Received: February 28, 2020 Revised: May 22, 2020 Accepted: June 16, 2020

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13243

Optimizing Deep Brain Stimulation Parameters in Obsessive–Compulsive Disorder

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ABSTRACT

Objectives: Deep brain stimulation (DBS) is an innovative and effective treatment for patients with therapy-refractory obsessive–compulsive disorder (OCD). DBS offers unique opportunities for personalized care, but no guidelines on how to choose effective and safe stimulation parameters in patients with OCD are available. Our group gained relevant practical knowledge on DBS optimization by treating more than 80 OCD patients since 2005, the world's largest cohort. The article's objective is to share this experience.

Materials and Methods: We provide guiding principles for optimizing DBS stimulation parameters in OCD and discuss the neurobiological and clinical basis.

Results: Adjustments in stimulation parameters are performed in a fixed order. First, electrode contact activation is determined by the position of the electrodes on postoperative imaging. Second, voltage and pulse width are increased stepwise, enlarging both the chance of symptom reduction and of inducing side effects. Clinical evaluation of adjustments in stimulation parameters needs to take into account: 1) the particular temporal sequence in which the various OCD symptoms and DBS side-effects change; 2) the lack of robust response predictors; 3) the limited sensitivity of the Yale-Brown Obsessive–Compulsive Scale to assess DBS-induced changes in OCD symptoms; and 4) a patient's fitness for additional cognitive-behavioral therapy (CBT).

Conclusions: Decision-making in stimulation parameter optimization needs to be sensitive to the particular time-courses on which various symptoms and side effects change.

Keywords: Deep brain stimulation, neuromodulation, obsessive–compulsive disorder, optimization, stimulation parameters

Conflict of Interest: Damiaan Denys and Rick Schuurman receive occasional fees from Medtronic for educational purposes. Rick Schuurman acts as consultant for Medtronic, Boston Scientific and Elekta. Damiaan Denys was, until recently, a member of the advisory board of Lundbeck. These connections did in no way influence the decision to write and submit this manuscript. All remaining authors have no conflicts of interest to disclose.

INTRODUCTION

Deep brain stimulation (DBS) is an innovative treatment for therapy-refractory obsessive–compulsive disorder (OCD) with an average of 50–60% patients responding (1,2). The efficacy of DBS is comparable to ablative neurosurgical procedures, such as anterior capsulotomy and cingulotomy (3). A crucial advantage over these techniques is that the effect of DBS is reversible, given the possibility of adjusting stimulation parameters.

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: Damiaan Denys, Rick Schuurman and Isidoor Bergfeld have received grants from the Netherlands Organization for Health Research and Development (ZonMw, 636310016) and Boston Scientific (in kind) for investigator-initiated trials of DBS for depression. Erik Rietveld is supported by the Netherlands Organisation for Scientific Research (NWO) in the form of a VIDI-grant and by the European Research Council in the form of ERC Starting Grant 679190 for the project AFFORDS-HIGHER. These funding sources did in no way influence the decision to write and submit this manuscript.

This article focuses on *DBS stimulation parameter optimization*. DBS optimization means maximizing treatment efficacy and minimizing side effects through patient-specific adjustments of stimulation parameters. Adjustable parameters include voltage, frequency, pulse width, and active contacts. Despite DBS optimization being a crucial treatment phase, clinical studies only mention it briefly. To our knowledge, no guidelines on how to choose effective and safe stimulation parameters in patients with OCD are available. This lack of evidence-based guidelines led authors of the only review on this topic to argue that "there is an urgent need for expert consensus" (4). Our group gained relevant practical knowledge on DBS optimization in treating more than 85 OCD patients since 2005. This article's objective is to describe our method of optimizing DBS in OCD, thereby offering guiding principles on DBS stimulation parameter optimization in OCD. Important to note is that these guiding principles are only partly based on empirical evidence and largely have the status of expert opinion.

First, we describe the guiding principles we currently use to optimize stimulation parameters. In the subsequent sections, we discuss the basis of these principles, focusing on the technical and neurobiological aspects of adjusting stimulation parameters and on the nuances of evaluating effects of stimulation parameter adjustments in clinical practice, while also comparing our way of working with how it is done in other centers.

GUIDING PRINCIPLES FOR OPTIMIZING DBS STIMULATION PARAMETERS

To clarify why we make particular choices with regard to DBS optimization we need to explain something about how, in our center, DBS consist of several consecutive treatment phases (Fig. 1). First, a neurosurgeon implants electrodes (model 3389; Medtronic, Minneapolis, MN, USA) in the ventral anterior limb of the internal capsule (vALIC) and connects these to an implantable pulse generator (IPG) (Activa PC or RC, Medtronic). Further details on the surgical procedure and inclusion-criteria are described elsewhere (2,5,6). Second, a psychiatrist or specialized nurse optimizes the IPG's stimulation parameters in order to best modulate symptoms. This is the treatment phase on which we focus in this article. Third, a psychotherapist expands and consolidates these effects with cognitive behavioral therapy (CBT).

To allow for recovery from surgery, the optimization phase starts at least two weeks after surgery. We verify the position of the implanted electrodes by fusing the preoperative magnetic resonance imaging (MRI)-scan with the postoperative computed tomography (CT)-scan. The two contact points closest to the target structure (see section "contact configuration") are set as cathodes. The IPG is switched on at 3.0 V, a pulse width of 90 μsec, and a frequency of 130 Hz. We evaluate whether 1) symptoms have reduced, 2) side effects have occurred, and 3) normal functioning of the device by measuring electrode impedance. These evaluations are done weekly for inpatients and biweekly for outpatients. To enable a proper evaluation of the effect, only one stimulation parameter is adjusted at a time. Once a clinically significant effect without intolerable side effects is achieved, no further adjustments are made. When there is no effect and no side effects, we make further adjustments in a fixed order described in Figure 2.

With this protocol, our first 70 patients, after 12 months of DBS, had a mean decrease in Y-BOCS scores of 13.5 points (SD = 9.4) (40%). Of these patients, 52% (n = 36) could be categorized as full responder (>35% Yale-Brown Obsessive–Compulsive Scale [YBOCS] reduction compared to baseline), with a mean Y-BOCS decrease of 20.9 points (SD = 6.4) (62%), and 17% of patients (n = 12) as partial responder (>25% YBCOS reduction), with a mean Y-BOCS decrease of 9.9 points (SD = 1.5) (29%). 31% of patients (n = 22) were categorized nonresponders, with a mean Y-BOCS decrease of 3.3 points (SD = 3.0) (10%) (2).

Of the current 85 patients in our center, 53 patients showed a full response at some point within two years from surgery. We analyzed the time to first response, which in days from surgery is: 10–36 days for the fastest 25% of patients; 36–186 days for the middle 50%, and between 186 and 612 days for the slowest 25% of patients. This implies that for most patients, it is a matter of months before they achieve full response by means of the above guiding principles on optimization. This also implies that it takes a long time before a patient can be qualified as nonresponder.

MODULATING STIMULATION PARAMETERS

The amount of current that is applied to the targeted brain area is determined by 1) the number of active contact points, 2) mono- or bipolar stimulation, 3) the number of electrical pulses per second (frequency), 4) the duration of these pulses (pulse width), and 5) the amplitude of these pulses (voltage in relation to the impedance of the circuit).

Contact Point Configuration

Which electrode contacts are activated first depends on the anatomical location of the electrodes. Originally, we placed the stimulation electrodes with the most ventral contact inside the core of the nucleus accumbens (NA) (6) (Fig. 3). Stimulation was initiated in the two contacts inside the NA, based on the hypothesis that OCD pathophysiology is related to reward processing, in which the NA is a prominent node (5,7). When our first patients did not show any response to stimulation of the ventral contacts inside the NA, we switched to the two dorsal contact points (5). Subsequent analysis found that of our first 16 patients, the nine patients who had active contacts located bilaterally in the vALIC (see Fig. 3) had an average YBOCS

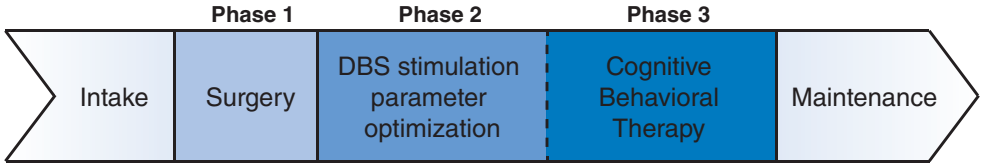

Figure 1 Phases in DBS treatment. [Color figure can be viewed at wileyonlinelibrary.com]

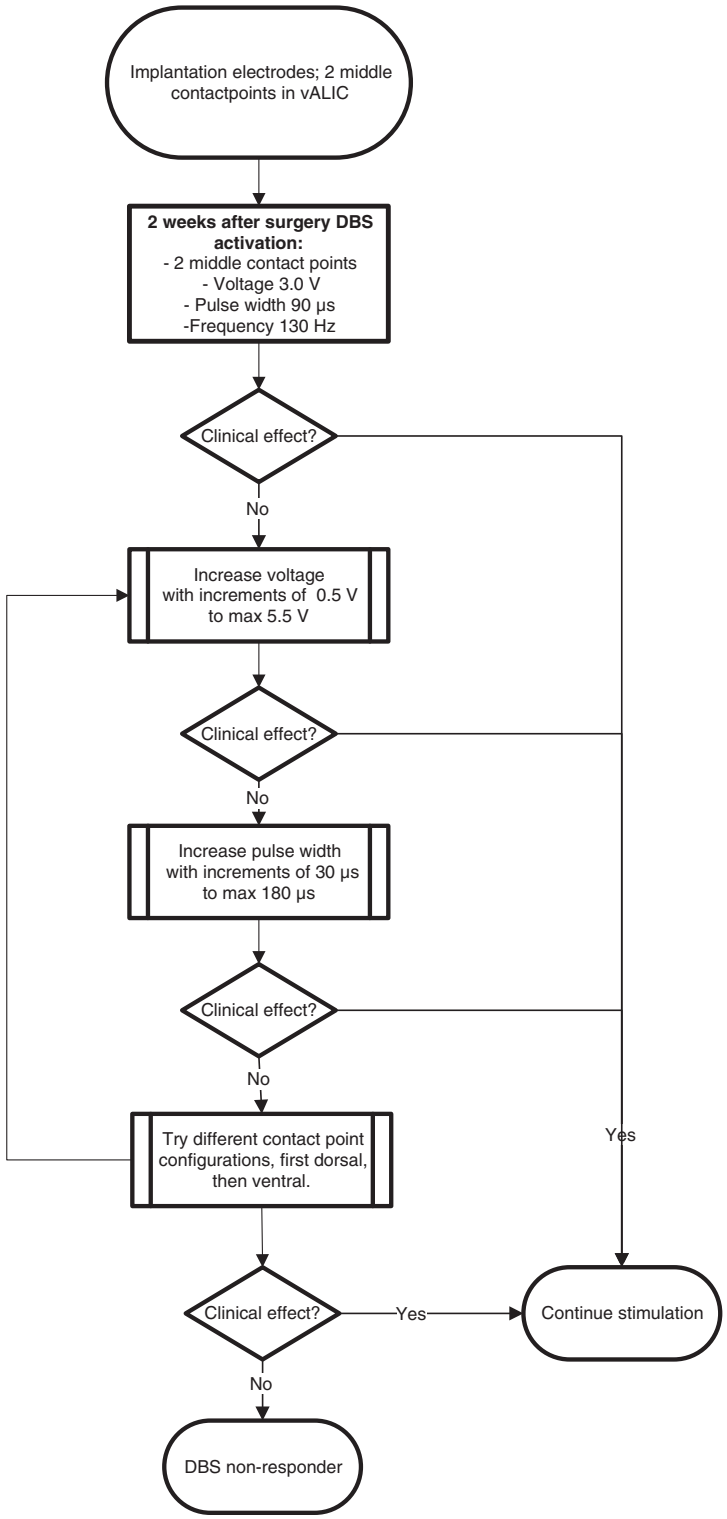

Figure 2 Flowchart OCD-DBS stimulation parameter optimization in OCD. vALIC, ventral anterior limb of internal capsule.

improvement of 73% (SD 18), whereas the other six patients with active stimulation sites elsewhere showed an improvement of only 42% (SD 28) (6).

In recent years, there has been an increased focus on reconstruction of white matter pathways with tractography to aid DBS surgical planning (8,9). Tractography implies the diffusion MRI-based 3D modeling of form and trajectory of white matter structures. Reasons for implementing tractography are high inter-individual variability in vALIC anatomy (10,11) and promising results for tractography-based targeting of the superolateral branch of the medial forebrain bundle (slMFB) in DBS for depression (8,12). A retrospective study in 16 of our patients

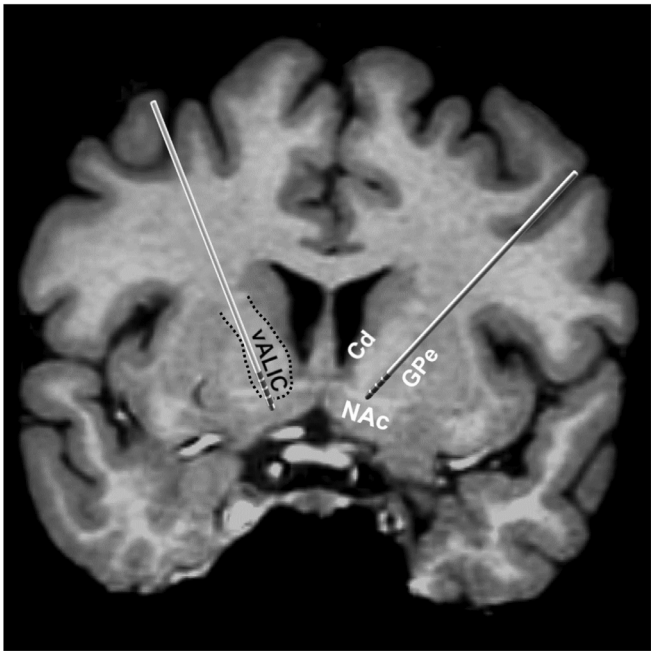

Figure 3 Targeting and contact point configuration. The anatomic relationship of several relevant structures is portrayed. vALIC, ventral anterior limb of the internal capsule; GPe, Globus Pallidus pars externa; Cd, nucleus caudatus; NAc, nucleus accumbens.

showed that patients with active stimulation sites closer to the slMFB had better treatment outcome than patients with active stimulation sites more proximate to the anterior thalamic radiation (13). Therefore, we currently select contact points closest to the slMFB and are evaluating whether prospective slMFB-targeted stimulation within the vALIC could yield better treatment outcomes.

Our insights on optimal targeting converge with the prevailing view that OCD pathophysiology is related to aberrant activity in hyperconnected brain areas organized in cortico-striato-thalamo-cortical (CSTC) circuits (14–17). Initially, DBS was assumed to interrupt this connectivity by means of a reversible lesion analogous to the permanent lesion that is established through neuro-ablative procedures, such as cingulotomy (3,18). Currently, most evidence supports the hypothesis that the effect of DBS on OCD pathophysiology is achieved through axonal activation (19,20). Depolarization of large passing axons in CSTC white matter tracts connecting frontal and thalamic and/or striatal brain areas appears to normalize connectivity between and activity within these areas. Our group, for instance, showed that VC/VS DBS normalized frontostriatal NAc-prefrontal (PFC) hyperconnectivity and NAc hypoactivity, which was associated with symptom reduction (21,22). Instead of interrupting connectivity, DBS improves connectivity.

Mode of Stimulation

We use monopolar stimulation, because the spherical form of current spread affects a larger volume of neuronal tissue than bipolar stimulation (Fig. 4). Normally, we do not adjust the mode of stimulation. In the case of side effects, the more narrow current flow of bipolar stimulation can be beneficial (23). There is a large variation among institutions in the use of either mono- or bipolar stimulation (4,24–28). In larger studies, monopolar stimulation is most often used.

Voltage

Increasing voltage is the most straightforward way of inducing a clinical effect as a larger volume of neural tissue is affected (19,29,30). We indeed observed that many patients who did not respond to the initial settings (3.0 V, 90 μsec, and 130 Hz) eventually responded when voltage was increased by increments of 0.5 V. Other clinical studies in OCD also found that more patients respond when voltage is increased (31–34). In an analysis of settings after one year in our first 80 patients, we found that the mean voltage was 4.42 V (SD 0.85). This is slightly lower than voltages reported in clinical studies from other institutions (4,24–28). A possible explanation for variations in voltage levels across institutions is targeting, as is shown by the considerably lower voltages in a study targeting the subthalamic nucleus (STN) (35,36). Furthermore, Greenberg et al. found that as the targeting evolved and became more precise, the voltage required to achieve an optimal effect decreased (37). We are currently evaluating whether voltages decreased in our cohort since we switched to prospective slMFB-targeting with tractography at the end of 2017.

Increasing voltage should always be weighed against the risk of inducing side effects (see section "side effects" below). We use 5.5 V as upper limit, since higher voltages hardly ever increased effectiveness, while the chance of inducing side effects strongly increased. Another reason for limiting the voltage to 5.5 V is that higher voltages, especially when combined with large pulse widths, cause faster battery depletion, which requires patients with a rechargeable battery to charge more frequently and patients with a nonrechargeable battery to have replacement surgery sooner.

Frequency

Research in preclinical models and in DBS for neurological disorders found that with high-frequency stimulation (>100 Hz) action potentials in the axon become coupled (time-locked) to the stimulation pulse train, overriding the input from the neural cell body (20). Clinical studies on DBS for OCD all use high-frequency stimulation, ranging between 100 and 185 Hz, but mostly 130 Hz (4,24–28). Currently, almost all our patients are stimulated at 130 Hz. There are no studies in DBS for OCD directly comparing different frequencies. One small double-blind cross-over study in a different target (subcallosal cingulate gyrus) in major depressive disorder (MDD) found higher efficacy in four patients stimulated at 130 Hz than in the two patients stimulated at 20 Hz after one year of follow-up (38).

Pulse Width

Preclinical research showed that the optimal pulse width to depolarize large myelinated passing axons lies between 60 and 150 μsec (19,30,39). The larger the axon diameter, the smaller the pulse width that is required to depolarize it (19,30). This is our rationale for decreasing the pulse width below 90 μsec in the case of side effects (see section below), as fewer axons are activated. We increase pulse widths above 90 μsec in situations where voltage increases produce no beneficial effect but only side effects. A single-blind sham-controlled study in five OCD-patients with VC/VS-DBS found that pulse widths >210 μsec did not result in further improvement of symptoms but only in an increase in side effects (33). In an analysis of the first 80 patient of our cohort,

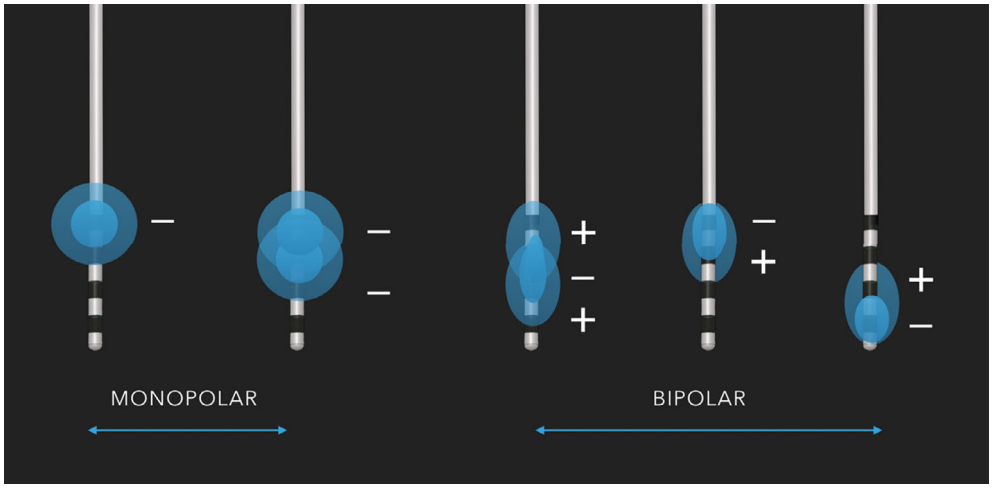

Figure 4 Modes of stimulation. With monopolar (cathodic) stimulation one or more contact points are set as cathodes (−), spreading a negative current evenly in all directions. With bipolar stimulation the electrode has both anodic (+) and cathodic (−) contact points, with a more narrow and intense flow of current between them. [Color figure can be viewed at wileyonlinelibrary.com]

after one year, the pulse width of the majority of patients was 90 µsec (73.4%). 15.2% was stimulated higher, between 120 and 180 µsec, and 11.4% of patients was stimulated lower, between 60 and 80 µsec. Pulse width varies considerably across published reports from other centers, ranging from 60 up to 450 µsec (4,24–28).

EVALUATING EFFECTS OF STIMULATION PARAMETER ADJUSTMENTS

OCD symptoms change in a particular temporal sequence following the start of DBS. Anxiety decreases within seconds to minutes, obsessions within days to weeks and compulsions and avoidance, which require the addition of CBT, take weeks to months to improve (5).

Acute Effects

Acute effects occur within seconds to hours after the DBS is first switched on or when stimulation parameters are adjusted. These changes include: a decrease in anxiety; euphoria; the experience that obsessions are less intrusive; a reduction in bodily tension; more modulation in voice and facial expression; an increased alertness and attention to surroundings; more spontaneous behavior and speech.

It is unclear whether acute effects are predictive for long-term improvement. In some of our patients long term reduction of OCD core symptoms was not preceded by clearly discernible acute effects, while there have also been nonresponders who did initially express acute effects. Moreover, acute effects are often transient. The euphoric mood and increased impulsivity, which are often accompanied by reduced sleep, typically subside within four days (5). One hypothesis is that this acute mood improvement temporarily covers the OCD symptoms and is related to a different mechanism than the eventual reduction of OCD core symptoms (40).

There have only been a few studies that systematically associated acute effects to particular combinations of stimulation parameters. An intraoperative trial in six patients and a postoperative trial in four patients assessed the presence of a smile response at several combinations of stimulation parameters in DBS in the ventral capsule/ventral striatum (VC/VS) (41–43). They found that patients with more smile-related combinations of stimulation parameters had a better outcome at 24 months follow-up in terms of YBOCS. Smile responses, however, could only be reproduced during surgery but not after surgery, neither were the correlated stimulation parameters related to those that were eventually effective in long term follow-up. To our knowledge, no other response predictors have been studied in relation to various stimulation parameter settings.

In virtually all clinical trials on DBS for OCD, a test stimulation survey is performed before chronic stimulation is initiated. A test stimulation survey implies the systematic testing of a number of stimulation parameter combinations in order to select a combination that is effective, safe and low in energy consumption (23,44). The number of settings that is tested varies, partly depending on whether test stimulation is intra- or postoperative. The time between parameter adjustments and the evaluation of effect varies between two minutes (45) and two hours (34), although several authors did not report how this was done exactly, and whether test stimulation was blinded. Efficacy and safety were evaluated by means of clinical impression and patient reports with the aid of visual analogue scales (VAS). Only two studies report more quantitative measures in the form of blood pressure and pulse, although it is not clear how this is used to select settings for chronic stimulation (45,46).

We do not perform test stimulation surveys in our patients, based on the limited evidence for a predictive value of acute effects and the lack of other robust response predictors. In our evaluation of DBS effects, we take into account that OCD is a strongly context-related disorder. Symptoms get tied to particular situations, most notably at home. In support of this view, one study found that patients, when tested in the atypical situation of the operation room, rated their OCD symptoms as 0 out of 10 (41). To give patients time to become aware of changes in their behavior and to make sure that the effects we evaluate are not transient, we evaluate DBS effects with intervals of two weeks.

Taking more time for changes to become apparent might be one of the reasons why our mean voltages are lower than in other centers (see section "voltage").

Of the six randomized controlled trials (RCT) on DBS for OCD, only the one in our center (5) and that by Luyten et al. (24) included an optimization phase with longer evaluation intervals of at least multiple days before the onset of the double-blind phase. In studies without such long-term optimization first, some patients may have received subtherapeutic levels of stimulation. Huff et al., who held parameter settings fixed in the first six months after the test stimulation survey, consider this an explanation for their low response rates in the double blind phase (32), although it might also be due to the uni- instead of bilateral stimulation they applied. They found their main decline in YBOCS-score during the open phase, when additional stimulation parameter adjustments were made. Another RCT also found improved response rates when switching to open phase and allowing changes in parameter settings (31). In most studies on DBS for OCD, randomized and nonrandomized, authors report *that* additional optimization of stimulation parameters was performed after the initial test stimulation survey or double-blind phase, although details are very limited on *how* they do this. However, these results emphasize the importance of taking time for optimizing stimulation parameters.

Long-Term Effects

The evaluation of severity of obsessions and compulsions, which take more time to improve than anxiety, relies on 1) reports from patient and family and our observations, 2) outcome on clinical rating scales, and 3) an assessment of fitness for cognitive behavioral therapy (CBT).

The initial effect of DBS on obsessions and compulsions can be very subtle. We look out for remarks that indicate that patients feel freer from their obsessions, such as *I still have thoughts but they make me less anxious*, *I do no longer believe them*, or *I can laugh about my thoughts*. Furthermore, we actively search for changes in OCD symptoms by systematically going through the patient's daily routine, which we documented before DBS implantation. We ask patients for changes in their activity pattern and whether they "accidentally" stopped avoiding an activity or place or whether there have been situations in which they "forgot" to perform compulsions. Remarkably, some patients themselves do not experience change even when quite profound changes in their behavior can be observed. Moreover, in some patients improvement is difficult to evaluate due to comorbidity or coping mechanisms that obscure any improvement in OCD symptoms. Therefore, we always ask family-members to be present, so that their observations can be weighed.

We use several rating scales to measure DBS effect. The most important instrument is the YBOCS, that quantifies symptom severity in OCD on a scale from 0 to 40. To evaluate changes in anxiety, we use the Hamilton Anxiety Scale (HAM-A). And because most patients suffer from comorbid depression, we use the Hamilton Depression Rating Scale (HDRS). When patients show a reduction of 35% or larger on YBOCS-score we usually stop making further adjustments in stimulation parameters. We noticed, however, that rating scales are often not sensitive enough to capture relevant DBS-induced symptom changes. When a patient, for instance, does no longer spend 14 hours a day having obsessions but only 10, we consider this a significant improvement. This improvement, however, is not represented in a change in YBOCS-score, as patients stay in the same category as long as they have more than eight hours of compulsions. Also we find that some patients who are nonresponders in terms of YBOCS have nonetheless an important improvement in quality of life (47). Although the YBOCS is of limited use in our real-time day-to-day decision-making on DBS optimization, it remains a useful measure to quantify eventual long-term improvement. To understand the effects of DBS treatment on the lived experience and personality of OCD patients over time, we have also done in-depth interviews with 18 patients. These studies showed that DBS treatment improves the patients' anticipation of relevant action possibilities and increases their self-confidence (48–50).

One particular way in which we evaluate the efficacy of stimulation parameters is fitness for cognitive behavioral therapy (CBT). Throughout the optimization phase, we encourage patients to do small exposure exercises. We, for instance, ask a patient with fear of contamination to wash his or her hands eight instead of ten times. When this succeeds, such a slight change in behavior can be an indication that the patient's anxiety is considerably reduced and CBT can be added. We found that CBT augments the effects of DBS and further expands and consolidates the effects of DBS (51). Therefore, most of our DBS-patients get adjunctive CBT, which consists of exposure with response prevention and cognitive restructuring. In total, 13 of our first 70 patients did not receive additional CBT because they no longer needed it ($N = 8$), had insufficient response to DBS ($N = 4$), or had physical complaints ($N = 1$) (2). Over the course of weeks to months, CBT further reduces compulsions and avoidance and restores healthy behavior. In our first 16 patients, the addition of 24 CBT sessions resulted in an additional 22% YBOCS reduction on top of the 25% YBOCS reduction that had been achieved by means of DBS stimulation parameter optimization (51).

Side Effects

DBS has been associated with a number of side effects, including increased anxiety, impulsivity, paresthesia, nausea, and dizziness (1). With regard to the management of side effects, it is important to distinguish stimulation-related side effects from complications of surgery or device-related problems. Therefore, we discuss the occurrence of side effects in a multidisciplinary team with neurosurgeons, psychiatrists, psychologists, and specialized nurses. Here, we focus only on stimulation related side effects.

The most often observed stimulation-related side effects in our patient cohort are sleeping problems (46% of patients), restlessness (33%), agitation (30%), and impulsivity (19%) (2,52). These symptoms often, but not always, co-occur and are associated with euphoria. Although this cluster of symptoms is often referred to as "(hypo)mania," we would propose to reserve this term for only those cases that meet DSM 5 criteria with regard to number of symptoms, severity and duration. Whether cases of DBS-induced increased impulsivity, euphoria, agitation and sleeping problems are associated with a pre-existing yet unrecognized comorbid bipolar spectrum disorder is not clear, although a case series in five patients with comorbid bipolar disorder found no significant changes in scores on the Young Mania Rating Scale (53). Nevertheless, we preventively admit patients with comorbid bipolar disorder during the optimization phase and start stimulation at 2.5 instead of 3.0 V. This is also the case for patients with dysfunctional coping mechanisms associated with specific personality disorders. Personality disorders, however, cannot always be clearly

diagnosed beforehand: the OCD might be so all-encompassing that psychological testing is not reliable.

Most stimulation-related side effects are transient. As we described above, many patients experience around four days of increased impulsivity, euphoria and sleeping problems after a stimulation parameter adjustment. This effect can occur after each adjustments in stimulation settings. If these effects are safe and tolerable, we wait for two weeks for them to subside. In case the side effects are not transient, we adjust stimulation parameters. Although we have no data to prove this, it is our clinical impression that the various stimulation-related side effects usually subside within one week after an effective adjustment in parameters. As adjustments might lead to a loss of beneficial effect, we sometimes accept a certain degree of side effects, which explains that 7% of our patients keeps having sleeping problems and 3% is still having signs of agitation (2).

We have observed that higher voltages, especially above 5.5 V, induce more side effects. This was also seen in a single-blind sham-controlled study in six patients, which associated amplitudes above 6 V with a strong increase in side effects (33). Therefore, a logical step is to decrease the voltage by increments of 0.2 V (or 0.5 V when symptoms are severe) until the side effect subsides. If the voltage reduction leads to a loss of OCD-response, we instead reduce the pulse width to 60 μsec or switch from two to one contact points. In rare cases of persisting manic symptoms despite stimulation parameter adjustments we add mood stabilizing medication.

Nonresponders

When patients do not respond after all the steps of the optimization protocol have been performed, other options are discussed in the team. Sometimes patients are admitted and various settings are tested again, while the effects are closely observed and patients get exposure exercises. In some nonresponders who were previously implanted without tractography guidance, adjustment of the electrode positions based on the reconstruction of the slMFB in the vALIC has been effective. In some patients, the positive effect on OCD is obscured or superseded by a comorbid personality disorder that needs to be treated first before DBS optimization can be tried again. Most nonresponders decide to keep the DBS as it offers them some benefit in mood. Some nonresponders, for instance, turn off the DBS every evening and activate it again the next morning in order to have the acute effect of transient improvement of mood to overcome the OCD symptoms.

DISCUSSION

Though a response rate of 60% in therapy-refractory OCD patients is a considerable advancement, still some patients do not benefit sufficiently from DBS. How can DBS optimization add to an improved response rate? Based on the above discussion of our preliminary expert-based guideline we now identify three directions for future research.

First, the YBOCS is felt being inappropriate to assess adequately DBS-induced changes in OCD symptoms. More precise assessment tools are needed to guide decision-making in stimulation parameter optimization. This might be achieved by a dimensional instead of categorical approach. For example, the amount of hours spent on obsessions and compulsions should be assessed gradually as with the Dimensional Obsessive–Compulsive Scale (DOCS). Furthermore, we think that future studies should look for ways to evaluate DBS effects that remain close to what patients experience. Given that various OCD symptoms change over different time courses, repeated interviews on different stages in the treatment course might reveal relevant changes in patients' lived experience which can become general signs of improvement.

Second, stimulation parameters are currently optimized through a fixed sequence of adjustments. This is a time-consuming process which typically takes several months. Future studies need to look for patient-specific predictors to directly select effective stimulation parameter settings. We expect that with increased precision in targeting of electrodes, as is currently investigated using tractography, fewer adjustments will be required to select effective stimulation parameters. A more direct selection of effective stimulation parameters might also be achieved by identifying particular patient profiles. These might be based on OCD symptom dimensions (54) and the DSM 5 specification of good vs. poor insight (55). Comorbidity profiles may as well be relevant, in part because (side-)effects of DBS overlap with particular symptoms of comorbid disorders. This is the case, for instance, with impulsivity and a comorbid bipolar or borderline personality disorder.

Third, an extremely relevant issue is the tapering off effect of DBS. Currently, patients who get DBS remain tied to their clinicians for regular check-ups and battery-replacements for the rest of their lives. It would be relevant to investigate in which patients, at which pace and to what degree tapering off stimulation is effective and safe. There is no data whatsoever on the nature and time course of relapse symptoms. We only know that when the DBS is switched off abruptly, a rebound effect can be observed: a decrease in mood to a level below the baseline measurement at the beginning of the treatment (56). It is unclear whether this is a transient phenomenon, as we studied it for a maximum of seven days.

Furthermore, there is a need for randomized controlled trials that systematically compare efficacy and safety of stimulation parameters, including: bilateral versus unilateral stimulation; one versus two contact points; monopolar versus bipolar stimulation; adjusting pulse width before adjusting voltage; 130 Hz versus other frequencies.

Finally, it would be interesting to compare optimization strategies across centers, both those that use the same brain target and those that target the electrodes at a different structure. This requires that reports on clinical trials provide more details on their optimization methods. One might also look at similarities and differences in optimization in DBS for other conditions, such as Parkinson's disease, where an acute sign for evaluating efficacy of stimulation parameters is available and where patients regularly suffer from psychiatric side effects, and major depressive disorder, where acute signs are also lacking and clinicians similarly observe that it takes time for patients to become aware of DBS-induced changes (57,58).

CONCLUSION

This study's objective was to describe our method of optimizing DBS stimulation parameters for OCD. Our group came up with guiding principles for DBS optimization. First, electrode contact activation is determined by the position of the electrode and more recently this is based more on the position of fibers as shown by tractography rather than being determined by anatomical landmarks only. Second, voltage and pulse width are increased

stepwise, increasing both the chance of symptom reduction and of inducing side effects. Clinical evaluation of adjustments in stimulation parameters needs to take into account: 1) the particular temporal sequence in which the various OCD symptoms and DBS side effects change; 2) the lack of robust response predictors; 3) the limited sensitivity of the YBOCS to assess DBS-induced changes in OCD symptoms; and 4) a patient's fitness for additional cognitive-behavioral therapy (CBT). In view of the limited predictive value of acute effects and the limited sensitivity of the YBOCS, expert clinical skills are required to evaluate how OCD symptoms change over time and to assess a patient's fitness for additional CBT.

Authorship Statements

Maarten van Westen prepared the manuscript draft and all other authors critically reviewed it. All authors approved the final manuscript.

How to Cite this Article:

van Westen M., Rietveld E., Bergfeld I.O., de Koning P., Vullink N., Ooms P., Graat I., Liebrand L., van den Munckhof P., Schuurman R., Denys D. 2021. Optimizing Deep Brain Stimulation Parameters in Obsessive–Compulsive Disorder.
Neuromodulation 2021; 24: 307–315

REFERENCES

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;10:1–16. https://doi.org/10.1371/journal.pone.0133591.
2. Denys D, Graat I, De Koning P et al. Efficacy of deep brain stimulation of the ventral anterior limb of the internal capsule for refractory obsessive-compulsive disorder: a clinical cohort of 70 patients. *Am J Psychiatr* 2020;177:265–271. https://doi.org/10.1176/appi.ajp.2019.19060656.
3. Greenberg BD, Rauch SL, Haber SN. Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. *Neuropsychopharmacology* 2010;35:317–336. https://doi.org/10.1038/npp.2009.128.
4. Morishita T, Fayad SM, Goodman WK et al. Surgical neuroanatomy and programming in deep brain stimulation for obsessive compulsive disorder. *Neuromodulation* 2014;17:312–319. https://doi.org/10.1111/ner.12141.
5. 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;67:1061–1068. https://doi.org/10.1001/archgenpsychiatry.2010.122.
6. van den Munckhof P, Bosch D, Mantione M, Figee M, Denys D, Schuurman P. Active stimulation site of nucleus accumbens deep brain stimulation in obsessive-compulsive disorder is localized in the ventral internal capsule. *Acta Neurochir Suppl* 2013;117:53–59. https://doi.org/10.1007/978-3-7091-1482-7_9.
7. Figee M, Vink M, de Geus F et al. Dysfunctional reward circuitry in obsessive-compulsive disorder. *Biol Psychiatry* 2011;69:867–874. https://doi.org/10.1016/j.biopsych.2010.12.003.
8. Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Mädler B. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. *J Neuropsychiatry Clin Neurosci* 2012;24:223–236. https://doi.org/10.1176/appi.neuropsych.11080180.
9. Riva-Posse P, Choi KS, Crowell AL et al. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. *Mol Psychiatry* 2017;23:843–849. https://doi.org/10.1038/mp.2017.59.
10. Nanda P, Banks GP, Pathak YJ, Sheth SA. Connectivity-based parcellation of the anterior limb of the internal capsule. *Hum Brain Mapp* 2017;38:6107–6117. https://doi.org/10.1002/hbm.23815.
11. Makris N, Rathi Y, Mouradian P et al. Variability and anatomical specificity of the orbitofrontothalamic fibers of passage in the ventral capsule/ventral striatum (VC/VS): precision care for patient-specific tractography-guided targeting of deep brain stimulation (DBS) in obsessive compulsive. *Brain Imaging Behav* 2016;10:1054–1067. https://doi.org/10.1007/s11682-015-9462-9.
12. Coenen VA, Schlaepfer TE, Goll P et al. The medial forebrain bundle as a target for deep brain stimulation for obsessive-compulsive disorder. *CNS Spectr* 2017;22:282–289. https://doi.org/10.1017/S1092852916000286.
13. 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 Stimul* 2019;12:353–360. https://doi.org/10.1016/j.brs.2018.11.014.
14. Robbins TW, Vaghi MM, Banca P. Obsessive-compulsive disorder: puzzles and prospects. *Neuron* 2019;102:27–47. https://doi.org/10.1016/j.neuron.2019.01.046.
15. Alexander GE. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986;9:357–381.
16. Karas PJ, Lee S, Jimenez-Shahed J, Goodman WK, Viswanathan A, Sheth SA. Deep brain stimulation for obsessive compulsive disorder: evolution of surgical stimulation target parallels changing model of dysfunctional brain circuits. *Front Neurosci* 2019;12:998. https://doi.org/10.3389/fnins.2018.00998.
17. Jakobs M, Fomenko A, Lozano AM, Kiening KL. Cellular, molecular, and clinical mechanisms of action of deep brain stimulation-a systematic review on established indications and outlook on future developments. *EMBO Moledcular Med* 2019;11:e9575. https://doi.org/10.15252/emmm.201809575.
18. Agnesi F, Johnson MD, Vitek JL. Deep brain stimulation: how does it work? In: Lozano AM, Hallett M, editors. *Handbook of clinical neurology brain stimulation*. Amsterdam: Elsevier B.V, 2013; p. 39–54.
19. Brocker DT, Grill WM. Principles of electrical stimulation of neural tissue. In: Lozano AM, Hallett M, editors. *Handbook of clinical neurology brain stimulation*. Amsterdam: Elsevier B.V, 2013; p. 3–18.
20. Mcintyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. *J Neurophysiol* 2004;91:1457–1469. https://doi.org/10.1152/jn.00989.2003.
21. Figee M, Luigjes J, Smolders R et al. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nat Neurosci* 2013;16:386–387. https://doi.org/10.1038/nn.3344.
22. Smolders R, Mazaheri A, van Wingen G, Figee M, de Koning PP, Denys D. Deep brain stimulation targeted at the nucleus accumbens decreases the potential for pathologic network communication. *Biol Psychiatr* 2013;74:e27–e28. https://doi.org/10.1016/j.biopsych.2013.03.012.
23. Volkmann J, Herzog J, Kopper F. Introduction to the programming of deep brain stimulators. *Mov Disord* 2002;17:181–187. https://doi.org/10.1002/mds.10162.
24. Luyten L, Hendrickx S, Raymaekers S, Gabriëls L, Nuttin B. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. *Mol Psychiatr* 2016;21:1272–1280. https://doi.org/10.1038/mp.2015.124.
25. 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 Stimul* 2019;12:344–352. https://doi.org/10.1016/j.brs.2018.11.012.
26. Islam L, Franzini A, Messina G, Scarone S, Gambini O. Deep brain stimulation of the nucleus accumbens and bed nucleus of stria terminalis for obsessive-compulsive disorder: a case series. *World Neurosurg* 2015;83:657–663. https://doi.org/10.1016/j.wneu.2014.12.024.
27. Menchón JM, Real E, Alonso P et al. A prospective international multi-center study on safety and efficacy of deep brain stimulation for resistant obsessive-compulsive disorder. *Mol Psychiatry* 2019. https://doi.org/10.1038/s41380-019-0562-6.
28. 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 Psychiatr* 2019;85:726–734. https://doi.org/10.1016/j.biopsych.2019.01.017.
29. Montgomery EB. *Deep brain stimulation programming: principles and practice*. New York, NY: Oxford University Press, 2010.
30. Ranck J. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res* 1975;98:417–440.
31. 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 Psychiatr* 2010;67:535–542. https://doi.org/10.1016/j.biopsych.2009.11.028.
32. 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;112:137–143. https://doi.org/10.1016/j.clineuro.2009.11.006.
33. Okun MS, Mann G, Foote KD et al. Deep brain stimulation in the internal capsule and nucleus accumbens region: responses observed during active and sham programming. *J Neurol Neurosurg Psychiatr* 2007;78:310–314. https://doi.org/10.1136/jnnp.2006.095315.
34. Abelson JL, Curtis GC, Sagher O et al. Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatr* 2005;57:510–516. https://doi.org/10.1016/j.biopsych.2004.11.042.
35. Mallet L, Polosan M, Jaafari N et al. Subthalamic nucleus stimulation in severe obsessive–compulsive disorder. *N Engl J Med* 2008;359:2121–2134.
36. Mallet L, Du Montcel ST, Clair AH et al. Long-term effects of subthalamic stimulation in obsessive-compulsive disorder: follow-up of a randomized controlled trial. *Brain Stimul* 2019;12:1080–1082. https://doi.org/10.1016/j.brs.2019.04.004.
37. Greenberg B, Gabriels L, Malone D Jr et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatr* 2010;15:64–79. https://doi.org/10.1038/mp.2008.55.

38. Eitan R, Fontaine D, Benoît M et al. One year double blind study of high vs low frequency subcallosal cingulate stimulation for depression. *J Psychiatr Res* 2018; 96:124–134. https://doi.org/10.1016/j.jpsychires.2017.09.026.
39. Kringelbach ML, Jenkinson N, Owen SLF, Aziz TZ. Translational principles of deep brain stimulation. *Nat Rev Neurosci* 2007;8:623–635. https://doi.org/10.1038/nrn2196.
40. de Koning P, Figee M, Endert E et al. Rapid effects of deep brain stimulation reactivation on symptoms and neuroendocrine parameters in obsessive-compulsive disorder. *Transl Psychiatry* 2016;6:e722. https://doi.org/10.1038/tp.2015.222.
41. Haq IU, Foote KD, Goodman WG et al. Smile and laughter induction and intraoperative predictors of reponse to deep brain stimulation for obsessive-compulsive disorder. *Neuroimage* 2011;54:247–255. https://doi.org/10.1016/j.neuroimage.2010.03.009.Smile.
42. Tsai H-C, Chang C-H, Hsieh H, Tsai S, Hung H, Chen S-Y. Acute stimulation effect of the ventral capsule/ventral striatum in patients with refractory obsessive-compulsive disorder – A double-blinded trial. *Neuropsychiatr Dis Treat* 2014;10:63–69. https://doi.org/10.2147/NDT.S54964.
43. Okun MS, Bowers D, Springer U et al. What's in a "smile?" intra-operative observations of contralateral smiles induced by deep brain stimulation. *Neurocase* 2004;10:271–279. https://doi.org/10.1080/13554790490507632.
44. Nuttin B, Gabriels LA, Cosyns PR, Meyerson BA. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery* 2003; 52:1263–1274. https://doi.org/10.1227/01.NEU.0000064565.49299.9A.
45. Greenberg BD, Malone DA, Friehs GM et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive – Compulsive disorder. *Neuropsychopharmacology* 2006;31:2384–2393. https://doi.org/10.1038/sj.npp.1301165.
46. Jiménez F, Nicolini H, Lozano AM, Piedimonte F, Salín R, Velasco F. Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. *World Neurosurg* 2013;80:17–25. https://doi.org/10.1016/j.wneu.2012.07.010.
47. Ooms P, Mantione M, Figee M, Schuurman PR, van den Munckhof P, Denys D. Deep brain stimulation for obsessive-compulsive disorders: long-term analysis of quality of life. *J Neurol Neurosurg Psychiatr* 2014;85:153–158. https://doi.org/10.1136/jnnp-2012-302550.
48. Kiverstein J, Rietveld E, Slagter HA, Denys D. Obsessive compulsive disorder: a pathology of self-confidence? *Trends Cogn Sci* 2019;23:369–372. https://doi.org/10.1016/j.tics.2019.02.001.
49. de Haan S, Rietveld E, Stokhof M, Denys D. Effects of deep brain stimulation on the lived experience of obsessive-compulsive disorder patients: in-depth interviews with 18 patients. *PLoS One* 2015;10:1–29. https://doi.org/10.1371/journal.pone.0135524.
50. de Haan S, Rietveld E, Stokhof M, Denys D. Becoming more oneself? Changes in personality following DBS treatment for psychiatric disorders: experiences of OCD patients and general considerations. *PLoS One* 2017;12:e0175748. https://doi.org/10.1371/journal.pone.0175748.
51. Mantione M, Nieman DH, Figee M, Denys D. Cognitive-behavioural therapy augments the effects of deep brain stimulation in obsessive-compulsive disorder. *Psychol Med* 2014;44:3515–3522. https://doi.org/10.1017/S0033291714000956.
52. Luigjes J, Mantione M, Van Den BW, Schuurman PR, Van Den MP, Denys D. Deep brain stimulation increases impulsivity in two patients with obsessive – Compulsive disorder. *Int Clin Psychopharmacol* 2011;26:338–340. https://doi.org/10.1097/YIC.0b013e32834af505.
53. Graat I, van Rooijen G, Mocking R et al. Is deep brain stimulation effective and safe for patients with obsessive compulsive disorder and comorbid bipolar disorder? *J Affect Disord* 2020;264:69–75. https://doi.org/10.1016/j.jad.2019.11.152.
54. Mataix-cols D, Ph D, Rosario- MC, Leckman JF. A multidimensional model of obsessive-compulsive disorder. *Am J Psychiatr* 2005;162:228–238.
55. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association, 2013.
56. Ooms P, Blankers M, Figee M et al. Rebound of affective symptoms following acute cessation of deep brain stimulation in obsessive-compulsive disorder. *Brain Stimul* 2014;7:727–731. https://doi.org/10.1016/j.brs.2014.06.009.
57. Ramasubbu R, Anderson S, Haffenden A, Chavda S, Kiss ZHT. Double-blind optimization of subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. *J Psychiatr Neurosci* 2013;38:325–332. https://doi.org/10.1503/jpn.120160.
58. Ramasubbu R, Lang S, Kiss ZHT. Dosing of electrical parameters in deep brain stimulation (DBS) for intractable depression: a review of clinical studies. *Front Psych* 2018;9:302. https://doi.org/10.3389/fpsyt.2018.00302.

COMMENTS

While DBS for OCD has been approved by the United States FDA via the HDE mechanism for over a decade, the numbers of actual implants, both US and worldwide, is less than that would be expected given the prevalence of the disease. The reasons for this are unclear, but likely include the lack of standardization of programming parameters. This contribution, the largest single-center retrospective review of OCD DBS implants, describes their experience with programming, and will be of benefit to many centers with a smaller number of, and less experience, with DBS for OCD.

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Prof. van Westen and coworkers have used DBS to treat a large cohort of patients with severe obsessive-compulsive disorder. Their experience is a valuable contribution to the literature and provides guidelines in programming. The programming is usually time-consuming and a wider range of stimulation parameters can be applied when compared to patients with Parkinson's disease. Another important lesson learned is that combining DBS with cognitive behavioral therapy results in better therapeutic outcome.

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