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Improving long term patient outcomes from deep brain stimulation for treatment-refractory obsessive-compulsive disorder

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Abstract

Introduction: Deep brain stimulation (DBS) has emerged as an effective treatment for patients with severe treatment-refractory obsessive-compulsive disorder (OCD). Over the past two decades, several clinical trials with multiple years of follow-up have shown that DBS offers long-term symptom relief for individuals with severe OCD, though a portion of patients do not achieve an adequate response.

Areas covered: This review sought to summarize the literature on the efficacy and long-term effectiveness of DBS for OCD, and to identify strategies that have the potential to improve treatment outcomes.

Expert opinion: Although this literature is just emerging, a small number of DBS enhancement strategies have shown promising initial results. More posterior targets along the striatal axis and at the bed nucleus of the stria terminalis appear to offer greater symptom relief than more anterior targets. Research is also beginning to demonstrate the feasibility of maximizing treatment outcomes with target selection based on neural activation patterns during symptom provocation and clinical presentation. Finally, integrating DBS with post-surgery exposure and response prevention therapy appears to be another promising approach. Definitive conclusions about these strategies are limited by a low number of studies with small sample sizes that will require multi-site replication.

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Declaration of interest

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Keywords

DBS; OCD; neuromodulation; depression; nucleus accumbens; internal capsule; ventral capsule; ventral striatum; subthalamic nucleus; stria terminalis

1. Introduction

1.1. Brief history

Deep brain stimulation (DBS) has emerged as an effective therapy for patients with severe treatment refractory obsessive-compulsive disorder (OCD) [1,2]. Deep brain stimulation was initially proposed as an alternative to capsulotomies in 1999, which had been the only surgical option for patients with treatment-resistant OCD for several decades [3]. Compared with neuroablation, DBS has the benefit of being reversible, more targeted to a specific anatomical location, and adjustable after the initial surgery. Nuttin and colleagues [4] initially tested DBS in four patients with OCD in the anterior limbs of the internal capsule (ALIC), the same anatomical target as prior capsulotomies for OCD. Since their promising initial report, several groups have tested DBS for OCD with different anatomical targets and over multiple years of follow-up. This growing body of research has allowed investigators to begin asking questions about treatment optimization through understanding predictors and moderators of treatment outcome, as well as examining different treatment enhancement strategies. The goal of this review is to summarize the efficacy, safety, and long-term clinical outcomes of DBS for patients with OCD, and to review strategies that may hold promise in improving DBS outcomes.

1.2. Neurobiological mechanisms underlying treatment

The 1980s – 1990s saw the emergence of cortico-striato-thalamo-cortical (CSTC) loop models of OCD, which describe how these regions functionally connect to coordinate behavior and affect relevant to OCD [5–7]. Various CSTC loop models have been studied, each responsible for different aspects of motor, emotional, and affective behavior. Within each loop, direct and indirect networks promote and inhibit the described behavior, respectively, such that a balanced state may be achieved. In particular, CSTC loops that incorporate the prefrontal cortex may be dysfunctional and hyperactive in patients with OCD, leading to an imbalance between the direct and indirect pathways, thereby driving subsequent uncontrolled, repetitive obsessions and compulsions [8,9]. More recent work has built off of these theories to emphasize other brain areas that appear to be dysfunctional in patients with OCD. These regions include limbic circuitry, the hypothalamus, and the amygdala [10,11]. Although various targets have been proposed in DBS for OCD, the majority have intervened on the CSTC at or near the ventral striatum [12–14].

1.3. The need for deep brain stimulation

Although evidence-based pharmacological and psychosocial treatments for patients with OCD exist, many patients do not achieve an adequate response even after multiple medication trials and intensive evidence-based therapy. Cognitive-behavioral therapy with exposure and response prevention (CBT-ERP) has the strongest evidence-base in the

psychosocial treatment of people with OCD [15], while the serotonin reuptake inhibitor (SRI) clomipramine as well as several selective SRIs have demonstrated efficacy in the treatment of OCD [16]. Regardless, a recent meta-analysis found that approximately 20% of patients do not adequately respond even to combined behavioral-psychopharmacologic treatment [15]. Antipsychotic medication and more intensive CBT-ERP can be used to augment treatment non-responders to CBT-ERP and SRIs [17–19], however, even augmented treatments do not benefit all patients. Noninvasive brain stimulation interventions are also beginning to be studied as an OCD treatment augmentation [20], and repetitive transcranial magnetic stimulation has recently received Food and Drug Administration approval to market for OCD [21]. Noninvasive brain stimulation is just beginning to be studied in this population, however, and thus follow-up data and clinical expertise in long-term symptom management are less clear. Further, while noninvasive procedures may be more approachable for many patients, they cannot target deeper neuroanatomical regions that are relevant in OCD pathology, and thus may result in less robust effects compared with DBS. Anterior capsulotomies have also been shown to be effective, but unlike DBS, these procedures are non-reversible and cannot be adjusted post-surgery. Understanding how to optimize DBS is critical to enhance long-term outcomes for the many patients who have exhausted all other treatment options.

2. Efficacy and safety of deep brain stimulation

We searched the literature using PubMed and Google Scholar for all studies documenting the effectiveness of DBS for individuals with OCD, as well as reference sections from recent reviews of DBS for OCD [1,2]. We excluded single case studies in the present review, but due to the relatively few reports on DBS for OCD, case series were included.

2.1. Efficacy compared with sham stimulation

Seven randomized sham-controlled trials were identified and are summarized in Table 1. The main outcome, OCD severity, was assessed by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [22] in every trial. Six trials followed a randomized crossover design, with patients randomly assigned to ‘on-off’ or ‘off-on’ sequences of stimulation [13,14,23–26]. One trial used a staggered-onset design [27]. Every trial reported lower mean Y-BOCS severity in the on condition relative to the off condition as assessed immediately following the stimulation period, though this difference only reached statistical significance in three of the six studies that employed significance testing (one study did not use significance testing due to a sample size of 4 patients [23]). Although three of these trials did not demonstrate statistically significant superiority of active vs. sham DBS, they all showed lower Y-BOCS scores in the active groups, and significant declines in Y-BOCS scores during the open phases of the trial (see ‘Long term clinical significance’ section) [24,26,27]. The three studies with relatively larger sample sizes (n s = 14–17) showed significant differences between sham and active DBS settings (differences in average post-DBS Y-BOCS scores of 8, 9, and 11 points) [13,14,25]. The three studies with significant OCD outcomes also tested depressive symptoms, with a corresponding significant improvement in short-term depressive symptoms in the on vs. off conditions in each [13,14,25]. Two studies also

assessed functional impairment using the Global Assessment of Functioning (GAF) [13,25], finding significantly higher functioning in the on vs. off conditions.

In sum, randomized, sham-controlled trials of DBS for OCD have shown that active DBS is associated with significant OCD symptom reduction. The three largest trials of DBS for OCD have demonstrated that active DBS is superior to sham stimulation, though smaller trials ($n < 10$) have been underpowered to detect significant differences.

2.2. Long term clinical significance

Nineteen studies investigating long-term outcomes of DBS for OCD are summarized in Table 2. Studies varied widely in their follow-up duration: all but one study included at least one year of follow-up and extended as far as 192 months post-implantation. Most studies fell within one and three years of follow-up ($k = 11$), though they often followed patients over varied amounts of time. Long-term outcomes of DBS also varied widely across studies; percent change in Y-BOCS scores ranged from 20% to 66%, and rates of treatment response using a 35% Y-BOCS reduction criterion ranged from 25% to 100%. Averaging treatment response rates from the longest follow-up point of each trial showed a pooled treatment response rate of 62%.

Five studies in particular have investigated long-term follow-up with larger sample sizes ($Ns = 14$ –26 compared to fewer than 10 in smaller studies), and give a more narrow range of estimates of treatment response rates and Y-BOCS reduction [12–14,28,29]. Follow-up durations for these four studies ranged from 12 to 48 months (though one study also had an open follow-up that was as long as 192 months [13]). Below, we report response rates based on intent-to-treat samples.

Denys and colleagues [14] followed 16 patients in their randomized crossover trial of bilateral NAcc DBS for 21 months of follow-up, finding a treatment response rate of 56%, and a mean reduction of Y-BOCS scores by 46%. Greenberg et al. [12] followed 26 patients across four collaborating sites that all targeted the ventral capsule and ventral striatum (VC/VS) three-years post-implantation, finding a response rate of 62%, and an average of 39% improvement in Y-BOCS scores. One of those sites [13] conducted their own follow-up with a subset of the patients included in the Greenberg follow-up, as well as a larger sample of their own patients, many of whom had stimulation of the bed nucleus of the stria terminalis (BNST) in addition to ALIC DBS. Their 24 patients showed a response rate of 67%, with a 66% Y-BOCS reduction at 4-year follow-up and a 45% reduction at the last follow-up, which was as many as 16 years post-implantation. Huys et al [29] followed 20 patients with DBS of the anterior limbs of the internal capsule (ALIC) for 12 months, finding a 40% treatment response rate and mean Y-BOCS reduction of 33%. Finally, Mallet and colleagues [28] assessed 14 patients who were enrolled in their randomized cross-over trial targeting the subthalamic nucleus (STN) at 16-month and 46-month follow-up. They found a treatment response rate of 64% based on a 35% Y-BOCS reduction, with a 52% mean Y-BOCS reduction at their 46-month assessment [28].

Taken together, these long-term follow-up studies suggest positive long-term outcomes from DBS for a substantial proportion of patients with treatment-refractory OCD, with clinically

significant improvement in OCD severity observed across studies for the majority of patients. They also suggest, however, notable non-response rates, with 38% of patients not meeting criteria for treatment response.

2.3. Secondary outcomes: comorbidity and functional impairment

Table 2 also summarizes information about changes in comorbid psychiatric symptoms, as well as changes in global functioning and functional impairment.

2.3.1. Depressive symptoms—Of the twelve studies that assessed depressive symptoms across time, ten reported statistically significant improvements, corresponding with improvement as high as 67% in depressive symptoms. Though one study reported an increase in depressive symptoms [30], this study reported a long-term follow-up of a cohort of six patients in which declines in depressive symptoms were noted at two other follow-up points [12,26]. Thus, this finding likely reflects the waxing and waning nature of depressive episodes among patients with severe OCD in DBS treatment. As described in the ‘Adverse event and side-effects’ section, increases in depressive symptoms are among the most common adverse events following DBS, often due to battery depletions or interruptions, though these must be considered in the context of significantly improved overall depressive symptoms reported in 10 of 12 studies that have tracked these symptoms across time.”

2.3.2. Anxiety—Eight studies also investigated measures of anxiety across time. Of the six that conducted statistical tests of anxiety improvement across time, five found significant reductions. Mean and median improvement in global measures of anxiety in the two studies with the largest sample sizes were 59% and 58%, respectively [12,13], indicating that significant relief from general anxiety symptoms may be another benefit of DBS for OCD (though one study of ALIC and NAcc DBS did not report significant changes in broad-based anxiety [29]).

2.3.3. Substance use disorders—One case series followed three patients with comorbid substance use disorders across three years, all three of whom continued struggling with substance use and reported no decline in urges, including one patient who died from an overdose [31]. It is worth noting, however, that a follow-up of patients with NAcc DBS for depression, anxiety, and OCD, described smoking cessation in 3/10 patients who were smokers pre-op without any other interventions targeting smoking [32].

2.3.4. Functional impairment—Ten studies used the GAF to assess overall functioning. Mean GAF ratings at baseline ranged from 35 to 44, and finished between 53 to 65. Three long-term follow-up studies with larger samples investigated changes in GAF, describing mean or median improvements of 24–30 points on the GAF. Two studies used the Sheehan Disability Scale [33] to investigate changes in functional impairment across time, finding significant improvements in social and family domains in both studies [14,34] and significant improvement in work functioning in one [14]. The study that did not find significant improvement in work functioning only included five patients. Two other studies that followed the same cohort of six patients found significant improvements in the General Health Perceptions and Social Functioning subscales of the Medical Outcomes Survey:

Short-Form-36 [35] at 12-month follow-up and in the Work/School activities subscale at 73–112 month follow-up.

Overall, these data suggest that DBS for OCD can confer significant benefits for co-occurring depressive and anxiety symptoms, overall functioning, and quality of life, though DBS does not appear to improve substance use problems.

2.4. Adverse events

Several adverse events (AEs) were noted in the above follow-up studies. Although there are often striking intraoperative effects of DBS (e.g. affective changes, autonomic changes, sensations such as smells and tastes [36]), in the current section we review serious AEs that have been observed to occur on a more sustained basis, in the interest of focusing on long-term outcomes.

2.4.1. Depression and suicidality—The most commonly reported severe AEs were depressive episodes and suicidal ideation. Depressive disorders are the most prevalent comorbid psychiatric conditions among people with OCD [37]; although DBS for OCD often corresponds with improvements in depressive symptoms in the long-term, major depressive episodes are common, and have often been linked to DBS battery depletions [23,28,29] or ‘off’ phases of cross-over trials [38]. An acute rebound of depressive symptoms has been observed to onset even more quickly than OCD symptoms following battery depletion [12]. These episodes were reported to occur in those with a history major depressive disorder (MDD), and generally did not exceed the severity of pre-surgical depressive episodes. Thus, these episodes could be considered both ‘disorder-related,’ as they were tied to pre-surgical psychopathology, as well as ‘DBS-related,’ as they often corresponded with changes in stimulation. These episodes were often severe, requiring hospitalization in multiple cases [23,24].

Suicidal ideation has also been commonly reported [12,13,23,24,29]. There were also eight suicide attempts noted in follow-up studies [13,28], including one death by suicide. In the case of the suicide, the investigators stated that the patient left a note prior to her death, in which she conveyed that life stressors primarily contributed to her suicide, rather than obsessive-compulsive symptoms or DBS [23].

2.4.2. Rebound of obsessive-compulsive symptoms—Similarly, a rebound of obsessive-compulsive symptoms were often observed when batteries were depleted or stimulation was not active [12,39]. Though one of the more commonly reported AEs, rebound symptoms were generally resolved with appropriate battery or settings changes, though these symptoms were noted to result in a hospitalization in one case [27].

2.4.3. Mania and hypomania—A spontaneous elevated mood is one of the most striking positive intraoperative effects of DBS for OCD, though more sustained hypomania, disinhibition, impulsivity, and even true mania have also been reported [24,29,40,41]. Huff et al. [24] described two patients out of ten with NAcc DBS to have hypomania episodes that last several days, and Greenberg et al. [12] described one episode of problematic hypomania and one episode of true mania out of 26 patients. Huys et al. [29] reported one hypomanic

episode in their twenty patients with ALIC and NAcc DBS. These data would suggest a relatively high prevalence of hypomania following DBS for OCD. Transient hypomania and/or impulsivity (30 minutes to 2–3 days) that did not correspond with overt problematic behavior was more commonly reported than full manic episodes and also generally resolved with stimulation reductions [12,14,28].

2.4.4. Procedure-related—Procedure-related adverse effects were rare and typically resolved without intervention. Hemorrhages were noted in rare cases (e.g. two instances each in Greenberg and colleagues' and Luyten and colleagues' follow-ups [12,13] and one in the study conducted by Mallet et al. [28]). Though they typically resolved without intervention, one case of a hemorrhage resulted in a permanent finger palsy [25]. Superficial infections following surgery were also noted occasionally and also resolved with minimal intervention (e.g. antibiotics [12]). One seizure during surgery was noted; phenytoin was prescribed prophylactically and no further seizures were noted post-implantation [12].

2.4.5. Device-related—Adverse events related to the DBS device were also rare. In one case each, Greenberg and colleagues [12] reported a break in a stimulation lead, an extension cord replacement, and discomfort with feeling the neurostimulator or extension leads in the chest. Others also occasionally reported patients' discomfort with the stimulator [42].

2.4.6. Therapy-related—Other sustained therapy-related AEs were occasionally reported, including self-reported cognitive issues like forgetfulness, mental sluggishness, and word-finding difficulties [14,24,29], though it is worth noting that the largest DBS for OCD trials have not found evidence for objectively measured neuropsychological sequelae of stimulation [12,25,29,43]. The other most commonly reported adverse events include weight gain [13,29,40], increased libido [13,14], and changes in sleep [13,24,29,30]. Finally, Luyten et al. [13] reported two instances of tonic-clonic seizures, as well as three partial epileptic seizures.

2.4.7. Summary of adverse events—In sum, a rebound of OCD or depressive symptoms, as well as hypomania, appear to be the most common clinically significant AEs that require clinical attention. Depleted or interrupted batteries have been frequently noted to cause a rebound of OCD or MDD, while excessive stimulation sometimes results in cases of hypomania or mania.

3. Possible predictors of deep brain stimulation effectiveness

Due to small sample sizes in DBS for OCD studies to date, it has been difficult to investigate predictors and moderators of long-term outcome, though preliminary investigations have begun to test patient and DBS-level predictors.

3.1. Clinical predictors

Huys and colleagues [29] tested a number of outcome predictors, not finding evidence for any of their tested variables, including OCD severity, OCD subtype, personality pathology, gender, or other OCD-specific characteristics assessed with single items on the Y-BOCS

(e.g. avoidance, insight). To our knowledge, two other studies have investigated baseline clinical predictors of outcome. The first found that an earlier age of OCD onset was associated with improved outcomes, but that baseline depression, broad-based anxiety, and age at surgery were not [28]. The second study used linear growth modeling to track symptom change over time, finding that greater pretreatment depressive symptoms corresponded with less improvement [44]. OCD illness duration, age of onset, and gender were not significant predictors [44]. Intraoperative predictors have been tested as well; interestingly, among six patients with ALIC-NAcc DBS, spontaneous intraoperative smiling and laughter was predictive of Y-BOCS reduction, likely reflecting a more potent effect of precise stimulation [36].

Leveraging data from 80 patients across multiple clinical trials, Alonso et al. [1] conducted a meta-analysis examining multiple clinical predictors of response, finding that treatment responders had an older age-of-onset and a greater proportion of sexual/religious symptoms (33% of responders compared with 0% of non-responders). Other symptom dimensions, anatomical target, age-at-surgery, duration of OCD, and baseline Y-BOCS were all not found to be significant predictors of response [1]. The finding that age-at-surgery was not a significant predictor of treatment outcome contrasts findings from the Parkinson's Disease DBS literature, which has identified older age as a predictor of less improvement in motor symptoms when off medications [45] and poorer quality of life [46], though this may be due to a smaller number of older adults with OCD DBS."

3.2. Neurocircuitry-based predictors

Unlike essential tremor and other neurological disorders treated with DBS, OCD is remarkably variable in symptom presentation. Obsessions and compulsions might take form in contamination and washing, symmetry and organizing, fears of harm and checking, and forbidden/taboo thoughts [47,48]. Additionally, patients most often present with combinations of these symptoms, or occasionally alternative symptoms altogether [47,48]. Functional MRI (fMRI) data reflects that groups of patients who share particular symptoms demonstrate increased activity in the same regions of the cortex and striatum following presentation of an OCD-relevant stimulus [49]. However, in patients who present with other symptoms, alternative regions of the cortex and striatum are activated [49]. The majority of trials of DBS for OCD have targeted the same regions (see section on lead location below). Thus, the modest differential efficacy of DBS for OCD (~60%) when compared to DBS for essential tremor (~90%) may reflect a limitation of treating a heterogeneous disorder in a homogeneous manner [50,51].

Supporting this hypothesis, one recent study found that targeting a region near the caudate nucleus was more effective in mitigating checking-centered symptoms, while targeting a region near the NAcc was more effective in treating washing-centered symptoms [26]. Additionally, this group found that by combining symptom presentation and fMRI data, they were able to accurately predict the optimal lead location for the best patient outcome [26]. In the Greenberg et al. [12] follow-up of 26 patients with VC/VS DBS, they described treatment response for patients with different primary subtypes of OCD symptoms, finding the highest response rate for patients with intrusive, harm-related thoughts and checking

rituals. Though preliminary due to the low sample size, these findings indicate that VC/VS DBS may be especially effective for patients who primarily present with harm-related OCD. Accordingly, the VS has been particularly implicated in patients with these symptoms [51]. A recent investigation found that while targeting either the VC/VS region or the STN were equivalently effective in mediating obsessive-compulsive symptoms, VC/VS stimulation significantly improved mood, while STN stimulation significantly improved cognitive flexibility [41]. Finally, building off of the idea that DBS enacts its effect by disrupting the flow of neural information, recent work has demonstrated that targeting specific neural pathways can alter specific symptoms in patients with OCD [52,53]. In one recent investigation, Baldermann and colleagues found that connectivity between stimulation targets and the medial and lateral prefrontal cortices was significantly related to symptom reduction among patients with NAcc/ALIC DBS [52].

Thus, symptom presentation and regional activation patterns during obsessive-compulsive symptom provocation appear to be potential predictors of treatment outcomes in patients undergoing DBS for treatment refractory OCD. Moreover, using these data to guide the optimal selection of DBS lead location is a promising direction for study and clinical application.

4. Optimization and augmentation treatments

4.1. Optimization of deep brain stimulation settings and lead target

4.1.1. Settings optimization—The process of optimizing stimulation conditions typically takes 6–12 months. During post-operative programming visits, DBS stimulation parameters are adjusted by an experienced psychiatrist with expertise in both OCD and DBS programming. The device is programmed telemetrically using a handheld tablet. As in DBS for movement disorders, the following stimulation parameters can be adjusted: selection of active contact(s) across the leads, amplitude, frequency, and pulse width. As the number of different possible permutations is enormous, programming algorithms built on prior clinical experience are followed to render this task more manageable. Initially, a monopolar survey is conducted with frequency typically set between 130–150 Hz at a constant pulse width of 90–150 microseconds. Amplitudes are gradually adjusted as tolerated and guided by bedside assessment of mood/affect, the ‘energy,’ or autonomic activation that the patient feels, and the patient’s anxiety. Acute induction of a mirth response is used to guide programming [36]. However, as noted, it is critical not to send the patient home on settings that produce hypomania. Future visits continue to modify stimulation settings while monitoring changes in OCD symptom severity as reflected by changes in Y-BOCS scores. Across time, the psychiatrist increases amplitude and voltage to the highest tolerated settings, as increased total energy output across time corresponds with optimal symptom reduction [24,54].

4.1.2. Comparative efficacy at different targets—Since the first attempt at DBS for OCD in 1999, several lead locations and combinations have been tested with variable efficacy. Yet, several targets have become widely accepted, and trends to guide lead placement have begun to emerge. The majority of these trials have targeted regions that are associated with reward and motivation, mostly within or near the ventral striatum (VS) and

ventral portion of the anterior limb of the internal capsule (ventral capsule, VC). See Figure 1 for a visual depiction of different anatomical targets of DBS for OCD.

The first trial of DBS for OCD targeted the ALIC. Although outcomes were not measured using the standard Y-BOCS metric, making it difficult to objectively quantify symptom improvement, the overall promising results (three out of four patients with symptom improvement) led to dozens of more attempts at using and improving DBS for OCD [4]. The next major attempt targeted the STN, and found active stimulation to be significantly superior to sham in a randomized controlled trial with 14 patients [25]. As noted, this group recently reported positive results in terms of long-term symptom reduction (52%) and response rates (64%) using the 35% Y-BOCS reduction criterion [28].

One study attempted unilateral DBS of the right NAcc, a region within the VS, and found insignificant differences between the active and sham-stimulated patients, and overall less robust symptom reduction (21%) and treatment response rates (40%), thereby providing evidence against unilateral DBS [24]. Subsequent studies targeting the NAcc bilaterally have shown significant efficacy compared with sham and more substantial symptom improvement that has been comparable with other trials (46% Y-BOCS reduction and 56% response rates) [14]. Post-hoc imaging analyses of these cases demonstrated that the active contact in these cases was not actually in the VS, but rather was found in the overlying VC white matter [55]. These findings support the hypothesis that DBS efficacy is primarily derived from network-wide changes gained by effecting a node within the network, rather than solely by the local effects of engaging a single brain region.

The collaborative, multisite effort that investigated DBS of the VC/VS region found significant symptom improvement across time in a large cohort, including a 62% treatment response rate [12]. These promising results with limited serious AEs led to the first Food and Drug Administration Humanitarian Device Exemption for DBS for OCD in 2009. Importantly, they found that posterior targets were more effective in decreasing symptom burden in these patients. From this work it became clear that targeting more posterior regions, specifically at the junction of the anterior capsule, anterior commissure (AC), and posterior VS, produced improved treatment outcomes.

In response to this observation, one of the collaborating sites reported a longer follow-up with a larger cohort of their patients ($n = 24$), with whom they had begun targeting the BNST, just posterior to the AC [13]. They found significantly improved outcomes among patients with BNST DBS, finding a remarkable difference compared with patients with stimulation targeted on the ALIC (80% vs. 17% Y-BOCS response rate).

Recently, a group targeted both the VC/VS and the STN in 6 patients, finding that both regions were effective targets for decreasing OCD severity. However, stimulating the VC/VS region was more effective in also decreasing depressive symptoms in these patients with OCD [41]. Similar to several previous studies, this group also found that the most effective contacts were in the white matter of the ventral ALIC and not in the gray matter of the VS.

Thus, over the course of the last two decades, we have uncovered a number of effective DBS targets near or within the VC/VS, including the ALIC, STN, NAcc, and BNST. More

recently, studies have demonstrated that posteriorly located targets (close to the AC) are more effective in decreasing symptom burden, and that white matter targets may be superior to gray matter targets in improving patient outcomes.

4.1.3. Adaptive DBS—Unlike in the movement disorder field, programming adjustments to the DBS device may not cause an immediately observable effect on the patient's symptoms. Thus, attributing causality to programming changes can be difficult. One current strategy used to handle this challenge is using DBS devices that can both record neural activity and stimulate the region of interest [56]. Recording local field potential activity from the DBS lead can allow for measurements of the local 'brain state.' Algorithms programmed into the DBS device will be trained to detect any relationships that exist between this electrical brain state and the patient's symptom profile. The device can then adjust the stimulation settings automatically to move toward healthy brain states and away from symptomatic ones. These so-called 'adaptive' or 'closed-loop' DBS systems have been proposed [56], and clinical trials are currently underway to develop and test these methodologies (e.g. [NCT03184454](#), [NCT03457675](#)).

4.2. Psychological treatment augmentation

Although it has been observed clinically that patients who qualify and receive DBS benefit from CBT-ERP after DBS [57], this observation has rarely been empirically tested or reported in a systematic way.

The largest study that investigated this question evaluated the effectiveness of CBT-ERP in 16 patients with NAcc DBS [58]. Once settings had been optimized and symptoms were stable for 6 weeks, patients participated in 24 weeks of CBT. Mean Y-BOCS scores declined further after CBT-ERP, falling from 34 to 25 after DBS optimization, and further to 18 after CBT-ERP [58]. However, symptoms rebounded to almost pre-surgical levels after turning off stimulation, indicating that DBS is needed to maintain behavior changes achieved through CBT-ERP.

Two case series of post-DBS CBT-ERP have not replicated the above findings. Abelson and colleagues [23] reported on two patients with NAcc DBS who participated in intensive CBT-ERP after several months of active DBS, with neither experiencing further clinically significant relief. Another case series of 6 patients participated in 12 weeks of inpatient CBT-ERP after 48 months of stimulation [41]. Y-BOCS scores reduced on average from 14 to 9, though this difference did not reach statistical significance [41].

4.3. Psychotropic medication

An additional benefit of DBS is that patients are often able to taper off psychotropic medication in the long-term. Participation in these studies usually requires patients to stabilize medication use before beginning DBS and maintain this use during the first few months of stimulation, though medication changes in the long-term are common.

Two studies have investigated whether changes in medication during DBS are predictive of outcome. Greenberg et al. [12] found that Y-BOCS reductions were greater across 36 months of follow-up among 15 patients with unchanged medication (54%) compared to 11

patients with increased or decreased medications (34%). Another study, however, did not find that medication changes were a significant predictors of outcome [24]. In studies that have tested this hypothesis, patients have changed medication according to clinical judgment rather than in a controlled or standardized protocol, and thus even with significant results, conclusions about causation would not be able to be made.

5. Treatment of psychiatric comorbidity

5.1. Depression and suicidality

Major depressive disorder is the most prevalent co-occurring psychiatric diagnosis among people with OCD [37]. Accordingly, MDD has been the most commonly reported comorbidity in DBS for OCD trials [12,14,25], and as noted, depressive episodes are common even after DBS, particularly when batteries are low. Thus, effective long-term care for patients with depressive symptoms and suicidal ideation should be a primary goal when considering how to improve long-term outcomes.

Most often, depressive symptoms are noted to resolve with setting adjustments or a battery replacement, and thus pre-emptive monitoring of DBS batteries, as well as increasing voltage or amplitude, should be the first line of intervention [23,28,29,38]. Measures should also be taken to ensure that battery depletions occur as infrequently as possible. One possible strategy to reduce the frequency of depressive episodes may be using rechargeable batteries, which have the benefit of lasting much longer before depletion, and thus may correspond with fewer rebound episodes. That said, patients often express a preference for fixed-life batteries due to a fear of forgetting to charge batteries and finding regular battery charges to be cumbersome [59].

Should settings changes not result in significant improvement in depressive symptoms, the evidence-based standard-of-care should be followed, including antidepressant medication and evidence-based psychotherapy, as well as adjunctive pharmacotherapy as needed [60,61]. Continued, regular safety monitoring is also critical, and hospitalizations may be necessary for patients at risk for suicide [23,24].

5.2. Mania and hypomania

Hypomania has been a relatively common adverse event in reports of DBS for OCD targeting the STN [25,40], VC/VS [12,42], and NAcc regions [24,29]. One small study investigated predictors of hypomania among people with DBS for OCD or MDD, finding that female sex and monopolar stimulation on the right side may predict hypomania. These findings, however, are based on less than twenty patients, and thus cannot be used to guide clinical decision-making yet [62]. If not treated early, hypomania may evolve to true mania, and thus vigilant monitoring and intervention are critical [63].

Interrupting stimulation or substantially reducing amplitude or voltage has been the most common approach to managing DBS-related hypomania [62–65]. Benzodiazepines [63], anticonvulsants [62,65], or antipsychotic medication [62] have also been used as indicated. Hospitalizations may also be necessary [63]. At least as important as treating active mania or hypomania may be preventing the onset of these episodes through iterative changes to DBS

settings with a close eye on maintaining the balance between tolerability and therapeutic response, as well as requiring patients to have frequent appointments during setting optimization [12].

6. Conclusion

This review sought to summarize the literature on the efficacy of DBS for OCD, as well as to describe predictors of response and optimization strategies for this therapy. Although active DBS is clearly superior to sham, long-term effectiveness data suggest that approximately 38% of patients are treatment non-responders, and many experience rebounds of obsessive-compulsive and depressive symptoms following battery depletions. DBS is still a relatively new treatment for OCD, and investigation of how to alter or augment this therapy to improve outcomes is preliminary, though a few small studies are beginning to point to some promising approaches.

A refined understanding of the neural circuitry underlying OCD has led to improved target selection and treatment outcomes, though clinical trials are just beginning to test new targets and ways to personalize treatment. One of the most exciting findings has been that more posteriorly targeted stimulation (close to the AC) appears to produce improved treatment outcomes, with targets such as the BNST and VC/VS region near the AC producing greater symptom reduction than more dorsally or anteriorly in the ALIC [12,13]. This incremental change represents one of the first target modifications in DBS for OCD and may foreshadow new targets in the years to come that will lead to even better clinical outcomes.

Treatment will likely be further bolstered by personalizing stimulation parameters based on individual clinical and neuroimaging data. This is particularly important among people with OCD, who show heterogeneous symptoms and patterns of neural activity along cortico-striato-thalamo-cortical loops. Personalizing contacts along the striatal axis based on fMRI data maximized therapeutic response in a recent pilot study, raising considerable interest in larger studies of this nature in the future [26].

Emphasizing a biopsychosocial perspective of OCD into DBS treatment may help improve treatment outcomes as well. CBT-ERP has been proven to be effective for most people with OCD, though people with severe manifestations of the disorder may not be able to engage in or tolerate this treatment. The ability of patients to participate in CBT-ERP after initial improvement from DBS may be one of the greatest benefits of this therapy, and initial data support an incremental benefit of participation in CBT-ERP after DBS optimization [58].

When considering how to improve long-term outcomes, providers should also consider managing psychiatric adverse events, most prominently depressive and hypomanic symptoms that may emerge. Innovations that will allow providers to preemptively renew implantation or increase stimulation before the onset of significant depressive episodes may help improve outcomes one step further. Equally challenging may be preventing hypomanic episodes; intraoperative changes in positive affect have been one of the only documented predictors of improved long-term outcomes, but positive affective changes may also be a

precursor to hypomania. Learning to better predict and detect the onset of hypomanic or manic episodes will be another important area for the future.

7. Expert opinion

Although recent efforts to improve DBS for OCD have been met with promising results for improving target selection and treatment augmentation, DBS for OCD is still a fairly recent development and studies to date have been limited by relatively small sample sizes. The largest trials have had less than 30 participants, limiting our ability to determine whether optimization strategies would produce reliable improvements for individual patients. Comparatively, multiple medication and CBT trials for OCD have exceeded 100 patients, including several augmentation trials that seek to improve standard treatment [15]. Though the number of people requiring DBS for OCD is only a small fraction of those who would pursue first-line OCD therapies, our understanding of how to improve outcomes has unfortunately been limited by these sample size restrictions. Randomized head-to-head comparison trials of different stimulation targets may be an important next step.

Personalizing stimulation based on individuals' circuitry dysfunction and clinical presentation continues to be an exciting area for future research, and may expand beyond traditional symptom presentations (e.g. harm vs. symmetry vs. contamination), and may move instead to dimensions of behavior that are more reliably tied to neural circuits and cut across diagnoses [66]. The Research Domain Criteria has encouraged mental health research to focus on how neural circuits are connected to dimensions of behavior, rather than diagnostic categories, and thus refocusing OCD DBS research on personalizing targets to specific behaviors (e.g. overt behavioral habits vs. avoidance) may offer a promising future avenue [66]. Relief of OCD symptoms will still be the primary goal, but targeting individual deficits that more specifically map onto neural circuits could help personalize treatment even further [66].

One obstacle to pursuing research with larger sample sizes and providing DBS to more patients with treatment-refractory OCD is the difficulty of obtaining reimbursement for these procedures in most countries, despite its approval for use in both Europe and the United States. Until reimbursement for OCD DBS becomes more universal, continuing to pursue multi-site trials that have the ability to recruit larger numbers of patients will be imperative to more definitively test ways to improve DBS.

Even with these advances, some of the most important considerations in maximizing DBS outcomes lie in clinical experience rather than systematic research. For example, understanding how to optimize stimulation without producing hypomania is a skill that comes from extensive training in clinical psychiatry as well as DBS. Further, managing OCD and MDD rebound episodes that occur following battery depletions is one of the most frequent challenges for OCD DBS practitioners, and can be best addressed with interdisciplinary clinical teams experienced in both neurosurgery and mental health.

Another clinical reality in DBS for OCD that has not been systemically studied is the possible importance of lifestyle rehabilitation and ongoing evidence-based psychosocial

support. Although CBT-ERP trials generally test short-term treatment, patients often stay in therapy much longer, particularly those with more severe OCD who do not achieve an initial positive response. Patients with OCD who require DBS often have so much of their life taken up by obsessions and rituals that other parts of their life have been completely neglected. As a result, they often face tremendous occupational and psychosocial impairment. Beyond short-term CBT-ERP that can help patients break the cycle of obsessions and compulsions, lifestyle-level rehabilitation and ongoing evidence-based psychosocial support are often critical to improving quality of life after DBS. Thus, in addition to pursuing research that will help identify more effective DBS targets, improving DBS outcomes will also depend on interdisciplinary clinical teams that can provide long-term comprehensive biopsychosocial care.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Alonso P, Cuadras D, Gabriëls L, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *Plos One*. 2015;10(7):e0133591. [PubMed: 26208305] • This meta-analysis pooled outcome data from over 100 patients, the largest analysis of OCD DBS outcomes to date.
2. Vázquez-Bourgon J, Martino J, Sierra Peña M, et al. Deep brain stimulation and treatment-resistant obsessive-compulsive disorder: A systematic review. *Rev Psiquiatr Salud Ment Engl Ed*. 2019;12(1):37–51.
3. Greenberg BD, Price LH, Rauch SL, et al. Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues. *Neurosurg Clin N Am*. 2003;14(2):199–212. [PubMed: 12856488]
4. Nuttin B, Cosyns P, Demeulemeester H, et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet*. 1999;354(9189):1526. •• This was the first report of DBS for OCD.
5. Saxena S, Brody AL, Schwartz JM, et al. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br J Psychiatry*. 1998;173(S35):26–37.
6. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*. 1986;9(1):357–381. [PubMed: 3085570]
7. Rauch SL, Jenike MA. Neurobiological models of obsessive-compulsive disorder. *Psychosomatics*. 1993;34(1):20–32. [PubMed: 8426888]
8. Maia T, Cooney R, Peterson B. The neural bases of obsessive-compulsive disorder in children and adults. *Dev Psychopathol*. 2008;20:1251–1283.
9. McGovern RA, Sheth SA. Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery. *J Neurosurg*. 2017;126(1):132–147. [PubMed: 27035167]
10. Lapidus KAB, Stern ER, Berlin HA, et al. Neuromodulation for obsessive-compulsive disorder. *Neurotherapeutics*. 2014;11(3):485–495. [PubMed: 24981434]
11. Karas PJ, Lee S, Jimenez-Shahed J, et al. Deep brain stimulation for obsessive compulsive disorder: evolution of surgical stimulation target parallels changing model of dysfunctional brain circuits. *Front Neurosci*. 2019;12 DOI:10.3389/fnins.2018.00998. [PubMed: 30778281]
12. Greenberg BD, Gabriëls LA, Malone DA Jr, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry*.

2010;15(1):64–79.. [PubMed: 18490925] •• This study summarized the three-year outcome data from four different sites on VC/VS DBS, finding that more posterior targets led to improved outcomes.

13. Luyten L, Hendrickx S, Raymaekers S, et al. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. *Mol Psychiatry*. 2016;21 (9):1272–1280. [PubMed: 26303665] •• This is the longest follow-up of DBS patients to date, which extended as long as 192 months post-implantation, and found superiority of the BNST compared with the ALIC.
14. Denys D, Mantione M, Figee M, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2010;67(10):1061–1068.. [PubMed: 20921122] • This was a randomized controlled trial supporting the NAcc as superior to sham stimulation
15. Öst L-G, Havnen A, Hansen B, et al. Cognitive behavioral treatments of obsessive-compulsive disorder. A systematic review and meta-analysis of studies published 1993–2014. *Clin Psychol Rev*. 2015;40:156–169. [PubMed: 26117062]
16. Skapinakis P, Caldwell DM, Hollingworth W, et al. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2016;3(8):730–739. [PubMed: 27318812]
17. Gregory ST, Kay B, Smith J, et al. Treatment-refractory obsessive-compulsive disorder in adults: a cost-effectiveness analysis of treatment strategies. *J Clin Psychiatry*. 2018;79:2.
18. Brakoulias V, Stockings E. A systematic review of the use of risperidone, paliperidone and aripiprazole as augmenting agents for obsessive-compulsive disorder. *Expert Opin Pharmacother*. 2019;20 (1):47–53. [PubMed: 30360669]
19. Simpson HB, Foa EB, Liebowitz MR, et al. Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2013;70(11):1190–1199. [PubMed: 24026523]
20. Brunelin J, Mondino M, Bation R, et al. Transcranial direct current stimulation for obsessive-compulsive disorder: a systematic review. *Brain Sci*. 2018;8(2):37.
21. Commissioner O of the. FDA permits marketing of transcranial magnetic stimulation for treatment of obsessive compulsive disorder. FDA. 2019 9 11 [cited 2019 Nov 2]. Available from: <http://www.fda.gov/news-events/press-announcements/fda-permits-marketing-transcranial-magnetic-stimulation-treatment-obsessive-compulsive-disorder>.
22. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown obsessive compulsive scale: I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46(11):1006–1011. [PubMed: 2684084]
23. Abelson JL, Curtis GC, Sagher O, et al. Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2005;57 (5):510–516. [PubMed: 15737666]
24. Huff W, Lenartz D, Schormann M, et al. Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: outcomes after one year. *Clin Neurol Neurosurg*. 2010;112(2):137–143. [PubMed: 20006424]
25. Mallet L, Polosan M, Jaafari N, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *N Engl J Med*. 2008;359(20):2121–2134.. [PubMed: 19005196] • This was a randomized controlled trial demonstrating the superiority of STN stimulation to sham.
26. Barcia JA, Avelillas-Chasín JM, Nombela C, et al. Personalized striatal targets for deep brain stimulation in obsessive-compulsive disorder. *Brain Stimul Basic Transl Clin Res Neuromodulation*. 2019;12(3):724–734..• This study demonstrated that feasibility of optimizing target selection based on fMRI and clinical data
27. Goodman WK, Foote KD, Greenberg BD, et al. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biol Psychiatry*. 2010;67(6):535–542. [PubMed: 20116047]
28. Mallet L, Montcel STD, Clair A-H, et al. Long-term effects of subthalamic stimulation in obsessive-compulsive disorder: follow-up of a randomized controlled trial. *Brain Stimul Basic Transl Clin Res Neuromodulation*. 2019.

29. Huys D, Kohl S, Baldermann JC, et al. Open-label trial of anterior limb of internal capsule-nucleus accumbens deep brain stimulation for obsessive-compulsive disorder: insights gained. *J Neurol Neurosurg Psychiatry*. 2019;90(7):805–812. [PubMed: 30770458]
30. Fayad SM, Guzick AG, Reid AM, et al. Six-nine year follow-up of deep brain stimulation for obsessive-compulsive disorder. *Plos One*. 2016;11(12):e0167875. [PubMed: 27930748]
31. Jiménez F, Nicolini H, Lozano AM, et al. Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. *World Neurosurg*. 2013;80(3): S30.e17–S30.e25.
32. Kuhn J, Bauer R, Pohl S, et al. Observations on unaided smoking cessation after deep brain stimulation of the nucleus accumbens. *Eur Addict Res*. 2009;15(4):196–201. [PubMed: 19622886]
33. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996;11(Suppl 3):89–95.
34. Lee DJ, Dallapiazza RF, De Vloo P, et al. Inferior thalamic peduncle deep brain stimulation for treatment-refractory obsessive-compulsive disorder: A phase 1 pilot trial. *Brain Stimulat*. 2019;12(2):344–352.
35. Ware JE, Sherbourne CD, The MOS. 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473–483. [PubMed: 1593914]
36. Haq IU, Foote KD, Goodman WG, et al. Smile and laughter induction and intraoperative predictors of response to deep brain stimulation for obsessive-compulsive disorder. *NeuroImage*. 2011;54: S247–S255. [PubMed: 20226259]
37. Ruscio AM, Stein DJ, Chiu WT, et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15(1):53–63. [PubMed: 18725912]
38. Nuttin BJ, Gabriëls LA, Cosyns PR, et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery*. 2003;52(6):1263–1274. [PubMed: 12762871]
39. Vora AK, Ward H, Foote KD, et al. Rebound symptoms following battery depletion in the NIH OCD DBS cohort: clinical and reimbursement issues. *Brain Stimulation*. 2012;5(4):599–604. [PubMed: 22305344]
40. Chabardès S, Polosan M, Krack P, et al. Deep brain stimulation for obsessive-compulsive disorder: subthalamic nucleus target. *World Neurosurg*. 2013;80(3):S31.e1–S31.e8.
41. Tyagi H, Apergis-Schoute AM, Akram H, et al. A randomized trial directly comparing ventral capsule and anteromedial subthalamic nucleus stimulation in obsessive-compulsive disorder: clinical and imaging evidence for dissociable effects. *Biol Psychiatry*. 2019;85 (9):726–734. [PubMed: 30853111]
42. Tsai H-C, Chang C-H, Pan J-I, et al. Pilot study of deep brain stimulation in refractory obsessive-compulsive disorder ethnic Chinese patients. *Psychiatry Clin Neurosci*. 2012;66(4):303–312. [PubMed: 22624735]
43. Mantione M, Nieman D, Figee M, et al. Cognitive effects of deep brain stimulation in patients with obsessive-compulsive disorder. *J Psychiatry Neurosci JPN*. 2015;40(6):378–386. [PubMed: 26107159]
44. Raymaekers S, Vansteelandt K, Luyten L, et al. Long-term electrical stimulation of bed nucleus of stria terminalis for obsessive-compulsive disorder. *Mol Psychiatry*. 2017;22(6):931–934. [PubMed: 27480493]
45. Rusmann H, Ghika J, Villemure J-G, et al. Subthalamic nucleus deep brain stimulation in parkinson disease patients over age 70 years. *Neurology*. 2004;63(10):1952–1954. [PubMed: 15557522]
46. Derost PP, Ouchchane L, Morand D, et al. Is DBS-STN appropriate to treat severe parkinson disease in an elderly population? *Neurology*. 2007;68(17):1345–1355. [PubMed: 17452578]
47. Bloch MH, Landeros-Weisenberger A, Rosario MC, et al. Meta-analysis of the symptom structure of obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165(12):1532–1542. [PubMed: 18923068]
48. Abramowitz J, Deacon B, Olatunji B, et al. Assessment of obsessive-compulsive symptom dimensions: development and evaluation of the dimensional obsessive-compulsive scale. *Psychol Assess*. 2010;22(1):180–198. [PubMed: 20230164]

49. Mataix-Cols D, Wooderson S, Lawrence N, et al. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2004;61(6):564–576. [PubMed: 15184236]
50. Limousin P, Speelman JD, Gielen F, et al. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry*. 1999;66(3):289–296. [PubMed: 10084526]
51. Harrison BJ, Pujol J, Cardoner N, et al. Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. *Biol Psychiatry*. 2013;73(4):321–328. [PubMed: 23200527]
52. Baldemann JC, Melzer C, Zapf A, et al. Connectivity profile predictive of effective deep brain stimulation in obsessive-compulsive disorder. *Biol Psychiatry*. 2019;85(9):735–743. [PubMed: 30777287]
53. Liebrand LC, Caan MWA, Schuurman PR, et al. Individual white matter bundle trajectories are associated with deep brain stimulation response in obsessive-compulsive disorder. *Brain Stimulat*. 2019;12(2):353–360.
54. Gabriëls L, Cosyns P, Nuttin B, et al. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatr Scand*. 2003;107(4):275–282. [PubMed: 12662250]
55. van den Munckhof P, Bosch DA, Mantione MHM, et al. Active stimulation site of nucleus accumbens deep brain stimulation in obsessive-compulsive disorder is localized in the ventral internal capsule In: Nikkhah G, Pinsky M, editors. *Stereotactic and functional neurosurgery*. Acta Neurochirurgica Supplement Pondichery, India: Springer Vienna; 2013 p. 53–59.
56. Widge AS, Ellard KK, Paulk AC, et al. Treating refractory mental illness with closed-loop brain stimulation: progress towards a patient-specific transdiagnostic approach. *Exp Neurol*. 2017;287:461–472. [PubMed: 27485972]
57. Dougherty DD, Greenberg BD. The past and future of circuit-based therapies for OCD. *Int OCD Found OCD Newsl*. 2016;30(4):4–6.
58. Mantione M, Nieman DH, Figee M, et al. Cognitive-behavioural therapy augments the effects of deep brain stimulation in obsessive-compulsive disorder. *Psychol Med*. 2014;44 (16):3515–3522. [PubMed: 25065708]
59. Khaleeq T, Hasegawa H, Samuel M, et al. Fixed-life or rechargeable battery for deep brain stimulation: which do patients prefer? *Neuromodulation Technol Neural Interface*. 2019;22 (4):489–492.
60. Greenberg AJ, Freeman MP, Markowitz JC, et al. Practice guidelines for the treatment of patients with major depressive disorder: Third Edition. 2010 [cited 2019 Nov 18]. Available from: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf.
61. McQuaid JR, Lin EH, Barber JP, et al. Clinical practice guideline for the treatment of depression across three age Cohorts American Psychological Association. 2019 6 [cited 2019 Nov 18]. Available from: <https://www.apa.org/depression-guideline/guideline.pdf>.
62. Widge AS, Licon E, Zorowitz S, et al. Predictors of hypomania during ventral capsule/ventral striatum deep brain stimulation. *J Neuropsychiatry Clin Neurosci*. 2015;28(1):38–44. [PubMed: 26404172]
63. Haq IU, Foote KD, Goodman WK, et al. A case of mania following deep brain stimulation for obsessive compulsive disorder. *Stereotact Funct Neurosurg*. 2010;88(5):322–328. [PubMed: 20714212]
64. Luijckes J, Mantione M, van den Brink W, et al. Deep brain stimulation increases impulsivity in two patients with obsess-sive-compulsive disorder. *Int Clin Psychopharmacol*. 2011;26 (6):338–340. [PubMed: 21857527]
65. Tsai H-C, Chen S-Y, Tsai S-T, et al. Hypomania following bilateral ventral capsule stimulation in a patient with refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2010;68(2):e7–e8. [PubMed: 20553748]
66. Widge AS, Deckersbach T, Eskandar EN, et al. Deep brain stimulation for treatment-resistant psychiatric illnesses: what has gone wrong and what should we do next? *Biol Psychiatry*. 2016;79(4): e9–e10. [PubMed: 26212895]

Article highlights

- Sixty-two percent of patients with treatment-refractory OCD are estimated to experience clinically significant long-term treatment response from DBS
- DBS for OCD results in long-term significant reductions in depressive symptoms
- Rebounds of OCD and depressive symptoms following battery depletions or interruptions appear to be the most common adverse events
- Posterior targets along the striatum and at the bed nucleus of the stria terminalis may produce more symptom reduction than more anterior targets
- Preliminary studies suggest that individual patient neural connectivity data may help optimize target selection

Figure 1.
Anatomical targets of deep brain stimulation for obsessive-compulsive disorder

Table 1.

Efficacy of active compared with sham DBS.

Study authors, year	Sample size	Age range; percent male	Anatomical target	Design	Y-BOCS reduction immediately after active vs. sham DBS ^a	Comorbid disorder symptom change	Functional impairment
Abelson et al., 2005 [22]	4	27–52 years-old; 50% male	ALIC	Double-blind on-off staggered design, with two 3-week on phases and two 3-week off phases. Patients were randomly assigned on-off schedule and symptom reduction during on period was compared with that during off period	DBS: 20% Sham: 12% Significant difference: ^b not tested	23% reduction in HAM-D scores during on phase compared with 7% during off phase. Significance testing not conducted. HAM-A scores were noted to track HAM-D scores.	GAF scores improved slightly without notable difference between on and off phases
Huff et al., 2005 [23]	10	25–44 years-old; 60% male	NAcc	Double-blind sham-controlled crossover trial. Patients received 3 months of sham followed by active stimulation or vice versa.	DBS: 13% Sham: 3% Significant difference: ^b ; $p = .21$	Not tested during crossover trial	Not tested during crossover trial
Mallet et al., 2008 [24]	16	29–56 years-old; 59% male	STN	Double-blind sham-controlled crossover trial with 1-month wash-out phase between 3-month on-off phases.	DBS: 41% Sham: 13% Significant difference: ^a ; $p = .01$	Depression was lower during on phase (BDI of 23 vs. 40)	Significantly higher GAF during on phase (56 vs. 43)
Denys et al., 2010 [14]	14	21–59 years-old; 56% male	NAcc	Double-blind crossover trial. Patients were randomly assigned to 2-week on or off conditions after 8 months of open stimulation	DBS: 36% Sham: 11% Significant difference: ^b ; $p < .001$	HAM-D and HAM-A scores were significantly lower during on phase (11 and 12 points lower)	Not reported
Goodman et al., 2010 [26]	6	27–52 years-old; 33% male	VC/VNS	Double-blind randomized staggered-onset trial. Patients were randomly assigned to be turned on or not for 30 days at 30 days post-implantation	DBS: 14% Sham: 0% Significant difference: ^b ; $p = .90$ (assessed at 12 months)	Not tested during staggered-onset phase	Not tested during staggered-onset phase
Luyten et al., 2016 ^c [13]	17	23–59 years-old; 50% male	ALIC/BNST	Double-blind sham-controlled crossover trial. Patients received 3 months of sham followed by active stimulation or vice versa. Patients had several weeks or months of open stimulation first. Phases could be terminated early due to patient suffering.	DBS ^d : 48% Sham ^d : 17% Significant difference: ^b ; $p < .017$	Depression and anxiety significantly improved in the on compared with off phase (HAM-D and HAM-A improvement of 58% and 67% greater, respectively)	Significantly more improvement in GAF scores during on phase (15 point greater improvement)
Barcia et al., 2019 [25]	7	28–46 years-old; 43% male	Caudate or NAcc (personalized along striatal axis)	Compared three stimulation settings: 3 months of sham stimulation; stimulation at the most distal contact on the lead; and stimulation at a “best contact.” Best contact was personalized based on frontal activation during symptom provocation. Lead contacts were selected based on expected projections from the striatal axis to the frontal cortex	DBS (best contact): 47% Sham: 35% Significant difference: ^b ; $p = .06$	No significant differences in anxiety (HAM-A or STAI-T) improvement based on sham vs. single distal contact vs. best contact	Not reported

Note: ALIC = anterior limbs of the internal capsules; BDI = Beck Depression Inventory; BST = bed nucleus of the stria terminalis; DBS = deep brain stimulation; GAF = Global Assessment of Functioning; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; NAcc = nucleus accumbens; OCD; obsessive-compulsive disorder; STAI-T = State Trait Anxiety Inventory - Trait scale; STN = subthalamic nucleus; VC/VS = ventral capsule/ventral striatum; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

^aPercent Y-BOCS reductions are expressed as reduction from baseline scores assessed at pre-implantation

^bSignificance testing based on that reported in the trial, though exact statistical analyses varied across studies

^cResults of the first seven of these patients were reported in Nuttin et al. (2003)

^dMean percent reductions are reported here, while in their study, they reported median reductions in Y-BOCS scores, and thus differ slightly from the figures in this table

Table 2.

Long-term clinical outcomes.

Study authors, year	N	Age range, percent male	Anatomical target	Length of follow-up	Responders ^a n (%)	Y-BOCS reduction	Comorbidity	Functional impairment
Niutin et al., 2003 [36]	7	Not reported	ALIC	3–24 months	4 (57%)	Not reported	Not reported	Not reported
Abelson et al., 2005 [22]	4	27–52 years-old; 50% male	ALIC	4–23 months after staggered phase	1 (25%)	20%	23% improvement in HAM-D scores. 1 patient experienced improved anxiety on HAM-A	GAF scores improved in all patients
Greenberg et al., 2006	10	22–59 years-old; 60% male	VC/VS	36 months	4 (40%)	36%	Significant improvement in HAM-D ($M = 21.1$ to 15.4) and HAM-A ($M = 18.2$ to 9.0)	GAF scores improved from $M = 37$ to $M = 54$
Denys et al., 2010 [14]	16	21–59 years-old; 56% male	NAcc	21 months	9 (56%)	46%	Significant improvements on HAM-A ($M = 20.9$ to 8.9) and HAM-D ($M = 19.5$ to 10.6)	Significant improvement in work, social, and family life domains of the Sheehan Disability Scale
Goodman et al., 2010 [26]	6	27–52 years-old; 33% male	VC/VS	12 months	4 (67%)	47%	Significant improvement in HAM-D ($M = 11.5$ to 6.7)	Significant improvement on work/school activities subscale of the SF-36. No significant change on other subscales
Greenberg et al., 2010 ^c [12]	26	23–39 years-old; 54% male	VC/VS	36 months	16 (62%)	39%	Significant improvement in HAM-D (43%) and HAM-A (59%)	GAF scores improved from $M = 35$ to $M = 59$
Huff et al., 2010 [23]	10	25–44 years-old; 60% male	NAcc	12 months	4 (40%)	21%	Significant improvement in BDI ($M = 22.7$ to 15.9) and HAM-D ($M = 21.6$ to 16.6), but not in measures of anxiety (HAM-A and STAI) or global psychiatric symptoms (SCL-90)	GAF scores significantly improved from ($M = 36.6$ to 53.1)
Roh et al., 2012	4	18–47 years-old; 75% male	VC/VS	24 months	4 (100)	60%	Significant improvement in HAM-D ($M = 21.0$ to 7.0)	Significant increase in GAF ($M = 44$ to 63)
Tsai et al., 2012 [40]	4	21–30 years-old; 100% male	VC/VS	15 months	2 (50)	33%	Significant improvement in HAM-D ($M = 36.3$ to 24.5)	Significant increase in GAF ($M = 44$ to 57)
Chabardès et al., 2013 [38]	4	35–43 years-old; 50% male	STN	6 months	3 (75%)	65%	Not reported	Not reported
Islam et al., 2013	8	33–59 years-old; 88% male	NAcc ($n = 4$) and BST ($n = 4$)	6–60 months	6 (75%); NAcc = 2 (50%); BST = 4 (100%)	Not reported	Not reported	Not reported
Jiménez et al., 2013 [30]	6	Mean age = 25 years-old (range not reported); 50% male	ITP	36 months	6 at 12-month (100); 3 at 36-month (100) ^d	51%	3/3 patients who presented with substance use disorders continued to misuse substances	68% increase in GAF

Study authors, year	N	Age range, percent male	Anatomical target	Length of follow-up	Responders ^a (%)	Y-BOCS reduction	Comorbidity	Functional impairment
Fayad et al., 2016 ^b [29]	6	27–52 years-old; 33% male	VC/VS	73 to 112 months	4 (67%)	56%	Significant increase in HAM-D ($M = 11.5$ to 17.3)	Significant improvement in General Health and Social Functioning domains of SF-36. No other significant changes in functioning
Luyten et al., 2016 [13]	24	23–59 years-old; 50% male	ALIC/BNST	48–192 months	16 (67)	66% (48-month), 45% (most recent)	Significant improvement in HAM-D (median 67% improvement) and HAM-A (median 58% improvement)	Significant increase in GAF (median 30 points)
Barcia et al., 2019 [25]	7	28–46 years-old; 43% male	Caudate or NAcc (personalized along striatal axis)	19 months	6 (86%)	51%	No significant difference between baseline HAM-A or STAI scores and any stimulation setting for 4 patients	Not reported
Huys et al., 2019 [28]	20	22–60 years-old; 50% male	ALIC and NAcc	12 months	8 (40%)	33%	No significant change in BDI or STAI	Significant increase in GAF
Mallet et al., 2019 ^e [27]	14	29–56 years-old; 59% male	STN	46 months	9 (64%)	52%	Significant improvement in depression (Montgomery-Asberg Depression Rating Scale $M = 13$ to 5 ; HADS-depression $M = 12$ to 3) and anxiety (Brief Anxiety Scale $M = 13$ to 4 ; HADS-anxiety $M = 16$ to 7)	Significant increase in GAF ($M = 35$ to 65). Significant improvement in Sheehan Disability Scale work, family life, and social life subscales
Lee et al., 2019 [32]	5	25–48 years-old; 40% male	ITP	21–85 months	5 (100)	52%	Trend-level improvement in HAM-D scores, with 4/5 patients experiencing improvement	Significant improvement in social and family subscales of the Sheehan Disability Scale
Tyagi et al., 2019 [39]	6	20–30 years-old; 83% male	STN and VC/VS for each patient	60 weeks	6 (100)	60%	Significant improvement in Montgomery-Asberg Depression Rating Scale	Not reported

Note: ALIC = anterior limbs of the internal capsules; BDI = Beck Depression Inventory; BNST = bed nucleus of the stria terminalis; GAF = Global Assessment of Functioning; HADS = Hospital Anxiety-Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; ITP = Inferior thalamic peduncle; NAcc = nucleus accumbens; SF-36 = General Health Perceptions and Social Functioning Subscales of the Medical Outcomes Survey; Short-Form-36; STAI = State Trait Anxiety Inventory; STN = subthalamic nucleus; VC/VS = ventral capsule/ventral striatum; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

^aResponders' were defined as experiencing at least a 35% reduction on the Yale-Brown Obsessive-Compulsive Scale. Percentages of responders used intent-to-treat sample sizes, and thus differ than those reported in original manuscripts in some cases.

^bLonger-term follow-up of Goodman et al. (2010)

^cThree-year follow-up of Goodman et al. (2010); Greenberg et al. (2006); and Nuttin et al. (2003)

^dIn this study, only three of the original six patients were accessible. One passed away, one stopped attending appointments after 18 months, and one was explanted due to tuberculous meningitis

^eOpen follow-up after Mallet et al. (2008) randomized on-off crossover trial