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Deep brain stimulation for psychiatric disorders: From focal brain targets to cognitive networks☆

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Abstract

Deep brain stimulation (DBS) is a promising intervention for treatment-resistant psychiatric disorders, particularly major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). Up to 90% of patients who have not recovered with therapy or medication have reported benefit from DBS in open-label studies. Response rates in randomized controlled trials (RCTs), however, have been much lower. This has been argued to arise from surgical variability between sites, and recent psychiatric DBS research has focused on refining targeting through personalized imaging. Much less attention has been given to the fact that psychiatric disorders arise from dysfunction in distributed brain networks, and that DBS likely acts by altering communication within those networks. This is in part because psychiatric DBS research relies on subjective rating scales that make it difficult to identify network biomarkers. Here, we overview recent DBS RCT results in OCD and MDD, as well as the follow-on imaging studies. We present evidence for a new approach to studying DBS' mechanisms of action, focused on measuring objective cognitive/emotional deficits that underpin these and many other mental disorders. Further, we suggest that a focus on cognition could lead to reliable network biomarkers at an electrophysiologic level, especially those related to inter-regional synchrony of the local field potential (LFP). Developing the network neuroscience of DBS has the potential to finally unlock the potential of this highly specific therapy.

Keywords

Neurostimulation; Cognitive neuroscience; Electrophysiology; Deep brain stimulation

1. Introduction

In the United States, roughly 20% of people are diagnosed with Major Depressive Disorder (MDD), and around 2% of the population is diagnosed with Obsessive Compulsive Disorder (OCD) in their lifetime (Tye *et al.* 2009, Hasin *et al.* 2018). In both disorders, over 20% of patients will not find relief from standard treatments. For those patients, deep brain stimulation (DBS) is a promising treatment option. DBS was approved for Parkinsons'

☆Abbreviations: Deep brain stimulation; Obsessive compulsive disorder; Major depressive disorder

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disease (PD) in 2002, followed by approvals for dystonia, epilepsy, essential tremor, and OCD (Gardner 2013). DBS continues to be explored for a variety of indications, including epilepsy, Tourette disorder, eating disorders, obesity, and a range of psychiatric disorders (Taghva *et al.* 2012, Lipsman *et al.* 2017, Lozano 2019, Mennitto 2019). Of those, only depression and OCD have advanced to randomized controlled trials (RCTs), with very mixed results. We review the brain targets tested to date for MDD and OCD and explore the rationale for each target. For each, we emphasize RCT data, which provide the most robust estimate of DBS' effects (See tables 1 and 2 for included studies) (Raymaekers *et al.* 2017, Pycroft *et al.* 2018). We then discuss the limitations of those trials, which center around two key problems. First, psychiatric disorders have neither objective diagnostic criteria nor symptom metrics, which make it difficult to select appropriate DBS candidates and appropriately titrate stimulation. Second, all psychiatric DBS has used stimulation parameters designed for Parkinson disease, which may not be appropriate for a very different set of brain circuits and specifically may not engage the pathophysiology of psychiatric disease. We outline a potential approach to overcome these limits, centered around understanding the cognitive functions linked to extant DBS targets, considering those targets from a network perspective, and directly targeting neurophysiology at the network level. Recent advances in DBS device technology make these strategies feasible in real-world clinical settings and should lead to a new generation of mechanism-driven psychiatric trials.

2. Overview of DBS for Depression

2.1. Who is a Candidate for DBS?

DBS for major depressive disorder (MDD) is reserved for patients with severe, treatment resistant depression. These patients have tried multiple lines of therapy without relief before pursuing DBS (Widge and Dougherty 2015, Widge, Malone, *et al.* 2018). This generally includes multiple trials of psychotherapy, medication, and (if possible) electro-convulsive therapy. Candidates for DBS are largely unable to work due to the severity of symptoms. Because of the number of failed therapies associated with DBS eligibility, most candidates are in their 40s or 50s.

2.2. DBS Targets for Depression

Researchers have identified several targets for DBS in patients with MDD, each believed to play a role in causing depressive symptoms. While there are variations in the names used for the targets across publications, there are three main targets for DBS in MDD: the subcallosal cortex (SCC), ventral capsule/ventral striatum (VC/VS), and the medial forebrain bundle (MFB).

2.3. Subcallosal Cingulate Cortex (SCC)

The first efforts to explore SCC targets stemmed from research linking an increase in depressive symptoms with an increase of activity in the SCC (Seminowicz *et al.* 2004). An early trial of SCC DBS found significant changes in relative glucose metabolism and blood flow in various brain regions for treatment responders (Lozano *et al.* 2008). The most significant changes were observed in areas connected to the SCC circuit including orbital

and medial frontal cortex, anterior midcingulate, and posterior cingulate (Lozano *et al.* 2008). These were some of the earliest evidence for network level biological changes as the basis for improvement in depressive symptoms. Additional open label trials continued to deliver positive results (Kennedy *et al.* 2011, Holtzheimer *et al.* 2012, Lozano *et al.* 2012, Puigdemont *et al.* 2012). The "first double-blinded, randomized, sham-controlled crossover study" followed, in which patients underwent a blinded discontinuation (Puigdemont *et al.* 2015). Of the eight patients, five showed clinically stable remission, suggesting the efficacy of SCC DBS (Puigdemont *et al.* 2015). However, during the blind crossover period, there was no statistical difference between active and sham stimulation, raising questions of patient/rater expectation bias.

The first and only (published) prospective RCT exploring the SCC target was conducted in parallel. This relatively large trial (n = 90) aimed to confirm the utility of SCC stimulation for depression. In that multi-center study there was no significant difference in depressive symptom reduction between active and sham groups (Holtzheimer *et al.* 2017). These negative results do not discredit previous research or the potential utility of SCC stimulation. They do, however, call for further study to understand the wide gap between open-label and RCT results. Current theories for inconsistent SCC outcomes include sub-optimal placement of electrodes at some centers and differences in depression types across study populations (Holtzheimer *et al.* 2017). More recent theories consider the idea that sub-optimal stimulation was delivered, causing low response rates (Widge and Miller 2019). SCC is still considered a viable DBS target for depression, with multiple active lines of study (see below).

2.4. Ventral Capsule/Ventral Striatum (VC/VS)

VC/VS stimulation for depression originated from findings that stimulation of VC/VS for OCD also had significant effects on depressive symptoms (Nuttin *et al.* 1999, Greenberg *et al.* 2006). Malone and colleagues then tested VC/VS stimulation in MDD patients (Malone *et al.* 2009). This trial had a 50% response rate at 12 months post-surgery, promoting further investigation into the efficacy of VC/VS stimulation. Another group proposed an open label trial with blinded discontinuation, to confirm the results of previous open label trials. However, the blinded discontinuation portion was abandoned due to severe worsening of symptoms during the off phase. That study also found an open-label response rate of roughly 50%. (Bewernick *et al.* 2010).

The first RCT of VC/VS DBS in MDD was conducted in the following years (Dougherty *et al.* 2015). In this trial, there was no significant difference between active and control group response rates. Only 3 (20%) active and 2 (14.3%) sham subjects responded to VC/VS DBS by the final endpoint. Neither group reached a response rate higher than 30% at any point during the blinded or open label portions of the trial. This contrasted against an over 50% response rate in an open label study from the same investigators (Malone *et al.* 2009).

The low response rate of the first RCT by Dougherty et al. was followed by higher response rates in another RCT conducted in parallel by a different group (Bergfeld *et al.* 2016). Much discussion has taken place surrounding why one trial met its endpoint, while another did not. Dougherty et al. note that their study as reported was not sufficiently powered to detect true

treatment differences; the trial had been planned for a much larger recruitment but was stopped early due to an interim futility analysis (Dougherty *et al.* 2015). Further, their blinded phase may have been too short to capture a long-term buildup of DBS benefits. The study design of Bergfeld et al. included a significantly longer optimization timeframe of up to 52 weeks, compared to only 4 weeks for Dougherty et al. Additionally, the Bergfeld RCT started with an open label phase, followed by a randomized, blinded crossover discontinuation. This approach may better control variability in multi-site RCTs because it reveals (and offers time to correct) surgical and programming differences that negatively affect efficacy (Widge, Malone, *et al.* 2018). At the same time, some patient cohorts do not tolerate discontinuation (Bewernick *et al.* 2010), which makes the crossover design more difficult to use.

The outlook for VC/VS stimulation is hopeful. Youngerman and Sheth (2017) examined potential ways that the trial design influenced the outcomes of VC/VS trials, endorsing the idea that differences in treatment effect could be attributed to the varying lengths of optimization. However, the long optimization period could introduce a nocebo effect, as participants are more likely to detect when stimulation has been turned off, and in turn believe they are losing benefit. This could explain the high level of difference seen in Bergfeld.

2.5. Medial Forebrain Bundle (MFB)

MFB was investigated specifically for benefit in depression with anhedonia (Schlaepfer *et al.* 2013). The rationale for targeting MFB derives from its role in reward anticipation, reward perception, grief seeking, and pleasure (Coenen et al. 2011, p., Schlaepfer *et al.* 2013). The open-label pilot study met its endpoint, with 85% (6) participants responding to MFB DBS. To date, two randomized controlled trials have been initiated for MFB (Coenen et al., 2019; Fenoy et al., 2016).

The FORESEE II (FOREbrain Stimulation dEprEssion, NCT01778790) trial was completed in 2018. This trial set out to assess the long-term efficacy of MFB stimulation and explore the optimal timing for MFB stimulation. The trial enrolled 16 patients in total. Arguably the most significant finding from this study is that all 16 patients responded during some portion of the trial. At 12 months, 50% (8) were considered remitters. The mean time to response was relatively short, averaging only 1 week. On average, patients spent 60% of the trial in clinical response. However, the response rate of active and sham stimulation could not be differentiated at the end of the 8 week blinded phase, pointing to a persistent microlesion effect of surgery or the presence of a placebo effect. The sustained response supports the hope that MFB stimulation can be efficacious over long periods.

An MFB trial that is still ongoing (NCT02046330) aims to better characterize how and why MFB has such a rapid effect. While still enrolling, the study team released results for the first four patients to complete the trial. Of the four enrolled patients, three (75%) responded. All patients experienced some drop in the Montgomery-Asberg Depression Rating Scale (MADRS) following 4-weeks of post-surgery sham stimulation, but this change was not significant. After one week of active stimulation, changes in MADRS scores became significant when compared against baseline and end of 4-week sham stimulation scores.

Additionally, MADRS scores continued to decrease with time, hinting to the maturation of DBS effectiveness with time as seen in other DBS targets (Dougherty *et al.* 2015, Bergfeld *et al.* 2016, Holtzheimer *et al.* 2017). MFB is relatively understudied compared to the prior two targets but remains equally viable given its unique capacity to produce very rapid clinical responses.

3. Overview of DBS for OCD

3.1. Who is a candidate for DBS?

DBS for OCD is considered for patients with severe, refractory OCD, which like MDD is defined by multiple treatment failures. The typical course of treatment for OCD begins with a selective serotonin reuptake inhibitor (SSRI) or a course of cognitive behavioral therapy (CBT), followed by a combination of the two. Additional SSRIs and other classes of drugs must be tried before DBS is considered (Widge and Dougherty 2015). Because a patient must have tried many therapies to be eligible for DBS, patients are often between the ages of 40 and 60.

3.2. DBS targets for OCD

Anterior capsulotomy lesion surgery was historically the last treatment option for OCD patients who had not responded to multiple lines of therapy (Abelson et al., 2005; Widge & Dougherty, 2015). While modern lesion surgery is generally safe, it is nonreversible, and in some cases can affect tissue well beyond the intended area (Rasmussen *et al.* 2018). DBS was proposed as a reversible approach that would achieve the benefits of a lesion. This target, the Ventral Capsule/Ventral Striatum (VC/VS), is part of the cortico-striato-thalamo-cortical (CSTC) loop circuitry that is hypothesized to be the basis of OCD symptoms (Zhang *et al.* 2017, Dougherty *et al.* 2018). An additional target was identified through DBS research in PD, where OCD symptoms were decreased for an individual when given subthalamic nucleus (STN) stimulation (Fontaine *et al.* 2004). The VC/VS and STN continue to be the main DBS targets explored for OCD.

3.3. Ventral Capsule/Ventral Striatum (VC/VS)

An early open label pilot study demonstrated a potential for VC/VS DBS to relieve symptoms of treatment resistant OCD (Nuttin *et al.* 1999). Building off these findings, the first RCT was conducted in the early 2000s (Abelson *et al.* 2005). While only one of the four patients was categorized as a responder, the benefit seen by this patient was dramatic. For this individual, changes in both OCD symptoms and mood tracked well with on-off cycling of the DBS. These early pilots defined targeting and stimulation techniques for VC/VS that are still in active clinical use, although they were refined throughout the early 2000s as investigators worldwide adopted the technique (Greenberg *et al.* 2010).

A US-based group verified those initial positive results, using a sham-controlled design but with more stringent response criteria (Goodman *et al.* 2010). The standard metric for determining response in OCD studies is a 35% reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). However, Goodman et al. only classified patients as responders if they both had a 35% reduction in Y-BOCS and reached a Y-BOCS lower than

16. Despite these higher standards, 67% (4) patients were responders. The two non-responders still chose to continue receiving stimulation due to subjective improvement of symptoms. That study, in turn, led to an NIH-funded multi-center RCT of VC/VS DBS for OCD, which was meant to provide definitive evidence for efficacy (NCT00640133). Despite completing enrollment in 2015, the results of that trial remain unpublished, raising concern that it may not have met the pre-specified endpoint. A contemporaneous trial was published using the same blinded-discontinuation design that was successful in MDD (Luyten et al., 2016). In that trial, 67% (16) of patients were DBS responders (Luyten *et al.* 2016).

The most recent RCT explored the effects that different DBS contacts within the VC/VS had on varying symptom dimensions (Barcia *et al.* 2019). The goal was to identify whether the optimal target was the same across symptoms, or if variations existed between obsessional content and structural connectivity. Secondarily, the study sought to confirm the efficacy of VC/VS stimulation. 6 of 7 patients (85%) did respond, but there was no significant difference between stimulation of the individually determined “best contact” and sham stimulation. There was similarly no relation between the location of effective contacts within the VC/VS and the patient’s predominant obsessions, although the others did find a potential correlation between provocation-induced fMRI changes and effective contact locations. Nevertheless, when the findings of this most recent RCT are combined with those of prior published studies, there appears to be solid support for VC/VS DBS in OCD, with a number needed to treat (NNT) of approximately 3 to achieve 1 clinical response (Martinho *et al.* 2020).

3.4. Subthalamic Nucleus (STN)

STN stimulation for OCD arose from a serendipitous discovery in a Parkinson disease case. In 2004, a patient who received STN stimulation for treatment of PD also reported dramatic reductions in OCD symptoms (Fontaine *et al.* 2004). This unexpected result suggested a role for STN in OCD symptomatology. Mallet et al. (2008) thus executed an RCT to study STN stimulation for OCD, in which 75% (6/8) of patients responded to active stimulation (compared to 3/8 responding to sham stimulation). However, this trial deviated from the standard responder classification by designating a responder as a 25% decrease in Y-BOCS score compared to the standard 35% decrease. With the standard thresh-old, the response rate to active stimulation appeared to be 50–60%.

3.5. Dual-target stimulation

The first dual-target RCT compared the efficacy of STN and VC/VS stimulation (Tyagi *et al.* 2019), on the premise that the two might have synergistic effects. Patients were implanted in both the STN and the VC/VS and received single-target or dual-target stimulation during separate study phases. Both targets alleviated OCD symptoms, and there was no significant difference in response rate between stimulation of the STN vs. VC/VS. Additionally, stimulating both sites simultaneously added no benefit. However, a second goal of this trial was to investigate cognitive effects and mood changes associated with DBS. Stimulation of the STN improved cognitive flexibility significantly more than did VC/VS stimulation. Similarly, stimulation of the VC/VS was associated with improved mood compared to STN

stimulation. While both targets alleviated OCD symptoms, these differences suggest different roles of STN and VC/VS in OCD pathophysiology.

4. Next steps: Improving psychiatric DBS outcomes

The exploration of DBS as an alternative to lesion surgery came from the desire to have a reversible surgery option with the capability to adjust and reshape the therapy through reprogramming. Given the origins of DBS in neurology and neurosurgery, much of the recent research (particularly in the context of trials that did not meet endpoints) has emphasized surgical/anatomic targeting. We briefly review those results, then argue that equal attention is needed on the question of DBS' neurophysiologic effects.

4.1. Location, location, location: The quest for improved DBS targets

Some of the strongest results supporting surgical target refinement have come from the pioneers of SCC DBS and have emphasized diffusion tensor imaging (tractography). In a retrospective analysis of their initial open-label data, they identified a confluence of white matter bundles that was near, but did not always overlap, the notional SCC target (Riva-Posse *et al.* 2014). When all three bundles were captured within the (inferred) DBS electric field, patients responded, but non-responders lacked engagement of at least one bundle. In a prospective open-label study, DBS implanted at this patient-specific target had an 80% response rate (Riva-Posse *et al.* 2018). The availability of open-source software to perform similar activation mapping (Horn and Kühn 2015) could make such techniques widely available, especially given the proliferation of high-quality tractography scanners/ software spurred by the Human Connectome Project. Other groups have found similar tractographic predictors of efficacy in VC/VS DBS for OCD (Hartmann *et al.* 2016, Baldermann *et al.* 2019, Li *et al.* 2020) and mapped the anatomic variation of that target (Makris *et al.* 2016).

Amid these promising results, there are also reasons for caution. In dystonia, a disorder with very localized deficits, electrode location was not significantly associated with clinical response (Volkmann *et al.* 2012). In a recent open label OCD trial, 60% of patients responded – but the most clinically effective DBS contact was outside the notional target region in over half of the cases (Menchón *et al.* 2019). In that same study, contacts associated with a greater than 65% improvement in Y-BOCS were near or overlapping sites with a 25%–35% improvement range. Most recently, an independent group of investigators attempted SCC DBS using the same three-bundle tractographic target reported in (Riva-Posse *et al.* 2018). They reported a 40% response rate even with patient-specific imaging (Ramasubbu *et al.* 2019). Thus, the key to high DBS response rates may not lie as much in the precise location of the implant, as in other aspects of high-volume centers' expertise (e.g., post-implant programming, patient selection criteria, or general clinical acumen).

4.2. From focal targets to cognitive networks

A key point is that the targets for psychiatric disorders tend to be white matter tracts, especially hubs where multiple white matter bundles converge (Haber and Heilbronner 2013, Riva-Posse *et al.* 2018, Widge, Malone, *et al.* 2018). This suggests that across indications, psychiatric DBS is not stimulating a single area, but a network – a set of brain regions acting

in concert. It is not yet clear at what level a “network” could/should be defined. That term, and its close cousin “connectome”, may refer to anatomic connections inferred through diffusion imaging (Haber *et al.* 2020), putative functional relationships inferred from correlations in slow hemodynamic signals (Smith *et al.* 2013, Eickhoff *et al.* 2018), or similar correlations identified in sub-second physiologic recordings (Sani *et al.* 2018, Provenza *et al.* 2019). All remain viable levels of analysis at present, and identifying the most useful is an ongoing area of DBS-related investigation. For this review, we accept all three as potentially valid, given the early state of the field.

For instance, the originators of SCC DBS have proposed a putative MDD network based on a mixture of tractography studies, known pharmacology connections, and observed anatomical connections (Mayberg 2009). That propsed network includes multiple prefrontal areas, hippocampus, amygdala, and basal ganglia. It is hypothesized that the SCC, VC/VS, and MFB are all different targets (Figure 1) that allow us to access this MDD network (Widge, Malone, *et al.* 2018). Similarly, OCD is linked to cortico-striato-thalamo-cortical (CSTC) circuitry (Dougherty *et al.* 2018). Similar to the MDD network, the CSTC circuitry may be accessible through both the VC/VS and the STN (Figure 1) (Bourne *et al.* 2012). The exact structures involved in each network, and the appropriate interactions between those structures, remain an area of active scientific debate. The original proposal of Mayberg (2009) overlaps, but does not completely match, newer conceptions of MDD networks derived from large neuroimaging datasets (Drysdale *et al.* 2017, Dinga *et al.* 2019) or invasive human brain recordings (Kirkby *et al.* 2018, Sani *et al.* 2018). Those newer concepts are also inconsistent with each other. A similar situation holds in OCD, where simple concepts of hyper-connected CSTC loops are rapidly giving way to a more nuanced view (Robbins *et al.* 2019). What is clear is that in both indications, adding stimulation to a brain network causes both local and long-distance changes. These presumably are mediated through the white matter bundles captured in the DBS electrical field (Albaugh & Shih, 2014). That view is supported by multiple lines of evidence. For instance, retrospective analysis of brain lesion studies show that disruption of white matter hubs and their connectivity can have both pathologic and therapeutic effects in OCD, effects that align with the VC/VS DBS target (Figee *et al.* 2013). Multiple groups have studied EEG effects from DBS in depression, and shown that stimulation affects a broad range of cortical regions (Waters *et al.* 2018, Widge, Zorowitz, *et al.* 2019). Those cortical effects align with the known white matter connectivity of the DBS targets.

Thinking about DBS at this network level shifts the focus, from finding the best target or the rules for hitting that target, to understanding what each target can do to a broad, distributed network. A clue comes from the fact that the networks accessed by extant DBS targets are linked to higher-order cognitions, such as decision making, emotional regulation, and adaptation. This suggests that DBS may modulate those cognitive processes, i.e. by remediating cognitive deficits. One key example is cognitive control – the ability to shift one’s response style in the face of changing information (Widge, Heilbronner, *et al.* 2019). DBS-linked networks contain key hubs of the cognitive control circuitry, most notably the prefrontal cortex (PFC) and dorsal anterior cingulate cortex (dACC). Further, cognitive control is impaired in psychiatric disorders that respond to DBS. In OCD, cognitive control deficits manifest as rigid, inflexible, and repetitive behaviors (Robbins *et al.* 2019).

Similarly, patients with MDD have difficulty shifting their attention away from automatic negative thoughts, or with breaking cycles of anhedonia and behavioral deactivation. Most importantly, clinically effective DBS can improve cognitive control. VC/VS DBS improved response times and augmented control-related PFC activity in a mixed sample of MDD and OCD patients (Widge, Heilbronner, *et al.* 2019). STN DBS in OCD had similar results, with improved performance on an extradimensional set-shifting task (Tyagi *et al.* 2019). Interestingly, these results suggest that DBS in psychiatric disorders may have a different mechanism of action than in movement disorders, despite using essentially the same stimulation settings. DBS for movement disorders is commonly believed to disrupt the function of pathologically hyper-connected motor circuitry (de Hemptinne *et al.* 2015, Herrington *et al.* 2015). The cognitive control results argue instead for an augmentation and possibly a hyper-activation of the stimulated networks.

More importantly, these results suggest a new approach to DBS: directly targeting cognitive deficits underpinning mental disorders, rather than the overt symptoms that arise from those deficits. Common DBS programming algorithms emphasize immediate mood or anxiety response, often seeking a phenomenon resembling a brief euphoria (Widge and Dougherty 2015). It is not clear that this is desirable – the opposite of depression or anxiety is not a state of active happiness, but a quiet contentment with an ability to buffer occasional setbacks. The current subjective process may not identify stimulation parameters that could, in the long run, be more likely to lead patients to euthymia. In fact, it may encourage the development of DBS-related psychological complications such as hypomania (Widge *et al.* 2016). Conversely, a reliable non-subjective way to assess outcomes in DBS patients might greatly improve cross-institutional standardization and thus outcomes (Fantino and Moore 2009, López-Pina *et al.* 2015, Raymaekers *et al.* 2017, Pycroft *et al.* 2018, Widge, Malone, *et al.* 2018). To that end, it is now feasible to measure cognition (as read out by standard laboratory cognitive tasks) in real time, and to adjust stimulation in response to cognitive changes (Widge *et al.* 2017, Ezzyat *et al.* 2018, Hampson *et al.* 2018, Yousefi *et al.* 2019). Automatic programming of DBS for tremor (in response to automatic tremor detection through a wristwatch) has already been demonstrated, paving the way for similar approaches in cognition (Malekmohammadi *et al.* 2016). Recent work from our group has demonstrated this real-time detection and enhancement specifically for cognitive control (Basu *et al.* 2020). That specific executive function is, however, only one “ingredient” in the complex “recipes” of cognitive and emotional dysfunctions that produce treatment-resistant MDD and OCD. A critical next step would be expansion to other domains of function, such as negative-valence affect perception, reward insensitivity, or uncertainty estimation (Admon and Pizzagalli 2015, Braunstein *et al.* 2017, Vaghi *et al.* 2017). Similarly, it will be important to develop psychometrically valid measures of these domains, i.e. measures that are both test-retest reliable within individuals and that display change with intervention. This has partially been done for the cognitive control example (Henderson *et al.* 2012), but in general, standard laboratory tasks are not well optimized to capture this kind of endophenotype (Enkavi *et al.* 2019).

4.3. From cognitive networks to network oscillations

Even if a focus on cognition makes DBS programming more objective, it leaves a deeper question open: how does DBS alter brain activity to achieve useful cognitive effects? This question reveals a core limitation of all of the clinical work to date: a very limited exploration of the vast space of neurostimulation parameters. DBS parameters for MDD and OCD are largely derived from those used in Parkinson disease (Dayal *et al.* 2017). In Parkinson disease (PD), frequencies above 130–185 Hz typically add no benefit and consume excessive energy from the DBS battery. Frequencies below 50 Hz have no significant effect on symptoms, and frequencies between 5 and 10 Hz actually worsen motor symptoms when compared to no stimulation. Thus, PD DBS is usually delivered in the 100–130 Hz range. 130 Hz in particular strikes a balance between power consumption and symptom reduction (Ramasubbu *et al.* 2018). Because 130 Hz DBS is known to be relatively safe, it has been the anchor for all psychiatric trials. However, there is no reason why psychiatric circuits involving association cortex would have the same frequency response as degenerated motor circuits linked to the STN. If the standard stimulation is not well-suited to every individual, it could explain why individuals stimulated in the same anatomical location can have such varied response levels. With recent advances in technology, it has become possible to record patients' brain activity directly from the DBS lead for long periods of time, often over a year (Stanslaski *et al.* 2012). In a recent psychiatric example, investigators showed local field potential (LFP) spectral changes over time during SCC DBS for MDD (Veerakumar *et al.* 2019), although it was difficult to demonstrate a clear and consistent correlation between any individual LFP feature and the clinical outcome.

That difficulty may arise from the same problem just highlighted with DBS programming: constructs such as "depression" are subjective and difficult to quantify. It is thus similarly difficult to find reliable physiologic correlates of symptoms (Widge, Bilge, *et al.* 2018), let alone to demonstrate that those correlates change in response to a particular DBS setting change. On the other hand, shifting the focus to cognitive deficits may also be helpful in overcoming this challenge. First, well-defined cognitive constructs (e.g., cognitive control, reward sensitivity, or negative affective bias) can be studied across species (Monteggia *et al.* 2018). This raises the possibility of modeling a specific construct in a non-human animal, performing an exhaustive search to identify a region of DBS parameter space that is well-suited to modulate that construct (and/or its neural correlates), then focusing patients' DBS programming around variants of those parameters (paired with a corresponding behavioral readout). For example, the balance between reward and threat perception can be assessed in approach-avoidance paradigms, some of which have shown good translation across species (Sierra-Mercado *et al.* 2015, LeDoux *et al.* 2017, Diehl *et al.* 2019, Zorowitz *et al.* 2019). Recent work from our lab suggests that circuit responses to DBS-like neurostimulation are sufficiently consistent across individuals to make this paradigm feasible (Basu *et al.* 2019). Similar approaches have been highly helpful in advancing DBS for movement disorders (Vitek and Johnson 2019).

Focusing on cognitive networks also suggests a potential physiologic target for creating more effective psychiatric DBS: rhythmic oscillations of the local field potential (LFP), and particularly the synchrony of those oscillations across brain regions. LFP oscillations,

especially in frequencies below 25 Hz, are often synchronized even when the oscillating structures are relatively distant from each other. A popular (if debated) theory considers LFP oscillations as organizers of the brain, synchronizing brain regions together into networks to execute complex tasks (Whitman *et al.* 2013, Fries 2015, Smart *et al.* 2015). In support of that theory, higher LFP synchrony correlates with better cognitive function across a wide range of species and assays (Schmidt *et al.* 2018, Widge and Miller 2019). Moreover, effective DBS modulates oscillations and their synchrony. This has long been recognized in movement disorders (Little & Brown, 2012), but recent psychiatric studies have also shown network-level oscillatory changes from DBS at psychiatric targets (Veerakumar *et al.* 2019). Continuing the theme that DBS may be more effective if it is titrated based on an objective marker, these physiologic changes are promising targets for a rational approach to psychiatric DBS. Multiple such strategies have found early clinical success in tremor-related disorders (Ramirez-Zamora *et al.* 2019, 2020), and there are prototypes of algorithms designed to control mood-related biomarkers (Sani et al., 2018; Yang et al., 2018). An even more advanced approach might be to link stimulation not to the presence or synchrony of LFP oscillations, but to the phase of individual oscillatory waves. This phase-locked stimulation can powerfully suppress or entrain communication across a network (Blackwood *et al.* 2018, Grado *et al.* 2018, Nadalin *et al.* 2019). In the near future, it should be possible to directly manipulate individual connections within putative cognitive or disease-related networks, improving on the distributed and non-specific effects of high-frequency DBS. It should be noted that the concept of manipulating network oscillation to treat psychiatric disorders is not exclusive to DBS. It has been explored in other non-invasive brain stimulation and in antidepressant pharmacotherapy (Leuchter *et al.* 2015) although this literature is complicated and presents some methodological issues (Widge, Bilge, *et al.* 2018).

5. Conclusion

Psychiatric DBS is a promising clinical and research technique, but still needs to establish a strong clinical evidence base. Much of the recent research effort has emphasized anatomic refinement, moving from targets defined by standard stereotaxic coordinates to imaging-based, patient-specific anatomy. A pure focus on anatomy, however, has not reliably yielded high response rates, and still leaves us with little understanding of why DBS works and for which patients. We propose that a focus on those mechanisms, and particularly on cognitive functions known to be linked to current DBS targets, may be a more productive next step. Emphasizing cognition and objectively measurable processes may aid in biomarker discovery, animal modeling, and near-term clinical programming. This, in turn, could bring us closer to DBS practitioners' vision of a highly precise, personalized treatment for mental illness.

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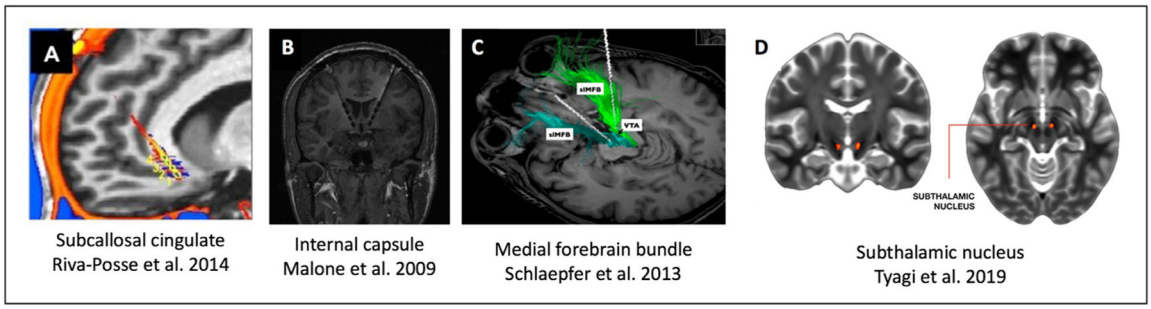

Fig. 1.

Illustrations of the four DBS targets targeted in RCTs for treatment of OCD and MDD. (A) Subcallosal Cingulate (SCC) (B) Internal Capsule (VC/VS) (C) Medial Forebrain Bundle (MFB) (D) Subthalamic Nucleus (STN).

Table 1

Randomized Controlled Trials of DBS for Depression

Study	N	Target	Stimulation Settings	Responder Criteria	Remission Criteria	At End of Trial Responders | Remitters	Primary Study Endpoint Met?	
Subcallosal Cingulate (SCC) (Holtzheimer *et al.* 2017)	90	SCG	130 Hz	≥ 40% reduction in MADRS from baseline	MADRS ≤ 10	*Control Group*: 5 (17%) *Treatment Group*: 12 (20%)	*Control Group:2* (7%) *Treatment Group:3* (5%)	No
Internal Capsule (VC/VS) (Dougherty *et al.* 2015)	30	VC/VS	Variable, primarily 130 Hz	≥ 50% reduction on MADRS from baseline	Not assessed	*Control Group: 3 (20%) Treatment Group: 2 (14.3%)*	N/A	No
(Bergfeld *et al.* 2016)	25	vALIC	130 Hz–180 Hz	≥50% reduction of the HAM-D-17 score compared with baseline	Not assessed	10 (40%)	N/A	Yes
Medial Forebrain Bundle (MFB) (Fenoy *et al.* 2016)	4 *(Ongoing)*	MFB	130 Hz	50% improvement on MADRS	Not assessed	3 (75%)	N/A	Ongoing
(Coenen *et al.* 2019)	16	siMFB	130 Hz	≥ 50% reduction in MADRS	MADRS < 10	16 (100%)	8 (50%)	No

Table 2

Randomized Controlled Trials of DBS for Obsessive Compulsive Disorder

Study	N	Target	Stimulation Settings	Responder Criteria	Remission Criteria	At End of Trial Responders | Remitters	Primary Study Endpoint Met?	
Internal Capsule (VC/VS)								
(Abelson et al., 2005)	4	Internal Capsule	130 Hz–150 Hz	≥ 35% decrease in Y-BOCS	Not assessed	25% (1)	N/A	No
(Goodman et al., 2010)	6	VC/VS	130 Hz–135 Hz	≥ 35% decrease in Y-BOCS AND final Y-BOCS score ≤ 16	Not assessed	67% (4)	N/A	Yes
(Luyten, Hendrickx, Raymaekers, Gabriels, & Nuttin, 2016)	24	Internal Capsule	85 Hz–130 Hz	≥ 35% decrease in Y-BOCS	Not assessed	67% (16)	N/A	Yes
(Barcia et al., 2019)	7	Internal Capsule	130 Hz	≥ 35% decrease in Y-BOCS	Not assessed	85% (6)	N/A	No
Subthalamic Nucleus (STN)								
(Mallet et al., 2008)	8	Subthalamic Nucleus	130 Hz	≥ 25% decrease in Y-BOCS	Not assessed	75% (6)	N/A	Yes
Combined VC/VS and STN								
(Tyagi et al., 2019)	6	VC/VS (Internal Capsule) and STN	130 Hz	≥ 35% decrease in Y-BOCS	Not assessed	100% (6)	N/A	Yes