Tracking the mechanisms of deep brain stimulation for neuropsychiatric disorders

J. Luis Lujan¹, Ashutosh Chaturvedi¹, Cameron C. McIntyre¹

¹Department of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, Ohio

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. DBS for Depression and OCD
4. Neural response to DBS electric fields
5. DBS tractography
6. Network components relevant for Depression and OCD
7. Network mechanisms of DBS in Depression and OCD
8. Future directions
9. Acknowledgements
10. References

1. ABSTRACT

Deep brain stimulation (DBS) has recently emerged as a potential treatment for medically intractable neuropsychiatric disorders. Pilot clinical studies with encouraging results have been performed with DBS of the ventral anterior internal capsule (VAIC) and subgenual cingulate white matter (Cg25WM) for the treatment of obsessive-compulsive disorder and depression. However, little is known about the underlying response of individual neurons, or the networks they are connected to, when DBS is applied to the VAIC or Cg25WM. This review summarizes current understanding of the response of axons to DBS, and discusses the general brain network architectures thought to underlie neuropsychiatric disorders. We also employ diffusion tensor imaging tractography to better understand the axonal trajectories surrounding DBS electrodes implanted in the VAIC or Cg25WM. Finally, we attempt to reconcile various data sets by presenting generalized hypotheses on potential therapeutic mechanisms of DBS for neuropsychiatric disease.

2. INTRODUCTION

Neuropsychiatric disorders such as major depression and obsessive compulsive disorder (OCD) are severely disabling conditions that interfere with the ability to work, interact socially, or live independently (1, 2). Depression is associated with disturbances in attention, motivation, sleep, motor and mental speed, as well as recurrent thoughts of death (3, 4). OCD is characterized by repetitive behaviors (compulsions) performed to neutralize the anxiety induced by undesired thoughts (obsessions) (5).

Depression and OCD are among the most common neuropsychiatric conditions, affecting 5% and 2% respectively, of adult Americans each year (4, 6-8).

Although most patients suffering from depression and OCD are treated effectively with a combination of medications (e.g., serotonin reuptake inhibitors) and/or cognitive behavioral therapy, 20 to 30% of patients fail to respond to treatment (4, 9) and, consequently, remain severely disabled. Despite the effectiveness of ablative surgical procedures (e.g., anterior capsulotomy, anterior
Mechanisms of DBS for neuropsychiatric disorders

cingulotomy, limbic leucotomy, and subcaudate tractotomy) for treating intractable depression and OCD, their destructive and irreversible natures prevent them from being used as a conventional form of treatment (10, 11).

Benabid and colleagues pioneered the concept of using high frequency cathodic electrical stimulation delivered directly into the surgical target to mimic the effect of a surgical lesion (12, 13). Their work led to the development of the commercial clinical technology known as deep brain stimulation (DBS), a reversible stimulation paradigm for treating intractable neuropsychologic disorders (14-16). DBS delivers electrical currents to the brain using electrodes connected to implanted pulse generators. These electrodes are permanently placed into specific anatomical targets and stimulation is adjusted by varying the stimulation mode (monopolar, multipolar), active contact(s), pulse amplitude and duration, and stimulation frequency. DBS represents an established therapy for movement disorders (e.g., Parkinson’s disease, essential tremor, dystonia) (17-19). However, the application of DBS for the treatment of neuropsychiatric disorders remains an experimental procedure, tested on a relatively small number of patients (1, 4, 8, 20-25).

3. DBS FOR DEPRESSION AND OCD

Limited understanding of the abnormalities in brain circuitry that are responsible for neuropsychiatric disorders, together with a limited availability of animal models, have hindered the identification of optimal stimulation targets for neuropsychiatric DBS. The surgical targets reported to date have been empirically selected from existing hypotheses on the pathophysiology of neuropsychiatric disease (16). Specifically, metabolic and imaging studies have been used to identify areas of the brain with abnormal activity levels in depression and OCD (5, 9, 26). Currently, stimulation of the ventral anterior internal capsule (VAIC) (1, 7, 14, 27-29) and the nucleus accumbens (2) are being evaluated for the treatment of both OCD and depression. Similarly, DBS of the subgenual cingulate cortex white matter (Cg25WM) is being evaluated for the treatment of depression (4).

Two of the larger DBS studies for neuropsychiatric disorders were performed by Mayberg et al. (4) and Greenberg et al (1). Mayberg et al. (4) reported remission or near remission of depression symptoms in three of six patients after six months of chronic stimulation of the fiber tracts near the subgenual anterior cingulate (Cg25). Continued antidepressant responses in four patients beyond the period of active stimulation showed long-term improvements in mood as well as cognitive ability. Greenberg et al. (1) extended on the work of Nuttin et al. (27) and reported gains in real-world functioning in a group of six of ten OCD patients after chronic stimulation of the VAIC and ventral striatum. Together, these and other clinical studies (2, 5, 27), demonstrate the potential for future use of DBS in the treatment of neuropsychiatric disorders.

Clearly, larger-scale randomized blinded clinical trials are necessary to address fundamental questions such as the most appropriate surgical target site, the most efficacious stimulation paradigms, as well as long-term clinical outcomes. Despite these limitations, existing evidence suggests that severely debilitated individuals can substantially benefit from DBS technology. However, one big question remains: how does DBS for the treatment of neuropsychiatric disorders work?

4. NEURAL RESPONSE TO DBS ELECTRIC FIELDS

The electric field generated by DBS is a three-dimensionally complex phenomenon that is distributed throughout the brain (30, 31). This electric field is applied to the three-dimensional geometry of the surrounding neural processes (i.e., axons and dendrites) surrounding the electrode. The response of an individual neuron to the applied field is related to the second derivative of the extracellular potential distribution along each neural process (32, 33). In turn, each neuron (or neural process) surrounding the electrode will be subject to both depolarizing and hyperpolarizing stimulation effects (34, 35). Extracellular stimulation can cause a neuron to be either activated or suppressed in different ways and in different neural processes. The specific neuronal response will depend on its positioning with respect to the electrode as well as the stimulation parameters. Neurons directly affected by the stimulation will impact network activity, and the network response will depend on the types of neurons affected and their interconnections.

In general, three classes of neurons can be affected by the stimulation: local cells, afferent inputs, and fibers of passage. Local cells represent neurons that have their cell body in close proximity to the electrode. Afferent inputs represent neurons that project axon terminals to the region of the electrode and whose axon terminals make synaptic connections with local cells. Fibers of passage represent neurons where both the cell body and axon terminals are far from the electrode, but the axonal process of the neuron traces a path that comes in close proximity to the electrode.

To date, it remains unclear which class, or combinations of different neuron classes, stimulated by DBS are responsible for its therapeutic benefit. Multiple studies in neural modeling (36-38), neural recording (39-41), microdialysis (42, 43), and functional imaging (44-46) have attempted to define the mechanisms of action of DBS. In-vitro and in-vivo experimental studies have shown DBS induced inhibition of somatic activity in local cells by activating axons of pre-synaptic inhibitory afferent inputs (47) and/or by blocking voltage-gated membrane channels (48). For this reason, DBS has been thought to produce therapeutic benefits by inhibiting neurons around the electrode. However, theoretical models and multiple experimental studies have found evidence of efferent axonal activation of local cells during therapeutic stimulation (38, 39, 41, 49). In an attempt to reconcile these conflicting experimental findings, theoretical studies have shown that although the soma of local cells can be
inhibited by DBS, stimulus-dependent efferent axonal depolarization results in axonal firing and efferent signal transduction (37, 38). These findings suggest that understanding the axonal response to DBS is paramount to understanding the network effects induced by DBS.

While the general mechanisms of DBS remain unknown and continuously debated, we propose that DBS-induced modulation of axonal activity may be an important aspect of these mechanisms. Understanding the axonal response to DBS in the context of neuropsychiatric disorders is of great importance because current surgical targets for electrode implantation lie within white matter areas. Although the direct effects of DBS on axonal activity will continue to be investigated over the coming years, several important findings have been elucidated. Theoretical models suggest that typical DBS parameter settings generate consistent axonal activation in response to supra-threshold stimulation (30, 50). These theoretical predictions of activation are corroborated by empirical and experimental measurements of stimulation spread into fiber tracts that generate behavioral outcomes consistent with axonal activation (e.g. corticospinal tract activation and subsequent muscle contractions with subthalamic nucleus DBS). Typically, stimulation-induced blocking of axonal activity begins only after stimulation frequencies have reached kilohertz levels (51). However, in vitro studies have observed axonal block in response to typical (~100 Hz) DBS frequencies (52). Irrespective of whether axons are activated or inhibited by DBS, defining the specific fiber tracts that are modulated by DBS is a first step toward deciphering its therapeutic mechanisms.

5. DBS TRACTOGRAPHY

Diffusion-tensor imaging (DTI) is a non-invasive imaging technique that can be used to define axonal trajectories through white matter areas of the brain (53-55). In an attempt to understand the geometry and relative positioning of various fiber tracts pertinent to DBS for neuropsychiatric disorders, we used DTI tractography to define axonal pathways surrounding the typical sites of therapeutic stimulation for depression (4) (Figure 1) and OCD (1) (Figure 2). We used the Wakana et al. (56) DTI brain atlas as the basis for our tractography analysis and used SCIRun / BioTensor (SCI Institute, University of Utah) to visualize our results. We defined a region of interest (ROI) with a 40 mm cube centered on each stimulating DBS electrode. Three-by-three tensors describing the direction and magnitude of water diffusion within each voxel in the ROI were used to calculate a set of eigenvectors that described the primary axonal trajectory in each voxel (57-60). Centered on the stimulating contact of the DBS electrode, we placed a 10 mm cube containing 125 equidistantly distributed seed points for streamline tractography (55). Given the high stimulus amplitudes commonly used in DBS for neuropsychiatric applications (14, 27, 29), the 10 mm cube was chosen to be representative of the general spread of direct axonal stimulation (30).

Individual fiber pathways within the stimulating electrode regions for depression and OCD are shown in Figures 1 and 2, respectively. Our results suggest three general axonal trajectories within the region of stimulation for Cg25WM DBS (Figure 1), and four for VAIC DBS (Figure 2). Analysis of the tractography data for both the Cg25WM or VAIC suggests that DBS would activate fiber pathways connecting the regions of orbitofrontal and subgenual anterior cingulate cortices with the ventral striatum (sometimes passing through the anterior pallidum), as well as inter-hemispheric connections. It should be noted that these streamline tractography results suffer from numerous limitations (e.g. normal subject brain, neglect of higher order tensor characterization to accommodate fiber crossings, and difficulty in determining terminations). However, the fundamental purpose of this analysis was to demonstrate the numerous fiber trajectories that surround DBS electrodes and the complex anatomical pathways that exist between brain regions affected by DBS.

Recently, Johansen-Berg et al. (61) used probabilistic tractography to define the likely connectivity of cingulate regions stimulated by DBS. Probabilistic tractography provides statistical details on how likely a given streamline is to connect one brain region to another. Their results show that the effects of Cg25WM DBS may be mediated via strong connections to orbitofrontal, anterior mid cingulate, hypothalamus, accumbens, and amygdala/hippocampus regions.

Our results (Figures 1 and 2) and the work of Johansen-Berg et al. (62) represent necessary first steps to identifying fiber pathways responsible for the therapeutic benefits of DBS for neuropsychiatric disorders. However to create a more complete picture, we (as a community) will need to integrate several additional pieces of information that can be derived from DTI and functional imaging data specifically acquired in neuropsychiatric patients treated with DBS. First, probabilistic tractography can be used to statistically define the most pertinent connected anatomical regions (61). Second, the fiber trajectories connecting these pertinent anatomical regions that also pass in close proximity to the DBS electrode can be defined (Figures 1, 2). Third, DTI-based electric field models can be used to solve for the voltage distribution generated by DBS along each fiber trajectory (30). Fourth, multi-compartment cable models of axons can be used to predict the spatial extent of action potential generation in response to specific stimulation parameter settings (62). Finally, correlation analyses can be performed with functional imaging data (fMRI and/or PET) to identify directly stimulated fiber populations, and their corresponding cortical and/or subcortical regions altered by the stimulation, that are also associated with clinical benefit or side effects. If such an exercise was performed on enough patients it may be possible to statistically define the “actual target” of the stimulation. This information would be highly important in defining an optimal electrode implantation location, and motivate the use of patient-specific tractography in pre-operative surgical planning.
Figure 1. Typical DBS electrode location and fiber trajectories around the subgenual cingulate white matter target for depression. The columns show sagittal, coronal, and axial projections, respectively. (A-C) Region of interest (white rectangular boxes) defined, and DBS electrode (Medtronic 3387) location. Contact 0 represented the center of the 10 mm cube seed region for tractography. (D-F) DTI tensors in the region of interest. The colors depict the individual fractional anisotropy values of the tensors (blue–0; red–1), while the shape and size describe directionality and magnitude, respectively. (G-I) Individual fiber pathways with the corresponding MR. The colors depict three distinct fibers trajectories. (J-L) Fiber pathways without the underlying MR.
Figure 2. Typical DBS electrode location and fiber trajectories around the ventral anterior internal capsule target for OCD. The columns show sagittal, coronal, and axial projections, respectively. (A-C) Region of interest (white rectangular boxes) defined, and DBS electrode (Medtronic 3887) location. Contact 0 represented the center of the 10 mm cube seed region for tractography. (D-F) DTI tensors in the region of interest. The colors depict the individual fractional anisotropy values of the tensors (blue–0; red–1), while the shape and size describe directionality and magnitude, respectively. (G-I) Individual fiber pathways with the corresponding MR. The colors depict four distinct fibers trajectories. (J-L) Fiber pathways without the underlying MR.
6. NETWORK COMPONENTS RELEVANT FOR DEPRESSION AND OCD

Depression and OCD are system-level disorders that cause a dysregulation of activity in cortico-striato-thalamocortical (CSTC) circuits (4, 8, 22, 63-66). Depression symptoms are associated with abnormal activity in the ventral striatum as well as orbitofrontal and Cg25 cortices (4). Normalization of activity in local (e.g., Cg25) and remote (e.g., prefrontal cortex) areas of the brain following successful DBS treatment suggest that the antidepressant benefits of DBS are correlated with reversal of the abnormalities found at baseline (4, 14). Similarly, increased symptomatic OCD episodes have been shown to be highly correlated with increased neuronal activity in the caudate nucleus, putamen, globus pallidus, inferior frontal gyrus, posterior cingulate gyrus, thalamus, and hippocampus (67-69). DBS of the VAIC, associated with therapeutic benefits for OCD, modulates activity in the dorsal striatum, Cg25, ventral globus pallidus, medial orbitofrontal cortex, and thalamus (5). These functional imaging results from OCD and depression make a clear case for DBS affecting multiple brain regions and show that stimulating a single region can generate complex changes throughout the interconnected network.

It has been hypothesized that the pathogenesis of depression and OCD may be caused by a combination of genetic defects and environmental factors that reduce the effectiveness of synaptic transmission in serotonergic, noradrenergic and dopaminergic pathways (70, 71). Antidepressant drugs, effective in treating both depression and OCD, increase the amount of neurotransmitter exposed post-synaptic neurons by delaying neurotransmitter degradation (72) and/or reuptake (73, 74), slowly increasing serotonin receptor sensitivity and therefore the effectiveness of serotoninergic synapses (71, 75). Thus, it is possible that DBS provides its therapeutic effects by manipulating serotonergic pathways. Serotonin receptors and transporters implicated in depression and OCD are highly expressed in the ventral striatum (76-78) while striatal activity is lower in OCD patients than in healthy individuals (79). The VAIC has fibers of passage connecting the subgenual cingulate and orbitofrontal cortices with striatum (Figure 2), and it is possible that stimulation of those fibers is modulating serotonin levels.

It has also been speculated that dysfunction of the nucleus accumbens, resulting in a disability to adequately modulate circuitry in the amygdala, basal ganglia, and prefrontal cortex, could be the origin of anxiety-disorders, depression, and OCD (2). The high stimulation amplitudes (6.5-10.5V) required to achieve therapeutic benefits when stimulating the VAIC suggest that the observed outcomes might have been the result of current spread to other nuclei (14, 29). Furthermore, lesions to the ventro-caudal part of the internal capsule, which are typically required for successful capsulotomies, are likely to include the nucleus accumbens (2). In turn, Greenberg et al. (1) concluded that the stimulating contacts closest to the nucleus accumbens might provide better therapeutic effects. Sturm et al. (2) confirmed significant symptom improvements with unilateral high-frequency stimulation of the right nucleus accumbens, indicating a major role for this nucleus as a central relay between the amygdaloid complex, basal ganglia, mediodorsal thalamus and the prefrontal cortex.

It is well known that the amygdaloid complex, especially the lateral nucleus, is involved in anxiety and fear reactions (80, 81). Pathological information flow from the lateral amygdaloid nucleus can be propagated to base-lateral and central amygdaloid nuclei before converging in the accumbens via both, the ventral amygdalofugal pathway and the extended amygdale (82, 83). The main efferents of the accumbens innervate the pallidum, striatum, mediodorsal thalamus, prefrontal and cingulate cortices, as well as mesolimbic dopaminergic areas. The nucleus accumbens could thus represent a central location for impulse-propagation from the amygdaloid complex to the basal ganglia, mediodorsal thalamus and prefrontal cortex, all of which are implicated in the pathophysiology of OCD (84). Inputs from the amygdaloid complex to the nucleus accumbens “gate” both fronto-striatal and hippocampo-striatal circuitry (2, 85-87). Thus, disruption of pathological impulse-flow by means of chronic high-frequency stimulation of the nucleus accumbens might explain the therapeutic benefits of DBS in both depression and OCD patients.

A multi-circuit model of OCD (Figure 3) has been defined to help develop a rationale for surgical intervention (8). The model emphasizes the functional interconnections between the orbitofrontal and anterior cingulate cortices, medial, dorsomedial, and anterior thalamic nuclei, Papez circuit, anterior cingulate cortex, and nucleus accumbens (8). This model suggests that obsessive-compulsive symptoms appear when striato-pallido-thalamic activity is abnormally decreased or when orbitofrontal-thalamic activity is abnormally increased. The OCD model is characterized by three main building blocks. The first block involves an excitatory glutamatergic positive feedback loop between the orbital cortex, the prefrontal cortex, and the dorso-medial thalamic nucleus, passing through the anterior limb of the internal capsule. The second block is an inhibitory GABAergic loop between the orbital and prefrontal cortices, the ventral caudate, the dorsomedial pallidum, and the anterior, dorsomedial and intralaminar thalamic nuclei. This component is thought to mediate the excitatory orbito-frontal-thalamic loop. The third block is a loop between the limbic system and the circuit of Papez (from the hippocampus to the mammillary body by means of the fornix, and onto the anterior thalamic nuclei). This model contains many projections from the anterior cingulate cortex to the nucleus accumbens in the striatum. According to this model, OCD symptoms could occur when striato-pallido-thalamic activity decreases and fails to modulate the activity in the positive fronto-thalamic loop (79).

An analogous model of depression (Figure 4) implicates failure to coordinate CSTC (including amygdale, hippocampus, and hypothalamic-pituitary axis) interactions...
Mechanisms of DBS for neuropsychiatric disorders

Figure 3. OCD model. The first component involves an excitatory and reciprocal positive feedback corticothalamic loop, in which the orbitofrontal and prefrontal cortices project onto the dorsomedial thalamus via the anterior limb of the internal capsule. The corticothalamic projection is mediated primarily by glutamate and aspartate, and the reciprocal thalamocortical projection is glutamate-mediated. The second component involves the orbitofrontal cortex, the ventral caudate, the dorsomedial pallidum, and the anterior, dorsomedial, and intralaminar nuclei of the thalamus. This component is thought to serve as a modulator for the orbitofrontal-thalamic loop through inhibition from the dorsomedial pallidum to the thalamus by means of gamma-aminobutyric acid. This component is also thought to involve inhibitory serotonergic projections from the dorsal raphe nuclei of the midbrain to the ventral striatum. The third component involves a pathway between the limbic system and the circuit of Papez. This pathway projects from the hippocampal formation to the mammillary body by means of the fornix and continues on to the anterior thalamic nuclei and finally onto the cingulate gyrus. Reproduced with permission from (8).

as a result of overactive paralimbic regions and hypoactive dorsal cortical sites (8, 88). This model proposes that depressive behaviors are modulated by explicit interacting regions. Depression is thus not simply a dysfunction of any single one of these regions, but a failure in coordination of interactions between brain nuclei in these regions (88). This depression model involves dorsal (attention-cognition), ventral (vegetative-circadian), and rostral (regulatory) compartments (8, 67, 88). The dorsal compartment mediates the cognitive aspects of negative emotion. It involves the premotor and prefrontal cortices, as well as the dorsal segment of the anterior cingulate cortex. The ventral compartment involves the Cg25, as well as the insula and orbitofrontal cortex. This compartment is known to mediate circadian and vegetative aspects of depression. The rostral compartment involves the pregenual anterior cingulate cortex, the amygdala, and the hypothalamic pituitary axis. It is thought to regulate the overall network activity by facilitating the interaction between the dorsal and ventral compartments. Metabolism in this region may predict antidepressant response in acutely depressed patients (88).
Mechanisms of DBS for neuropsychiatric disorders

Figure 4. Depression model. The dorsal compartment is principally involved with the motor and cognitive aspects of depression. Projections to the dorsal striatum from prefrontal, dorsal anterior cingulate, and premotor cortices continue on to the thalamus by means of its projections from the dorsomedial portion of the pallidum. Thalamocortical projections close the loop. The ventral compartment, involved with affective aspects of depression, is composed of a closed loop involving paralimbic and subcortical components as well as regions of the brainstem. Specifically, the subgenual anterior cingulate (Cg25), orbitofrontal and insular cortices, project onto the ventral striatum, medial/rostral pallidum, and finally to the anterior and dorsomedial thalamus. The ventral compartment communicates with regions of the ventral compartment through the rostral and dorsal anterior cingulate, caudate-putamen, mediodorsal thalamus, and posterior cingulate. The modulatory compartment is thought to regulate relative ventral-dorsal component activity. It consists of the pregenual anterior cingulate, the amygdala, and the hypothalamic-pituitary axis. The amygdala drives activity in the ventral compartment and the pregenual anterior cingulate sends inhibitory projections to both compartments. The hippocampus, in turn, modulates activity in hypothalamic axis. Thus, reciprocal inhibitory connections between dorsal and ventral compartments combined with amygdala hyperactivity and abnormal hippocampal activity could lead to depression symptoms. Reproduced with permission from (8).

The models described above show that neuropsychiatric disorders appear to be rooted in the dysfunction of highly complex networks. Development of schematic diagrams of the pertinent brain regions associated with the disease processes are of fundamental importance in designing intervention strategies. However, analogous to movement disorders, it must be recognized that the actual brain networks are complex dynamical systems, and modulation of one node in the network can cause cascades of non-intuitive changes throughout the entire network on multiple time scales. Thus, DBS provides a unique and exciting opportunity to expand our understanding of the networks involved in neuropsychiatric disorders.

7. NETWORK MECHANISMS OF DBS IN DEPRESSION AND OCD

Although neural responses to electrical stimulation have been well characterized for single cells over short time scales, there is currently little understanding of the cellular mechanisms responsible for network responses to DBS in neuropsychiatric disease. In general, the slow progression of the therapeutic effects of stimulation (e.g., only limited improvements in patient mood and anxiety are evident with acute DBS) suggests that acute disruption of pathological network activity may not be the principal mechanism of DBS for neuropsychiatric disease (1, 2, 4, 14). For the most part, improvement of depression and OCD symptoms requires months of chronic stimulation (1, 4, 89), resulting in progressive symptom improvement and normalization of metabolic activity (9). Sleep disturbances typically normalize within the first week of chronic DBS, while energy, interest, and psychomotor improvements occur within a few weeks. These are followed by increased interest and pleasure in social interactions, as well as improved ability in planning and task initiation and completion. Furthermore, progressive symptom worsening can be observed if stimulation is turned off. Interestingly, the metabolic changes observed with DBS (90) linger after chronic stimulation (4). These results suggest that DBS reproduces the therapeutic benefits of antidepressants by inducing long-term changes in network activity through continuous excitation/inhibition of serotonergic and noradrenergic pathways (91).
Given the overlap in symptom control, the similar neural circuitry affected by the stimulation, and the progressive improvement in symptoms over long-term stimulation, it is possible that DBS has similar underlying therapeutic mechanisms in both OCD and depression. One logical hypothesis is that DBS for neuropsychiatric disease has acute (fast) and chronic (delayed) therapeutic components. Acute improvements would most likely be the result of an immediate disruption of pathologic activity in serotonergic and noradrenergic circuits, whereas chronic improvements would be the result of long-term changes in synaptic effectiveness and/or synaptic connectivity (92).

In addition to acute and chronic changes, DBS may induce local and remote effects (93). PET studies have shown that successful treatment of both depression and OCD are associated with normalization of abnormal (hyper/hypo) basal metabolism and induced metabolic changes in remote (previously-normal) regions of the brain (3). Specific brain functions can be associated with distinct regions of the brain or with highly parallel, reciprocal, and overlapping processing networks, where the function of each neuronal group is determined by its dominant inputs (94, 95). By altering these inputs as a consequence of disease and/or slowly-developing brain lesions, large-scale reorganization of the brain (i.e., not confined to changes within the lesion area) can be induced (96, 97). This type of cerebral reorganization has been shown to be proportional to the progression of neuropsychiatric disease (94). Diaschisis has been described in the basal ganglia and internal capsule, suggesting that pathologic activity within cerebral loops is a possible mechanism for the remote metabolic abnormalities observed in neuropsychiatric disease (4, 98, 99). Although the correlation between metabolic pattern changes and recovery is uncertain, it is likely that modulation of metabolic activity through cerebral loops is responsible for some (if not all) recovery. However, it remains unclear how this DBS-induced modulation generates chronic therapeutic effects.

Acute changes in activation levels in remote areas could occur as an indirect consequence of trans-synaptic effects or direct activation of projection neurons (100). In depression, acute symptom improvements are consistent with acute deactivation of hyperactive Cg25 and areas monosynaptically connected to it (4). Mayberg et al. (4) suggested that suppression of abnormally-elevated baseline activity in Cg25 could result from DBS-induced activation of inhibitory GABAergic afferents and/or high frequency stimulation induced synaptic or metabolic failure. However, it is also possible that stimulation directly affected the network dynamics of those cerebral loops passing through Cg25 in ways that cannot be simply understood with block diagram network models (100, 101).

Acute disruption of pathological activity can be achieved by inducing changes in neuronal membrane excitability, imbalances between excitatory and inhibitory inputs (e.g., as a result of changes in tonic inhibition), and/or short/long-term potentiation/depression (100, 102). Conversely, anatomical changes (e.g., formation of new synapses, growth of new connections into different regions of the brain) and synaptic potentiation/depression may produce changes in brain circuitry associated with delayed therapeutic benefits. Several activity-dependent mechanisms, which depend on prolonged stimulation, may cooperate to achieve synaptic plasticity that could underlie the therapeutic effects of DBS. Thus, long-term benefits may be the result of global changes in neural network properties (i.e., synaptic plasticity).

Below is a hypothetical example of how DBS induced activity could result in long-term network changes. Supra-threshold high frequency DBS continuously activates a large number of axons and increases glutamatergic and serotoninergic exposure in the striatum (Figures 1 and 2). Activation of serotonin receptors results in protein kinase phosphorylation and activation of second messenger systems that regulate gene transcription (103, 104). Activated genes induce long-term potentiation (LTP) as well as the growth of synaptic connections (105). The high-frequency stimulation also induces spine enlargement and increases the number of glutamate receptors (106). These synaptic changes then impact the excitability of the striatum and alter its integration of cortical inputs. In parallel, analogous changes in cortical regions could also be occurring (100). The sum result would be a substantial alteration of the CSTC network dynamics, alleviating the pathological activity patterns. Clearly this generalized hypothesis is untested, speculative, and missing important details (i.e. how CSTC network dynamics actually work), but given our current understanding of the system, we believe it is plausible.

8. FUTURE DIRECTIONS

The preliminary clinical effectiveness of DBS for intractable neuropsychiatric disorders makes it a promising therapeutic alternative for a large number of patients (4, 8). However, our limited understanding of both the pathophysiology of neuropsychiatric disorders and the effects of DBS on the nervous system, make wide-scale use of DBS technology a tenuous proposition from a scientific perspective. However, clinical outcomes will drive clinical adoption of this technology, and similar to DBS for movement disorders, scientists will have to play catch up.

Although a large number of DBS procedures have been performed worldwide, only a few have been intended for treatment of neuropsychiatric disorders (10), and as such, study populations have been small. The limited documentation of parameter adjustments utilized in these studies makes it difficult to identify the direct effects induced by various device settings. As such, the optimal target and stimulation parameters remain unclear. Interestingly, data suggests that stimulation of the nucleus accumbens may play a critical role in normalization of activity and increased therapeutic benefits in both depression and OCD (9, 65, 69). In addition, it is also possible that optimal therapeutic benefits might be achieved by stimulating a combination of targets within the network, potentially allowing a more complex manipulation of the entire neural circuitry involved in
neuropsychiatric disorders. However, before embarking on speculative analyses of alternative targets, it may be more prudent to perform larger double blinded studies, with longer follow-up periods to clearly demonstrate the efficacy of DBS with currently accepted stimulation paradigms.

Scientifically, an almost endless number of questions remain to be addressed. For example, a fascinating aspect of DBS for neuropsychiatric disorders is the relatively slow progression of therapeutic benefits, even though acute effects can often be seen in the operating room. Another interesting question is why, if DBS replicates the effects of antidepressant drugs, has it been effective in treating patients where antidepressants have failed? These questions and many more will make for interesting discussion and debate as the scientific and clinical worlds converge to elucidate the therapeutic mechanisms of DBS for neuropsychiatric disorders.

9. ACKNOWLEDGEMENTS

This work was supported by funding from the National Institutes of Health (NS050449, NS059736). The authors also thank Susumu Mori for providing the diffusion tensor brain atlas data set and Christopher Maks for assistance in the tractography analysis.

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Mechanisms of DBS for neuropsychiatric disorders

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Mechanisms of DBS for neuropsychiatric disorders


Mechanisms of DBS for neuropsychiatric disorders


Abbreviations: DBS: Deep brain stimulation; VAIC: ventral anterior internal capsule; Cg25WM: subgenual cingulate white matter; OCD: obsessive compulsive disorder; DTI: diffusion-tensor imaging; ROI: region of interest; CSTC: cortico-striato-thalamocortical; LTP: long-term potentiation

**Key Words:** Deep Brain Stimulation, Psychiatric Disorders, Depression, Obsessive Compulsive Disorder, Tractography, Neurostimulation, Neuromodulation, Review

Send correspondence to: Cameron C. McIntyre, Department of Biomedical Engineering, Cleveland Clinic Foundation, 9500 Euclid Avenue ND20, Cleveland, Ohio. 44195, Tel: 216-445-3264, Fax: 216-444-9198, E-mail: mcintyecycleff.org

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