex and the right dorsolateral putamen from acute high-frequency (clinically effective) DBS. Similarly, Dougherty and colleagues<sup>46</sup> also observed increased regional CBF in patients with OCD in the dorsal anterior cingulate cortex when the stimulation DBS contact was more ventral in ventral capsule/ventral striatum. This effect also significantly correlated with improvements in the depressive symptom severity of patients with OCD. However, with more dorsal stimulation, the network activation changed and regional CBF increases were observed in the thalamus, striatum, and globus pallidus. Taken together, these results suggest that DBS must influence wide networks to be clinically effective. The wide network hypothesis is supported by recent diffusion tensor imaging studies.<sup>50,51</sup> For example, Riva-Posse and colleagues<sup>50</sup> recently identified 4 white matter bundles that were uniquely activated in a cohort of DBS responders. The researchers then used the identified bundles as DBS targets in a new cohort of MDD patients. This advanced targeting yielded response rates of 73% at 6 months and 82% at 1 year in the new prospective (albeit unblinded) cohort,<sup>50</sup> much higher than those in a recent nontargeted DBS trial.<sup>52</sup>

Optogenetics, the use of light in modulating neural activity,<sup>53</sup> is another state-of-the-art technique that informs network-oriented DBS. In animal models, optogenetics

allows stimulation of specific connections between brain nuclei, allowing researchers to narrow the mechanisms of DBS to subnetworks. In a recent example, Gradinaru and colleagues<sup>54</sup> tested whether the effect of DBS in PD is due to inhibition of STN, or instead due to disrupted connectivity between STN and the motor cortex. They reported that, in hemiparkinsonian rats, precise inhibition of STN did not lead to improvements in symptoms of PF. The only optogenetic manipulation improving PD symptoms was exciting the afferent motor cortex neurons that projected into STN. Similar studies should be possible in animal models of psychiatric illness; indeed, optogenetic stimulation of specific projections has dramatic effects on a variety of laboratory behaviors that model aspects of mental illness.<sup>55</sup>

### ***Next Steps: From Diagnoses to Dimensions***

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Changes in brain physiology, including information flow, oscillatory synchrony, and synaptic weighting, may each play a role in the therapeutic effects of DBS. Each of these factors seems to act more at the network level than on any single brain structure. As described elsewhere in this article, specific DBS protocols and/or combinations of DBS with targeted pharmacology can produce equally specific physiologic changes. Novel closed loop and recording systems will soon be able to monitor those changes and adjust stimulation intensity without immediate physician involvement.<sup>30,56,57</sup> This is a powerful toolbox, and its main limitation is that we do not know which physiologic changes may be beneficial for which mental illness. There is an extensive literature on attempts to find physiologic biomarkers, especially in MDD.<sup>58</sup> The results are very mixed, and our group's attempts to independently replicate candidate markers have failed.<sup>59–61</sup> We argue that this problem arises from the heterogeneity of categorical psychiatric diagnoses.<sup>62</sup> MDD, OCD, and other DBS-targetable disorders are too phenotypically diverse to arise from only 1 neurologic impairment. The National Institute of Mental Health's Research Domain Criteria initiative seeks to recast mental illnesses not as diagnoses, but as quantitatively described impairment in specific functional domains.<sup>3,5</sup> This domain- and circuit-oriented approach to illness may be particularly useful for psychiatric DBS. DBS modulates specific circuits, which in turn might lead to focused behavioral changes that cut across traditional diagnoses.<sup>62</sup> Multiple groups are now identifying cross-diagnostic network signatures in psychiatric populations,<sup>63,64</sup> and stimulation based on these signatures may change psychiatrically relevant behaviors.<sup>57</sup>

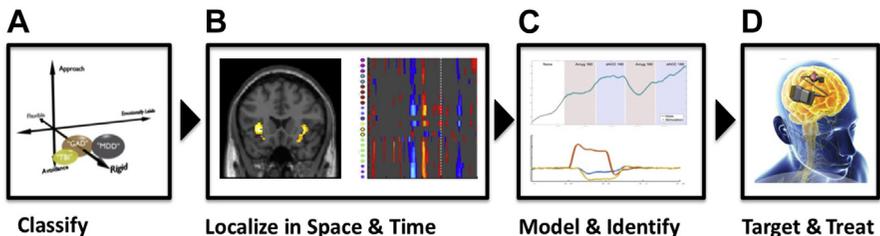
### ***Next Steps: Closed Loop, Activity-Dependent Stimulation***

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DBS as practiced to date is "open loop." That is, the physician takes clinical data into account, sets the stimulation parameters, and then a single pattern of stimulation is applied to the patient's brain for the next several weeks to months.<sup>8</sup> This practice is substantially based on trial and error<sup>65</sup> and the decisions are based on physicians' subjective evaluations and indirect behavioral assessment.<sup>3–5</sup> "Closed loop" DBS is an emerging alternative. In this paradigm, a neural biomarker that captures an essential aspect of disease is identified, such as increased beta band activity in the STN in PD.<sup>23,24</sup> The DBS system then directly measures the biomarker and uses this information to adjust stimulation parameters.<sup>30</sup> DBS systems currently in production (eg, Medtronic's PC+S, Medtronic, Minneapolis, MN) can record LFPs from lead contacts at the site of stimulation.<sup>29</sup> Stimulation parameters may be adjusted by predictive algorithms to achieve a desired neurophysiologic signature.<sup>57</sup> Preliminary demonstrations of this approach in PD have equaled and, in some cases, exceeded the performance of traditional DBS.<sup>43,66</sup>

As noted, biomarker development is a major challenge for closed loop DBS algorithm development in psychiatry. We suggest a domain-oriented approach applied in 4 steps (Fig. 1). *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*, based diagnoses (eg, general anxiety disorder and major depressive disorder) that may share a common phenotype (eg, cognitive rigidity). These phenotypes may be identified through a combination of self-report questionnaires (eg, for the cognitive rigidity example, the Brief Inventory of Executive Functioning<sup>67</sup>), standardized behavioral assessments (eg, a cognitive interference task<sup>68</sup>), and imaging techniques. Patients who demonstrate the phenotypic impairment of interest could then be studied with high temporal resolution recordings (eg, LFP and electroencephalogram) to identify candidate predictive algorithms.<sup>30,57</sup> The developed algorithms could then aid the DBS physician in adjusting stimulation settings. With full closed loop DBS, the adjustment process could be transferred to an automatic controller in the DBS system itself. It should be noted that closed loop DBS in psychiatry remains more of a vision than a near-term guarantee. There have been successful pilots in Parkinsonism,<sup>43</sup> and reports of early psychiatric closed loop demonstrations in laboratory environments,<sup>57</sup> but the concept remains to be validated in a clinical setting. The essential test for its efficacy is how it performs in comparison with the current open loop approaches.

A recent demonstration by Wu and colleagues<sup>56</sup> exemplifies the approach. The authors selected a phenotypical component of hypersensitivity to reward, then modeled this phenotype by creating a group of mice prone to binge eating. The LFPs from NAc of the mice had higher delta-band (ie, 1–4 Hz) power in NAc when these mice anticipated food. This biomarker was used to trigger a DBS-like neurostimulator in the NAc, disrupting the reward hypersensitivity. This closed loop neurostimulation extinguished animals' tendency to binge on high-fat chow. Additionally, a similar delta band signature of reward anticipation was identified in NAc LFPs of a pilot human subject, demonstrating this biomarker's potential translational relevance. Based on this result, the authors hope to implement delta-locked closed loop DBS in disorders of human reward hypersensitivity, including binge eating and drug addiction.



**Fig. 1.** A closed loop deep brain stimulation pipeline example. (A) The patients' dysfunction is individually assessed. The emphasis is in measuring patients' (dys)function in multiple cross-diagnostic domains. (B) Activity correlated with domain/function impairment is localized to brain structures that are amenable to neurostimulation. (C) Computational modeling quantifies the relationship of behavior to brain activity and formulates a control relationship between brain and behavior. (D) Based on this quantification, closed loop treatment specific to individual patients is administered. GAD, generalized anxiety disorder; MDD, major depressive disorder; TBI, traumatic brain injury. (From Widge AS, Ellard KK, Paulk AC, et al. Treating refractory mental illness with closed loop brain stimulation: progress towards a patient-specific transdiagnostic approach. *Exp Neurol* 2017;287(Part 4):470; with permission.)

### ***Next Steps: Ethical Foundations for Deep Brain Stimulation in Psychiatry***

DBS aims to improve psychiatric outcomes by altering emotion-related brain function. This DBS effect raises concerns around patient autonomy,<sup>69</sup> decisional capacity,<sup>70</sup> subject selection,<sup>71</sup> control over the device's function, and informed consent.<sup>72</sup> DBS may alter a patient's sense of authenticity, create a sense of alienation from that "authentic self," or change interpersonal dynamics.<sup>73</sup> For instance, Klein and colleagues<sup>74</sup> conducted a study of MDD and patients with OCD who had undergone DBS surgery. Although many patients found it a challenge to decipher how much of their emotional state was the direct result of DBS, a few stated that DBS had, indeed, helped them return to their "true self."<sup>75</sup> In line with those results, de Haan and colleagues<sup>76</sup> found that the clinical experience of DBS is not limited to psychopathologic symptoms. It instead pervades the participants' sense of self-reliance and basic trust. The authors suggested offering participants options to contact other DBS participants, because the unusual nature of the intervention may lead them to experience isolation. Another potential issue with DBS consent is subjects' impaired ability to make informed decisions. For instance, Fisher and colleagues<sup>77</sup> found that, despite an intact decisional capacity in patients with Treatment resistant-depression (TRD), 64% displayed therapeutic misconception, an inability to differentiate between treatment and clinical research. Remedying this issue requires educating participants, preferably, by individuals who are not directly involved in the study.<sup>77</sup> These considerations will become more important as advanced technologies, including those with some capacity for self-adjustment, become available. The next generation of DBS studies will likely incorporate ethical review and/or research ethicists directly into their design.

### **SUMMARY**

Based on the experimental evidence reviewed herein,<sup>12,15,54,65</sup> DBS likely exerts its effect at the network level. Probable mechanisms include affecting information transmission between brain structures,<sup>20</sup> disrupting pathologic oscillations,<sup>26</sup> and inducing long-term plasticity.<sup>36,37,39</sup> These mechanisms are all aspects of the phenomenon of interneuronal communication. Accordingly, conceiving of DBS as a network therapy may help understand its effects and uses.<sup>57</sup>

Manual programming of DBS parameters by clinicians may not be an effective way to modulate networks. Closed loop DBS technology, which uses neural signal-based algorithms to adjust treatment parameters dynamically,<sup>29,30</sup> has demonstrated early efficacy in movement disorders.<sup>43</sup> Pilot closed loop investigations are also underway in psychiatric disorders.<sup>57</sup> A more dimensional approach to psychiatry should help to identify the circuit bases of mental illness, in turn indicating which patients may benefit most from DBS at a given target site. Understanding these mechanisms and the basis for patient-specific DBS is critical to achieve the clinical promise of this innovative, but still nascent therapy.

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