HHS Public Access

Author manuscript

Psychiatr Clin North Am. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

Psychiatr Clin North Am. 2018 September ; 41(3): 373–383. doi:10.1016/j.psc.2018.04.003.

Deep Brain Stimulation in Psychiatry: Mechanisms, Models, and Next-Generation Therapies

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SYNOPSIS

Deep brain stimulation (DBS) has preliminary evidence of clinical efficacy, but has been difficult to develop into a robust therapy. This is in part because its mechanisms are incompletely understood. We review evidence from movement and psychiatric disorder studies, with an emphasis on how DBS changes brain networks. From this, we argue for a network-oriented approach to future DBS studies. That network approach, in turn, requires methods for identifying patients with specific circuit/network deficits. We describe how dimensional approaches to diagnoses may aid that identification. Finally, we discuss the use of network/circuit biomarkers to develop self-adjusting “closed loop” systems.

Keywords

Closed-loop DBS; network-oriented DBS; DBS in psychiatry; mechanisms of DBS; dimension-oriented psychiatry

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DISCLOSURE STATEMENT

ASW receives consulting income and device donations from Medtronic, which manufactures DBS systems. ASW has also filed multiple patent applications related to closed-loop deep brain stimulation, none of which is yet commercially licensed.

Introduction: The Promise and Frustrations of DBS in Psychiatry

As discussed in the companion article by Dougherty[1] 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 DBS' success in Parkinson Disease (PD), where it has become part of standard care[2]. 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[3,4]. Our symptom measures are also less robust, diluting the clinical signal[5,6]. For example, a meta-analysis of depression questionnaires showed that general factors, such as mood, explain more variance than any specific MDD symptom[7]. In the DSM-5 field trials, comorbidity was more common than "pure" diagnoses, suggesting that diagnostic criteria and rating scales do not measure separable entities[8].

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 anatomical components. We argue that DBS in psychiatry depends on both function and anatomy, viewed at the circuit/network level. Here, 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 DBS

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[9,10]. Several studies reported decreased neural activity at the DBS site[11–13]. Yet, DBS-like stimulation can also increase neural activity, depending on how the electric field is oriented relative to individual cells[14,15]. DBS also appears to increase brain metabolism at structures connected to the target[16–18]. This 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 (over 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[19], reducing the amount of information sent between network nodes in a mathematical sense[20]. This might make the overall network function better. For instance, in a hemiparkinsonian rat model of PD, the amount of information (i.e., neuronal entropy) in the globus pallidus and substantia nigra increased after the onset of Parkinsonism[21]. DBS of those regions reduced local information but increased the information transmission between these regions[21]. 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[22].

Disruption of Pathological Oscillations

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)[23] and scalp electroencephalogram (EEG). 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[24]. In PD, however, cortico-basal circuits remain in synchronized (i.e., coherent) beta oscillation, which is believed to produce PD's core symptoms of bradykinesia and rigidity[25,26]. Patients receiving DBS for the first time showed decreased beta-gamma synchrony (cross-frequency coupling) between subthalamic nucleus and motor cortex[27]. Similarly, the extent to which the power of gamma band activity (above 40 Hz) was nested within alpha/beta band activity decreased with DBS of ventral striatum/ventral capsule in OCD patients[28], although this effect did not replicate in an independent sample[29]. This touches a much broader difficulty with identifying oscillatory biomarkers of psychiatric illness, to which we return below. 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[30]. Those systems offer an unparalleled view into brain function[31].

DBS' effect 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[32] or beta band in PD[25,33]. This approach was taken in a PD DBS study, where phase dependent DBS (i.e., DBS delivered in synchrony with beta band activity) was superior to consistent, high-frequency DBS[33]. In depression, a transcranial magnetic device operating on similar frequency-locked principles has evidence of possible efficacy[34]. The authors have launched a trial specifically designed to modify oscillations in cortico-striatal 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

Neuroplasticity underlies the brain's long-term learning and reorganization capabilities[35]. Psychiatric DBS changes symptoms over a slow time course consistent with plasticity effects[17,26,36], implying that DBS may work through neuroplasticity. This hypothesis is supported by animal studies[37–40]. Hamani et al.[37] 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 et al.[38] demonstrated that DBS of ventromedial prefrontal cortex, a putative rodent homologue of human subcallosal cingulate, increased synaptic density. Last but not least, Creed and colleagues[40] 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 DBS' potential 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[41,42].

Network Mechanisms and Targets for DBS

Modern neuroscience focuses on networks as units of study[43]. Psychiatric dysfunctions are commonly believed to be dysfunctions of neural networks, and DBS likely acts at the network level. For example, subthalamic nucleus (STN) and globus pallidus internus (GPi) are both parts of the cortico-basal ganglia network[44], and DBS at either site can be effective in PD. DBS of 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[45]. This ultimately normalizes activity throughout the cortico-basal loop, decreasing the motor signs of PD[46]. Similarly, dysfunctions of cortico-striato-thalamo-cortical[10,47,48] circuits are associated with OCD, and nodes in these loops are targeted for OCD neurosurgery[47,49,50]. With the advent of modern imaging technologies, such as diffusion tensor imaging (DTI) and functional connectivity MRI, researchers can better study structural and functional networks[51]. This is enabling more rigorous empirical and computational studies of DBS' mechanisms at a network level[52].

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[13] 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 et al.[16] found increased CBF in right medial orbitofrontal cortex (OFC) and right dorsolateral putamen from acute high-frequency (clinically effective) DBS. Similarly, Dougherty and colleagues[47] observed increased regional CBF in OCD patients in dorsal anterior cingulate cortex (dACC) when the stimulation DBS contact was more ventral in VC/VS. This effect also significantly correlated with improvements in the depressive symptom severity of the OCD patients. However, with more dorsal stimulation, the network activation changed and rCBF increases were observed in 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 DTI studies[51,52]. For example, Riva-Posse et al. recently identified 4 white matter bundles that were uniquely activated in a cohort of DBS responders[51]. 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 six months and 82% at one year in the new prospective (albeit unblinded) cohort[51], much higher than those in a recent non-targeted DBS trial[54].

Optogenetics, the use of light in modulating neural activity[55], 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 DBS' mechanisms to sub-networks. In a recent example, Gradinaru et al.[56] tested whether the effect of DBS in PD is due to inhibition of STN, or instead due to disrupted connectivity between STN and motor cortex. They reported that in hemiparkinsonian rats, precise inhibition of STN did not lead to improvements in PD symptoms. 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[57].

Next Steps: From Diagnoses to Dimensions

Changes in brain physiology, including information flow, oscillatory synchrony, and synaptic weighting, may each play a role in DBS' therapeutic effects. Each of these appears to act more at the network level than on any single brain structure. As described above, 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[31,58,59]. 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[60]. The results are very mixed, and our group's attempts to independently replicate candidate markers have failed[61–63]. We argue that this problem arises from the heterogeneity of categorical psychiatric diagnoses[64]. MDD, OCD, and other DBS-targetable disorders are too phenotypically diverse to arise from only one neurologic impairment. The National Institute of Mental Health's Research Domain Criteria (RDoC) initiative seeks to re-cast mental illnesses not as diagnoses, but as quantitatively described impairment in specific functional domains[4,6]. 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[64]. Multiple groups are now identifying cross-diagnostic network signatures in psychiatric populations[65,66], and stimulation based on these signatures may change psychiatrically relevant behaviors[59].

Next Steps: Closed-Loop, Activity-Dependent Stimulation

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[9]. This practice is substantially based on trial and error[67] and the decisions are based on physicians' subjective evaluations and indirect behavioral assessment[4–6]. "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[24,25]. The DBS system then directly measures the biomarker and utilizes this information to adjust stimulation parameters[31]. DBS systems currently in production (e.g., Medtronic's PC+S) can record local field potentials (LFP) from lead contacts at the site of stimulation[30]. Stimulation parameters may be adjusted by predictive algorithms to achieve a desired neurophysiologic signature[59].

Preliminary demonstrations of this approach in PD have equaled and, in some cases, exceeded the performance of traditional DBS[44,68].

As just noted, biomarker development is a major challenge for closed-loop DBS algorithm development in psychiatry. We suggest a domain-oriented approach applied in four steps (see Figure 1). DSM-based diagnoses (e.g., General Anxiety Disorder and Major Depressive Disorder) may share a common phenotype (e.g., cognitive rigidity). These phenotypes may be identified through a combination of self-report questionnaires (e.g., for the cognitive rigidity example, Brief Inventory of Executive Functioning[69]), standardized behavioral assessments (e.g., a cognitive interference task[70]), and imaging techniques. Patients who demonstrate the phenotypic impairment of interest could then be studied with high-temporal-resolution recordings (e.g., LFP and EEG) to identify candidate predictive algorithms[31,59]. 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[44], and reports of early psychiatric closed-loop demonstrations in lab environments[59], but the concept remains to be validated in a clinical setting. The essential test for its efficacy is how it performs in comparison to the current open loop approaches.

A recent demonstration by Wu et al.[58] 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 (i.e., 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. On the basis of this result, the authors hope to implement delta-locked closed-loop DBS in disorders of human reward hypersensitivity, including binge eating and drug addiction.

Next Steps: Ethical Foundations for DBS in Psychiatry

DBS aims to improve psychiatric outcomes by altering emotion-related brain function. This DBS effect raises concerns around patient autonomy[71], decisional capacity[72], subject selection[73], control over the device's function, and informed consent[74]. DBS may alter a patient's sense of authenticity, create a sense of alienation from that "authentic self", or change interpersonal dynamics[75]. For instance, Klein et. al[76] conducted a study of MDD and OCD patients who had undergone DBS surgery. While 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"[77]. In line with those results, de Haan et al.[78] found that the clinical experience of DBS is not limited to psychopathological 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 et al.[79] found that despite an intact decisional capacity in TRD patients, 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[79]. 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.

Conclusion

Based on the experimental evidence reviewed above[13,16,56,67], DBS likely exerts its effect at the network level. Probable mechanisms include affecting information transmission between brain structures[21], disrupting pathological oscillations[27], and inducing long-term plasticity[37,38,40]. These mechanisms are all aspects of the phenomenon of inter-neuronal communication. Accordingly, conceiving of DBS as a network therapy may help understand its effects and uses[59].

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[30,31], has demonstrated early efficacy in movement disorders[44]. Pilot closed-loop investigations are also underway in psychiatric disorders[59]. A more dimensional approach to psychiatry should help 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.

Acknowledgments

Preparation of this work was not sponsored or supported by any commercial entity. ASW, AG, and MTB were supported by grants to ASW from the Brain & Behavior Research Foundation, National Institutes of Health (MH109722, MH111320, and NS100548), and Defense Advanced Research Projects Agency (Cooperative Agreement W911NF-14-2-0045). The views, opinions, and/or findings expressed are those of the authors and should not be interpreted as representing the official views or policies of any sponsor or funding source.

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KEY POINTS

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

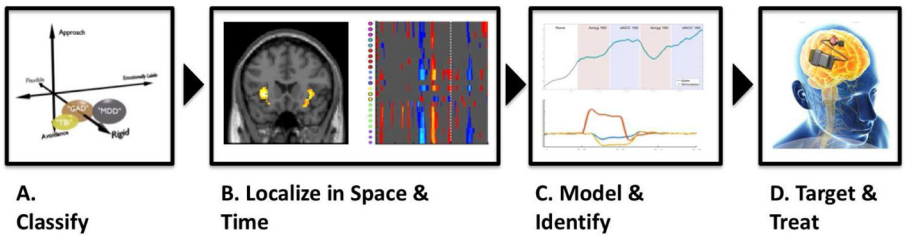

Figure 1.

A closed-loop DBS pipeline example. (A) 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.

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