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Deep Brain Stimulation for Psychiatric Disorders

ALIK S. WIDGE, AMANDA R. ARULPRAGASAM,
THILO DECKERSBACH, and DARIN D. DOUGHERTY

Abstract

In this monograph, we briefly review the rationale for deep brain stimulation (DBS) for psychiatric illness, beginning with current noninvasive treatment options and progressing to the evolution and success of DBS as a therapy. This discussion will focus on obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) particularly, as these are the only two diagnoses that have been subjected to adequately controlled DBS trials to date. The majority of the essay then describes the significant limitations that DBS is currently facing and emerging approaches to address them. This will lead into a discussion of new technologies such as patient-specific modeling of electric fields and closed-loop DBS systems and how we can best utilize these to increase our understanding of DBS and the overall efficacy of this novel therapy.

INTRODUCTION: THE RATIONALE FOR DBS IN PSYCHIATRY

The most common treatments for psychiatric disorders are medications and psychotherapy. However, several large scale studies have shown that even best-evidence treatment fails to help a substantial fraction of patients (Manschreck & Boshes, 2007; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007).

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder that affects approximately 3% of the world's population. Presently, first-line treatment options include cognitive-behavioral therapy and medications such as serotonergic reuptake inhibitors (SSRIs) (Koran, Hanna, Hollander, Nestadt, & Simpson, 2007). Approximately one third of patients may not experience substantial benefit despite receiving both medication and behavioral therapy (Kronig *et al.*, 1999). Major depressive disorder (MDD) is one of the leading causes of disability in the world and affects approximately 14.8 million American adults with a lifetime prevalence rate of 19.2% (Bromet *et al.*, 2011). It is estimated that 50–60% of these patients fail to fully respond to an antidepressant in which adequate dosing and duration have occurred

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(Fava, 2003). For depression, other options such as electro-convulsive therapy (ECT) or transcranial magnetic stimulation (TMS) also exist. For OCD, once medications and intensive therapy have failed, patients have few further treatment options.

During the last 10–15 years, we have witnessed a major paradigm shift in the conceptualization of psychiatric disorders (Mayberg, 2009). Basic research has significantly advanced our understanding of the anatomy and physiology of brain networks and their mechanisms for processing cognition, behavior, and emotion. An example of such a circuit can be shown in Figures 1 and 2. The advancement of our knowledge in neural circuitry has had a major impact by transforming our understanding of psychiatric pathophysiology, and has also set the stage for new treatment modalities that directly modulate disease-relevant circuits (Arulpragasam *et al.*, 2013).

One such treatment that has been shown to modulate maladaptive circuitry is DBS. DBS is a nonlesion-based, reversible neuromodulation therapy. DBS

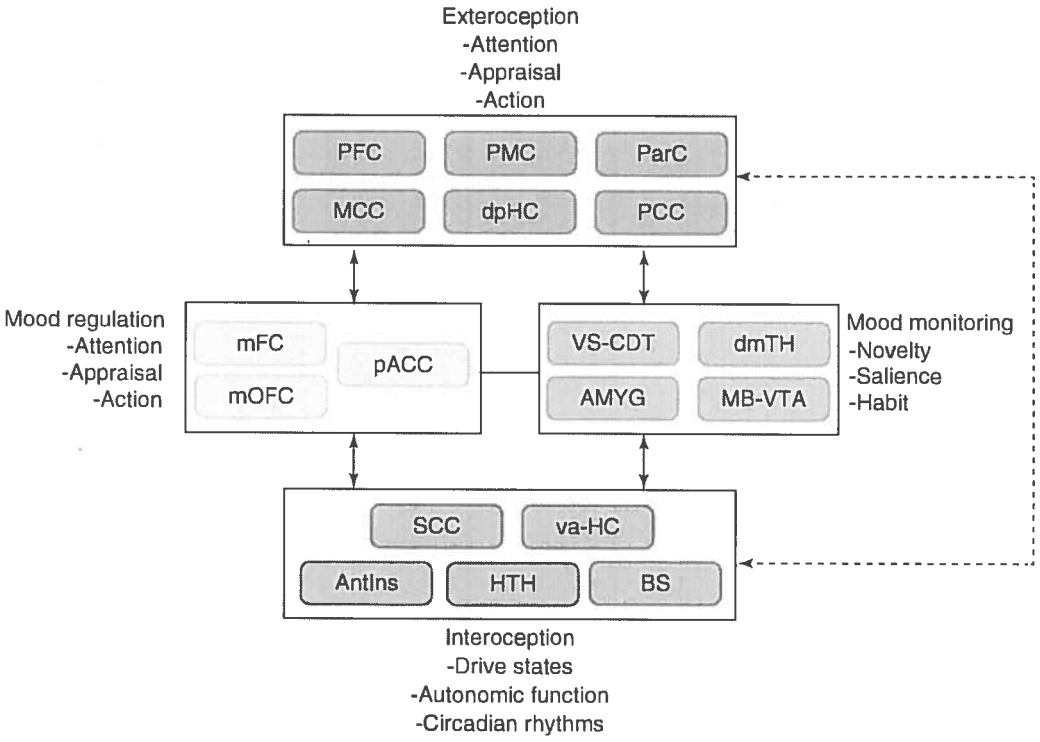

Figure 1 The functional neurocircuitry of obsessive-compulsive disorder (OCD) as described by Corse *et al.* 2013. Hypoactivity of the cortico-striatal-thalamic-cortical (CSTC) loop (between the OFC and striatum) or hyperactivity of the corticothalamic (CT) loop (between the OFC/PFC and the thalamus) may result in OCD symptoms. ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; PFC = prefrontal cortex.

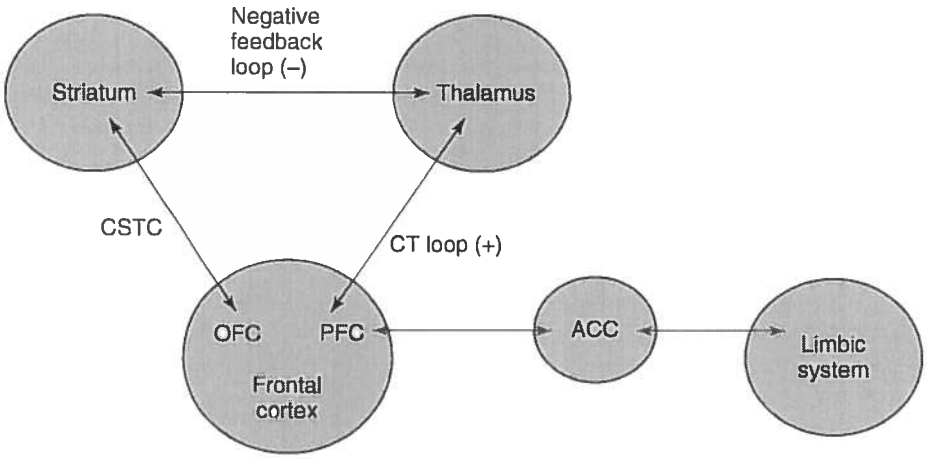

Figure 2 Circuit model of MDD. Adapted from Mayberg, 2009. Regions with known anatomical interconnections that show consistent changes across converging imaging experiments form the basis of this model. Regions are grouped into four main compartments, reflecting general behavioral dimensions of MDD and regional targets of various antidepressant treatments. Regions within a compartment all have strong anatomical connections to one another. Black arrows identify cross-compartment anatomical connections. Solid colored arrows identify putative connections between compartments mediating a specific treatment. AntIns = anterior insula; AMYG = amygdala; BS = brainstem; dmTH = dorsomedial thalamus; dpHC = dorsal-posterior hippocampus; HTH = hypothalamus; MB-VTA = midbrain-ventral tegmental area; MCC = medial cingulate cortex; mFC = medial frontal cortex; mOFC = medial orbital frontal cortex; pACC = the perigenual area of the anterior cingulate cortex; ParC = parietal cortex; PCC = posterior cingulate cortex; PFC = prefrontal cortex; PMC = premotor cortex; va-HC = ventral-anterior hippocampus; SCC = subcallosal cingulate; VS-CDT = ventral striatum-caudate.

involves surgically implanting electrodes at specific target locations within the brain and delivering electrical pulses of adjustable frequency and intensity through those electrodes (Corse *et al.*, 2013). In the early 1960s, it was shown that electrical stimulation of the ventrolateral thalamus could alleviate tremor (Hassler, Riechert, Mundinger, Umbach, & Ganglberger, 1960) and in the early 1990s, DBS was further developed for the treatment of essential tremor and Parkinson's disease (PD) (Benabid *et al.*, 1991). Since then, the safety and efficacy of DBS for movement disorders such as PD, essential tremor and extrapyramidal dyskinesia has been repeatedly demonstrated in rigorous clinical trials (Deuschl *et al.*, 2006; Mueller *et al.*, 2008). The FDA approved the use of DBS for PD in 2002, and since then, over 70,000 patients have undergone DBS for this specific indication (Bronstein *et al.*, 2011).

The success of DBS in modulating pathological circuitry in movement disorders suggests that it may be a viable option for treating disorders that result from maladaptive changes in brain circuits leading to pathological processing of affective and behavioral information, in patients who do not respond to medication, psychotherapy, or other less invasive treatment modalities. This definition of "maladaptive changes in brain circuits" encompasses most, if not all, psychiatric disorders. As such, exploration and investigation of the potential benefits of DBS in refractory psychiatric illness is justified.

FOUNDATIONAL AND CUTTING-EDGE WORK: STATE OF THE ART OF DBS IN PSYCHIATRY

DBS was first investigated by Nuttin and colleagues in 1999 (Nuttin, Cosyns, Demeulemeester, Gybels, & Meyerson, 1999) in patients with refractory OCD, in what was also the first ever recorded case series of DBS performed specifically for a psychiatric indication. This early report prompted ongoing investigations, which continued to demonstrate similar, successful results (Abelson *et al.*, 2005; Gabriels, Cosyns, Nuttin, Demeulemeester, & Gybels, 2003). The internal capsule site most commonly studied for OCD is derived from the location for ablative procedures for treatment-resistant OCD and anterior capsulotomy (Corse *et al.*, 2013) DBS at this site was expected to modulate of circuitry specifically implicated in the pathophysiology of OCD.

Over time, the target moved to a location slightly more posterior than a traditional capsulotomy. This new location is thought to be the junction of the anterior commissure, internal capsule, and striatum (Greenberg *et al.*, 2010), and thus is called the "ventral capsule/ventral striatum" (VC/VS). At this target, the mean improvement in Yale-Brown Obsessive-Compulsive Scale (YBOCS) score was 38%, from 34 to 21 (Greenberg *et al.*, 2010) Depression also improved, with a mean drop of 43% in Hamilton Depression Rating Scale (HDRS) and 50% of patients meeting criteria for depressive remission (HDRS < 7) at their last follow-up visit (Kaur *et al.*, 2013) These positive results led to the US Food and Drug Administration approving (on a limited basis) DBS for treatment-resistant OCD at the VC/VS target in 2009 (Corse *et al.*, 2013). This was the first and remains the only approval for use of DBS for a refractory psychiatric illness in nonresearch practice.

Intriguingly, DBS at VC/VS seemed to also alleviate comorbid depression. Thus, Malone *et al.* (2009) conducted the first VC/VS DBS open-label, multicenter trial for treatment resistant depression (TRD) at three collaborating clinical sites: the Cleveland Clinic, Butler Hospital/Brown Medical School, and the Massachusetts General Hospital. This pilot study demonstrated a 40% MDD remission rate. An expanded cohort reported in 2010 showed

similar results, with a 71% response rate at the last follow-up (Malone, 2010). Surprisingly, a multi-center randomized trial conducted following these open-label reports did not reach significance and was stopped because of interim analyses [D. Dougherty, unpublished results]. In parallel, the Mayberg-Lozano group at the University of Toronto and Emory University conducted a very similar trial at a different target, the subgenual cingulate gyrus (Cg25) (Mayberg *et al.*, 2005). That target was rationally selected based on over a decade of neuro-imaging studies, and had also shown positive open-label results (Mayberg, 2009). Despite this, the Cg25 trial also failed to achieve its primary endpoint.

THE CRITICAL NEED: GREATER UNDERSTANDING FOR TRULY EFFECTIVE DBS

These previous studies demonstrated the promise of DBS in the field of neuropsychiatry, but also highlighted its current shortcomings. It is clear that the research community has not yet identified the anatomic targets or electrical parameters that can deliver on that promise. There is much more we need to know and investigate to optimize DBS.

First, a better understanding of how DBS works and how this stimulation actually affects individual neurons and larger brain circuitry would enable more rational therapeutic design. As described above, most DBS targeting is based on anatomy—on regions that are hyper-active during brain imaging or where neurosurgeons have successfully treated disease by lesioning tissue. The clinical trials have shown us that it is not enough to have the electrode in the right part of the brain. Instead, we need to understand what exactly the electrical stimulation is doing to the neurons in that tissue, and how the signal might be propagating through the complex circuitry of the brain.

Secondly, state of the art DBS devices are open loop systems. Present DBS systems deliver energy continuously at a pre-programmed frequency and amplitude, with parameter adjustments only occurring during relatively infrequent clinical programming visits (roughly every 3 months) (Widge, Dougherty, & Moritz, 2014). DBS needs to progress to becoming "closed loop"—to being able to monitor its efficacy in real-time and to automatically adjust stimulation in response to that monitoring. While these systems have demonstrated therapeutic benefit, they incorrectly assume that psychiatric symptoms are static. Clinically symptoms of many disorders vary day to day or moment to moment. Systems that can monitor and respond to these changing symptoms may have greater tolerability or better response rates.

Lastly, psychiatric diagnoses may not map well to brain entities that can be targeted through DBS. The categorical nature of psychiatric diagnosis means that two patients with the same disorder may have very little overlap

in symptoms. Further, most patients with severe psychiatric disorders have co-occurring diagnoses. Symptoms overlap across diagnostic boundaries. Therefore, a trans-diagnostic approach that focuses on underlying functional dimensions may improve the mapping between symptoms and neural activity. The remaining portion of this essay will expand on these three points and provide insight and ideas as to how we believe the field can move forward.

EMERGING TREND: DEEPER UNDERSTANDING OF THE NEURAL MECHANISMS OF DBS

To improve the efficacy of DBS, we must better understand its underlying mechanism of action. Previously, it was thought that DBS merely simulated the effect of lesioning tissue (Bronstein *et al.*, 2011). However, we now believe the mechanism to be much more complicated.

While the exact mechanism of action remains unknown, there are several current theories. McIntyre, Grill, Sherman, & Thakor (2004) noted that several experimental studies have produced contradictory results, showing inhibition of activity in the stimulated target, but increased inputs to projection nuclei. To explain these seemingly opposite findings, they studied stimulation using a computational model that incorporated representations of a clinical DBS electrode and a thalamocortical relay neuron.

They found that the response of the neuron to DBS was primarily dependent on the position and orientation of the axon with respect to the electrode and the parameters of stimulation (McIntyre *et al.*, 2004). Intracellular stimulation applied within the cell body generated action potentials that were transmitted down the axon with the same stimulus frequency. However, extracellular DBS (the actual modality used clinically) resulted in independent firing of the cell body and axon at high stimulation frequencies. This suggests that during high frequency stimulation, cell body activity may be decoupled from axonal activity, and a single neuron may simultaneously be inhibited at its soma (where it receives input from other cells) and excited in its axon (its output to downstream cells) (McIntyre *et al.*, 2004). This creates an "information blockade"—there is no meaningful relationship between the firing of cells upstream of the stimulated neuron and the output that the neuron sends to its targets. It is no longer able to perform a computational function. Depending on where the stimulated neuron falls in a brain circuit, this could act as a lesion of the tissue, or it could act as though the stimulated nucleus were hyperactive. Detailed computer modeling of DBS is continuing to emerge as a powerful technique to enhance our understanding of the effects of DBS and to create a virtual test platform for novel stimulation strategies (McIntyre & Foutz, 2013). The next step will be expanding this

modeling to a wide range of tissues and electrode configurations, a task which will be mathematically and computationally difficult.

Alongside computational modeling, there is growing interest in recording while using DBS in patients to better understand the underlying neural mechanism of DBS. Figee *et al.* (2013) used functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to investigate nucleus accumbens (NAc) DBS in 16 OCD patients. By alternating between a DBS ON and DBS OFF state, they were able to measure differences in NAc activity as a result of stimulation. During DBS OFF, the NAc activity in patients was lower than in controls, whereas during DBS ON, patients had similar NAc activity as healthy controls (Widge *et al.*, 2014). This suggests that DBS has the capacity to normalize NAc activity—the exact opposite of the classical "lesion" hypothesis. They also found that DBS targeted at the NAc within OCD patients reduced excessive connectivity between the NAc and prefrontal cortex (PFC) and also attenuated the increase in low-frequency PFC activity elicited by symptom provocation (Figee *et al.*, 2013). Thus, there is support for a theory that DBS may act in psychiatric illness not by modulating a single brain area, but instead by altering connectivity patterns between multiple areas.

Using a similar method of alternating between DBS ON and DBS OFF states, Cavanagh *et al.* (2011) measured changes in subthalamic nucleus (STN) activity through EEG in patients with STN DBS for PD (Cavanagh *et al.*, 2011). They used a reinforcement learning and choice conflict task in which participants were asked to select between novel stimulus combinations involving low (win–lose) or high (win–win and lose–lose) decision conflict (Cavanagh *et al.*, 2011). They found that during the DBS ON condition, patients responded faster when making suboptimal (poorer) choice than when making optimal choices. There was no difference in response time during the DBS OFF condition (Cavanagh *et al.*, 2011). In other words, DBS of this site caused a subtle psychiatric symptom—a tendency toward premature responding that drove them to make poor, impulsive choices. EEG recordings in the medial PFC (mPFC) predicted slower response times during high-conflict trials in healthy control participants and patients in the DBS OFF condition, but not in the DBS ON state (Cavanagh *et al.*, 2011). Here again, it appears that multiple structures (at least mPFC and STN) are communicating in a network to produce a cognitive phenomenon (decision-making), and DBS can alter that communication to produce behavior change.

As the available base of patients with DBS at different brain sites increases, studies such as these will become increasingly feasible. Furthermore, advances in imaging and recording technology, along with signal processing, will make it easier for neuroscientists to interpret the findings of these

studies. It can also be expected that there will be more and better behavioral tasks developed, which will help us understand how DBS of each brain region subtly alters patients' behavior. The clinical use of DBS according to anatomic targeting rules will help us produce the neuroscientific data that will lead to much more rational targeting and programming.

A closely related trend is patient-specific modeling of the spread of the electric field and its effects on cells and circuits. Riva-Posse *et al.* (2014) used diffusion tensor imaging (DTI, a method of mapping connections in the brain) to model white matter connections and identify the pathways that govern DBS response for depression. In this study, preoperative MRI data, including DTI, were acquired in 16 TRD patients. The patients then received DBS implants at the subcallosal cingulate (Cg25) target. Postoperatively, computerized tomography was used to locate DBS contacts. The activation volume around the contacts used for stimulation was then modeled for each patient and patient-specific tract maps were calculated (Riva-Posse *et al.*, 2014). The patients were then clinically assessed for therapeutic response at 6 months and 2 years post implant. DBS responders at 6 months ($n = 6$) and 2 years ($n = 12$) shared bilateral pathways from their individual activation volumes to the medial frontal cortex, rostral and dorsal cingulate cortex, and subcortical nuclei. Nonresponders, on the other hand, did not show these connections consistently (Riva-Posse *et al.*, 2014). This is a preliminary, but exciting result—it suggests that it may be possible to define, for each individual patient, the exact anatomic coordinates that would place their DBS at a "hub" connected to a wide variety of brain areas. If the network-modulation hypothesis is correct, DBS at a highly-connected hub should be much more effective. Future years will hopefully show us prospective tests of this method.

EMERGING TREND: CLOSING THE LOOP

Psychiatric symptoms are not static. Symptoms flare and subside, on a timescale of minutes to hours. Existing DBS strategies have been unable to effectively treat such fluctuations, because they occur on significantly shorter timescales than the relatively infrequent clinical programming visits. It has been proposed that the stimulator could become "closed loop"—it could actively monitor the patient's current emotional state, then adjust stimulation to compensate. Ideally, stimulation could go from the present paradigm continuous operation (always on, fixed parameters) to an intermittent, responsive mode (on only when the patient needs it, with dynamically adjusting paramters) (Widge *et al.*, 2014). In many ways, this is the same problem as brain-computer interfaces (BCIs), a technology currently used to treat paralysis by "decoding" movement commands

from the motor cortex. In a psychiatric DBS, the BCI would continuously monitor emotional state and adjust stimulation parameters to maintain the patient in an optimal range (Widge *et al.*, 2014). The emotional state signals are already established to occur within the brain, particularly within the PFC, which specifically serves emotional regulation functions (Hamilton *et al.*, 2012). A responsive system would assume some of that regulatory function to compensate for circuits that have become either dysfunctional or hypofunctional. Moreover, it would deliver electrical stimulation that is appropriate to the patient's immediate need. This would in turn reduce the side effects associated with over-stimulation, alleviate residual symptoms related to under-stimulation, and optimize power consumption, leading to slower battery depletion (Widge *et al.*, 2014). Major funding agencies in the United States have committed to developing these closed-loop systems,[1] and DBS manufacturers have already released hardware that could implement them (Afshar *et al.*, 2013).

The development of closed-loop emotional DBS is a promising new approach but it has been hindered by a lack of feasible electrical biomarkers. That is, it is unknown what the electrical signature of psychiatric illness or remission looks like within the brain. Until we know what the DBS should sense, it is difficult to build a closed-loop controller that decodes critical psychiatric information from neural firing. fMRI can provide insights into activity across the whole brain (Sitaram *et al.*, 2011), however, most fMRI sequences are not fully compatible with DBS implanted devices and thus, unfortunately, cannot be utilized. Second, decoding modalities that support continuous recording may not function properly in the presence of psychiatric disorders (Widge *et al.*, 2014). EEG has been a very successful method for noninvasive emotion decoding in human volunteers (Kim, Kim, Oh, & Kim, 2013). However, all successful EEG emotion decoding has only been shown in healthy control participants. Patients with mental illness, by definition, do not have normal neural circuits or activation. Therefore, measures that accurately classify healthy controls may not transfer over to this population. Furthermore, there is a consensus that clinical diagnoses oftentimes contain multiple neurologic entities and that the same clinical phenotype might arise from diametrically opposite changes in the brain (Cuthbert & Insel, 2013). This could present a potential challenge for clinical translation of existing emotional decoders (Widge *et al.*, 2014). Third, even if BCIs are able to function in the presence of clinical symptoms, they may not be able to adequately distinguish pathologic states from normal states (Widge *et al.*, 2014). Psychiatric disorders are marked by extremes of emotions that are normally occurring in everyday life. The difference

1. http://www.technologyreview.com/news/527561/military-funds-brain-computer-interfaces-to-control-feelings/. [cited 2014 Jun 14].

is not severity or type, but rather its context and appropriateness in a given situation. In post-traumatic stress disorder (PTSD) for example, patients may overgeneralize from a fearful event and later experience high vigilance and arousal in contexts that are objectively safe. The question is differentiation—can we tell whether a patient is having a PTSD flashback (where the BCI-DBS system should intervene to reduce his/her fear) or watching a thrilling movie (where the BCI-DBS should allow the patient to enjoy this normal and healthy human experience)? A system that fails to distinguish could actually be more harmful than the symptoms it seeks to treat.

The search for those biomarkers will be a critical trend in DBS research in the coming decade. However, equally important is the question of whether we might be able to create a closed-loop DBS while foregoing biomarkers entirely. Recent demonstrations have suggested a completely new approach—direct volitional control of the neurostimulator. In such a device, a patient would sense that current stimulation parameters are not well matched to his/her clinical needs, then directly communicate this to the stimulation by deliberately modulating specific aspects of brain activity (Widge *et al.*, 2014). This is even more directly a use of the BCI technologies described above—those technologies were developed for exactly this kind of "intention decoding". In this scenario, we would not need to worry about the BCI's ability to classify an emotion as pathologic vs. healthy—the patient would "tell" the stimulator directly whether the current emotional experience was desirable or undesirable. This could occur in real-time, changing stimulation moment-to-moment to track experienced symptoms, rather than waiting weeks between programming visits. Heterogeneity of biomarkers would also be a moot point – the only important variable would be the patient's own intention to receive mood-altering stimulation (Widge *et al.*, 2014). A proof-of-concept demonstration of this approach has recently occurred in an animal model. Rats have used such a system to directly trigger stimulation to the medial forebrain bundle (MFB), a structure within the reward pathway where electrical stimulation is known to be reinforcing (Widge & Moritz, 2014). This volitional pathway to closed-loop DBS has much work to be done before it becomes a clinical reality, but offers the exciting possibility that patients could literally regain their capacity for self-control.

EMERGING TREND: RATIONAL DESIGN AND TRIALS OF PSYCHIATRIC NEUROTHERAPEUTICS

In discussing the potential for closed-loop systems, we have described the present lack of identified, treatable neural biomarkers of DSM disorders. One

reason for this is that symptom-based psychiatric diagnoses may not be neurological entities (Cuthbert & Insel, 2013; Insel & Wang, 2010). That is, if a single disorder/diagnosis can be achieved by a wide variety of symptom clusters, it is reasonable to believe that those clusters might be produced by a variety of underlying problems in brain structures and circuits. If this is true, the failure to find a neurological basis of psychiatric illness is not surprising—a search for specific brain dysfunction cannot lead to significant findings if only a small subset of studied patients actually have that dysfunction. To produce a clearer picture of the mapping between symptoms and neural activity, we likely need to move away from focusing on categorical diagnoses which lead to extraneous overlap and instead focus on modeling, targeting and treating the functional problems that underpin those diagnoses (Cuthbert & Insel, 2013; Insel, 2014).

There are known correlates and behavioral tests for working memory (Gazzaley & Nobre, 2012), impulsivity (Bari & Robbins, 2013), emotion regulation (Price & Drevets, 2012), and many other behaviors that cut across mental illnesses. Instead of treating heterogeneous disorders, one could develop tests for those functional domains, and then target stimulation to domain-specific symptoms and circuits. Doing so would address what is actually pathological for each individual patient. Furthermore, moving to a domain-oriented diagnosis and treatment system would better leverage extensive animal work in brain stimulation. Psychiatric treatment screening in animals is limited, because there is no evidence that animal behavioral tests produce analogues of human emotion. There is, however, proof for observable behavior changes on standardized tests. A transdiagnostic approach would focus on what can be precisely measured in both animals and humans, and could thus allow us to treat real, quantifiable phenomena.

One such example for the application of this new approach is extinction learning. There is a rapidly evolving literature on fear extinction and the fear-safety learning network, which includes the ventromedial PFC, amygdala and hippocampus (Marin, Camprodon, Dougherty, & Milad, 2014; Milad & Rauch, 2007; Milad *et al.*, 2007). There is considerable overlap between this fear extinction network and several brain regions associated with symptom severity in psychiatric illnesses such as OCD, MDD and most notably, PTSD (Marin *et al.*, 2014; Milad *et al.*, 2008). This suggests that if we could work out a DBS that specifically targeted the fear network (leveraging the emerging evidence on network effects of DBS), that single intervention could be applicable to numerous mental disorders (Marin *et al.*, 2014).

This transdiagnostic approach would face numerous hurdles. Most of the existing scientific literature is disease/disorder oriented, making it difficult to re-tool studies to address domains. Further, there would be substantial regulatory hurdles—at least in the United States, devices are

usually approved to treat specific diagnoses. Funding agencies have begun to propose the transdiagnostic approach, (Insel, 2014) but it will be some time before this idea is well adopted, let alone suitable for use in clinical practice. Nevertheless, this represents the progression of psychiatry (and interventional psychiatry in particular) into a genuinely rational field, and is a trend to be encouraged.

CONCLUSIONS

DBS for psychiatric illness has had great promise, but has stumbled in converting that promise to clinical reality. Much of that relates to a lack of understanding—of the mechanisms of action, biomarkers of efficacious treatment, and the appropriate selection of patients/impairments to be treated with implantable devices. Numerous investigators are actively researching solutions to these problems, and the next decade promises great advances.

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