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Review

Deep Brain Stimulation for Major Depression and Obsessive-Compulsive Disorder—Discontinuation of Ongoing Stimulation

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Abstract: Deep brain stimulation (DBS) is currently under research for the treatment of psychiatric disorders, e.g., obsessive-compulsive disorder (OCD) and treatment-resistant depression (TRD). Since the application of DBS in psychiatry has been in use for about 20 years, it is necessary to evaluate its long-term use now. A main issue in the long-term treatment of DBS concerns the effects of a discontinuation of stimulation due to intended as well as unintended reasons. In this contribution, the literature describing discontinuation effects following DBS in OCD and TRD is reviewed. Furthermore, a patient is reported in depth who experienced an unintended discontinuation of supero-lateral medial forebrain bundle (slMFB) DBS for TRD. In this case, the battery was fully depleted without the patient noticing. DBS had led to a sustained response for seven years before discontinuation of stimulation for just several weeks caused a progressive worsening of depression. Altogether, the rapid occurrence of symptom worsening, the absence of a notification about the stimulation status and the difficulties to recapture antidepressant response represent important safety aspects. For a further understanding of the described effects, time courses until worsening of depression as well as biological mechanisms need to be investigated in double-blind controlled trials.

Keywords: deep brain stimulation; treatment-resistant depression; discontinuation of stimulation; supero-lateral medial forebrain bundle

1. Introduction

Deep brain stimulation (DBS) of the nucleus subthalamicus (STN) was first introduced in 1994 as a treatment for Parkinson's disease (PD) [1,2]. Since then, over 160,000 patients worldwide have been treated with DBS for several indications, most commonly PD [3]. In PD, a continuous stimulation is

necessary in order to maintain clinical effects of DBS. Motor symptoms such as tremor, bradykinesia, rigidity and axial signs occurred acutely after the cessation of STN DBS [4]. After the re-onset of stimulation, the described symptoms diminished acutely. This effect is described as a two-way effect, meaning a change of symptoms caused by the stimulation that works in both directions (improvement with onset of stimulation as well as aggravation with offset of stimulation). In that study, discontinuation was conducted in a planned and controlled setting. In other case reports, where stimulation was accidentally stopped or where stimulation could not be restored immediately due to the need for battery replacement, other serious symptoms are described, including potentially life-threatening symptoms [5–8]. In PD, discontinuation of stimulation should be regarded as a safety issue because it has been associated with rebound symptoms requiring emergency care. Altogether, it seems probable that PD patients may need permanent stimulation for the rest of their lives [9].

With regards to psychiatric interventions, DBS can be used under the special circumstances of a Humanitarian Device Exemption (HDE) in the United States for treatment-resistant obsessive-compulsive disorder (OCD) since 2009 [10]. Furthermore, it is currently being investigated for several other psychiatric indications, e.g., treatment-resistant depression (TRD). Different brain areas are under research for the placement of DBS electrodes. For treatment-resistant OCD and TRD, the following brain areas are most commonly targeted: anterior limb of the capsule interna (ALIC), ventral capsule/ventral striatum (VC/VS), nucleus accumbens (NAcc), subgenual cingulate cortex (SCG) and supero-lateral medial forebrain bundle (slMFB) [11,12]. The results of studies investigating the efficacy of DBS in OCD [13] as well as TRD are promising [14]. Besides rapid and acute effects of DBS, recently published long-term data could show a sustained efficacy for the continuous treatment of OCD [15] and TRD [16–18]. These studies have demonstrated that the treatment effect can be maintained over years if stimulation is kept active.

Effects of a discontinuation of stimulation, whether intently or accidentally, are of obvious key importance for the long-term DBS treatment in psychiatric indications where the new occurrence of symptoms might counteract the patient's compliance. In clinical studies, unintended DBS interruption is often just briefly mentioned, especially in larger articles focusing mainly on the efficacy following the onset of stimulation. In these articles, the described effects of a discontinuation are easily underestimated. Therefore, the aim of this article is to review studies describing discontinuation effects of DBS for OCD and TRD. There are several occasions resulting in a discontinuation of stimulation. (1) Firstly, stimulation can be discontinued accidentally due to battery depletion, internal pulse generator (IPG) failure or inactivation by metal detectors (for a detailed description of effects of electromagnetic interference on deep brain stimulators see [19]). In those cases, the patient and clinician are unaware of the stimulation status and the interruption of stimulation might be noticed far too late, for example, at a time where the patient already experiences a worsening of symptoms. Regarding the need for a frequent battery replacement reported in OCD [20] as well as the high rate of hardware complications (8.4–10.3% per electrode per year), unintended discontinuation of DBS is an important issue [21]. (2) Secondly, stimulation can be switched off consciously by the patient or by the clinician, and, (3) thirdly, stimulation can be discontinued as part of a study protocol investigating effects of discontinued stimulation in a double-blind cross-over design.

This paper aims to give an overview of the effects of DBS discontinuation in psychiatry and to report another single case that experienced an unintended discontinuation of supero-lateral medial forebrain bundle (slMFB) DBS after seven years of continuous stimulation. Additionally, we have reviewed data that have been reported in the literature so far, including studies investigating cessation effects in a controlled double-blind setting as well as case reports describing unintended cessation of stimulation.

2. Methods and Materials

A review of the literature was conducted, and data describing effects of a DBS discontinuation in the treatment of OCD and TRD are summarized. For the literature review, pubmed, pubpsych,

Web of Science and Google Scholar were searched with the keywords "DBS (and) discontinuation", "DBS (and) interruption" and "DBS (and) cessation". As the effects of DBS discontinuation often are described as part of larger RCTs, there were only a small number of articles that were found with the above-described keywords. Here, we have also included articles that briefly mention effects of DBS discontinuation in the section adverse events or discussion. We scanned articles describing short and long-term effects of DBS in OCD and TRD for the words "discontinuation", "interruption" and "cessation". Furthermore, the experience of one of our patients is reported. Seven years after the onset of slMFB DBS, stimulation was stopped unintendedly. The surgery as well as the treatment method is described elsewhere in detail [22]. The patient signed a written informed consent for the publication of this case.

3. Review of the Literature

3.1. Obsessive-Compulsive Disorder (OCD)

(1) *Unintended Cessation:* Four articles mention in total 16 patients with DBS for treatment-refractory OCD having experienced an unintended cessation of DBS due to battery depletion, IPG failure or inactivation by metal detectors [20,23–25]. In most cases (n = 13), OCD symptoms worsened acutely after DBS interruption of the ventral caudate nucleus (VC) [23,24] or the anterior limb of the internal capsule (ALIC) [20,25]. Furthermore, in all reports except one [23] mood disturbances are also described as a consequence following DBS interruption. In these cases, exacerbation of affective or anxiety symptoms was observed within days after DBS cessation. In some patients, affective symptoms were reported even more rapidly and more markedly compared to OCD symptoms [24,25]. DBS non-responders (two out of nine cases) did not experience any change after DBS discontinuation [24]. In one case (out of six), psychiatric symptoms even exceeded baseline scores (described as rebound phenomenon) and discontinuation of stimulation caused acute suicidal ideation [20]. After the re-onset of stimulation (device replacement or recharge of battery), the described symptoms normalized and improved back to pre-discontinuation levels [20]. While the return to remission levels is described as being rather quick in two cases [25], it took three months in another case until a stable response was recaptured [23].

(2) *Intended Cessation:* In a single unblinded study, DBS of the nucleus accumbens (NAcc) was discontinued with the knowledge of the patients and the clinicians for seven days (n = 16) [26]. Patients had received continued DBS for at least one year and showed a stable pattern of OCD, mood and anxiety symptoms for at least five months before stimulation was ceased. One day after the cessation of stimulation, nine patients reported subjective worsening of OCD and 11 patients experienced a worsening of anxiety and depression. On average, Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores increased by 50%, Hamilton Anxiety Rating Scale (HAM-A) scores by 80% and Hamilton Depression Rating Scale (HAM-D) scores by 83%. Two patients even experienced rebound symptoms reporting HAM-A scores exceeding baseline levels by 39% and HAM-D scores by 36%. Similar results have been reported in two cases with a blinded discontinuation of DBS of the ALIC during the follow-up period (six months after DBS implementation) [27]. One of the two patients experienced a sudden increase (within a few hours) in anxiety, depression and frequency, as well as severity of OCD symptoms. The patient developed suicidal thoughts and HAM-D scores as well as Y-BOCS scores exceeded baseline levels. The other patient experienced a course with slower worsening of symptoms with a peak after one week without experiencing a total rebound. Restoration of stimulation resulted in a return to the previously obtained improvements in both patients.

(3) *Controlled Trials:* Four studies included a double-blind cross-over phase with randomization of patients to either ON-OFF or OFF-ON stimulation [28–31]. Two of the studies with DBS of the ALIC were conducted in a very small sample size ($n \leq 6$), and results are described in a more anecdotal manner [28,29]. In both studies, severe worsening of mood as well as an increase of OCD symptoms was described. For two patients, the sham period needed to be abridged due to suicidal thoughts [28],

while two patients in another trial did not experience any or only small but clinically not meaningful effects [29]. The further two studies included bigger sample sizes of 16 OCD patients with STN-DBS [30] and 14 OCD patients with NAcc DBS [31]. In both studies, an acute increase of OCD symptoms was reported after cessation of stimulation. These symptoms improved immediately with the re-onset of NAcc DBS [31].

3.2. Treatment-Resistant Depression (TRD)

(1) *Unintended Cessation:* In the field of TRD, several cases with an unintended cessation of DBS in different brain targets have been briefly mentioned in articles describing primarily the antidepressant efficacy of DBS (e.g., paragraphs adverse events or discussion) [16,17,32–35]. Due to the shortness of information in these articles, the overall number of cases is unknown. Three reports describe the effects of an unintended discontinuation of DBS in six cases in detail [36–38]. In one case, classified as responder to DBS of the subcallosal cingulate gyrus (SCG), sudden battery depletion after 26 months resulted in a suicide attempt as well as sudden increase of suicidal thoughts when battery was again depleted 56 months after DBS onset [37]. Four cases of slMFB-DBS experienced different time courses until a worsening of depressive symptoms occurred [38]. Another article reported that an interruption of VC-DBS led to an increase in craving and smoking in one case resulting in an increase of cigarette consumptions by 50 to 200% per day [36]. Altogether, the briefly mentioned descriptions as well as detailed reports link the interruption of DBS of different brain targets to a clear worsening of depressive symptoms, although different time courses are described. While some patients experienced a slow and gradual decline of symptoms over a period of four to six weeks [33], worsening of depression occurred rather rapidly in other cases [34,37]. The restoration of stimulation always led to an improvement of symptoms. Here, time until pre-discontinuation levels of antidepressant response were recaptured differed individually, too. In some cases, re-onset of stimulation was associated with an improvement of depressive symptoms within two to four weeks [33], while it took several months in another case [17]. Even in the same patient, time courses to regain symptom levels before discontinuation differed between a very rapid stabilization of mood within 24 h and a slower improvement within two to four weeks [37,38].

(2) *Intended Cessation:* One case with an intended DBS discontinuation in an open setting (patient and clinician were aware of stimulation status) is reported [38]. In this case, slMFB stimulation had to be switched on again four days after DBS switch off due to a rapid worsening of depressive symptoms. The patient had shown a stable response to DBS treatment for two and a half years before. Nocebo effects and effects of negative expectations are discussed in this case. Nonetheless, it seems rather improbable regarding another single case that showed a massive worsening of depressive symptoms following SCG DBS discontinuation in a blinded setting [39]. Here, the patient with the most robust and best-sustained clinical response showed an increase of depressive symptoms as well, although antidepressant effects could be sustained longer. A progressive increase of depressive symptoms including loss of energy and drive is described over a period of three to four weeks following the cessation of stimulation. In both cases, antidepressant effects could be re-captured rather fast after the re-onset of stimulation within 24 to 48 h.

(3) *Controlled Trials:* There are two studies investigating the effects of a discontinuation of DBS in TRD in a double-blind randomized trial with comparison of ON-OFF versus OFF-ON stimulation [40,41]. In a small randomized trial, three out of five patients relapsed with cessation of SCG stimulation, while two patients did not experience any clinical change [40]. Instead, for those two patients therapeutic effects of DBS lasted over the whole OFF period. Furthermore, an unexpected moderate worsening in the ON-OFF group was reported while the stimulation was still active. An explanation for this effect is negative expectations. Patients are faced with the possibility of a discontinuation of stimulation, and this alone seems to result in a worsening of symptoms. In the largest trial, investigating 16 patients after a stabilization phase of 52 weeks, eight responders and two non-responders showed increased depressive symptoms within a day when DBS of the ALIC was ceased [41]. Here, HAM-D scores were significantly lower in the active phase (13.6) than the sham phase (23.1). Patients had to be

prematurely crossed over to active stimulation to prevent a full relapse into depression independently, whether they were classified as responder or non-responder before. Within a day following the re-initiation of DBS, the antidepressant effect was recaptured in the responders. In two studies, blinded discontinuation of NAcc stimulation [42] and SCG stimulation [43] was abandoned from study protocol due to significant worsening of depressive symptoms in the first three patients in each study. Ethical concerns were expressed regarding the fact that patients experienced significant distress, increased suicidal ideation and a rapid return of depressive symptoms. Furthermore, depressive symptoms did not improve immediately after the re-initiation of stimulation as hypothesized before, which was decisive for the elimination of this study phase for subsequent patients [43].

4. Case Presentation

The patient we describe here is a German male, and at the time of writing 44 years old. Until the onset of depression, he experienced a happy and joyful family life with his wife and his son, born 2002. Seven years later, in 2009, without any triggering event, he was severely depressed. One year later, a severe episode of a major depression was firstly diagnosed. Since then, he was hospitalized several times and treated with numerous different psychiatric medications, including antidepressants and anticonvulsants. He had psychotherapy with different psychotherapists and electroconvulsive therapy as well. None of these treatments led to a significant improvement, and the depression was classified as treatment-resistant in 2012. The patient was no longer able to work in his job as a police officer or to interact with his son. He experienced a low quality of life and a high degree of psychological burden and strain.

In 2012, DBS surgery was conducted within a study [22]. DBS electrodes were implanted bilaterally in the supero-lateral medial forebrain bundle (slMFB) to stimulate this brain region in order to treat the chronic, severe and treatment-resistant depression [44]. In the first week after the implantation, depressive symptoms were immediately reduced significantly. In the following years the patient showed a stable reduction of depressive symptoms (mean Montgomery–Åsberg Depression Rating Scale (MADRS) reduction over seven years in percent = 63.56 (17.40)) (see Figure 1). Although depressive symptoms fluctuated over time, depression severity never reached pre-implantation levels (see Figure 2). Furthermore, the patient stated that depression severity never exceeded baseline levels after DBS surgery (MADRS sum at baseline = 31 points).

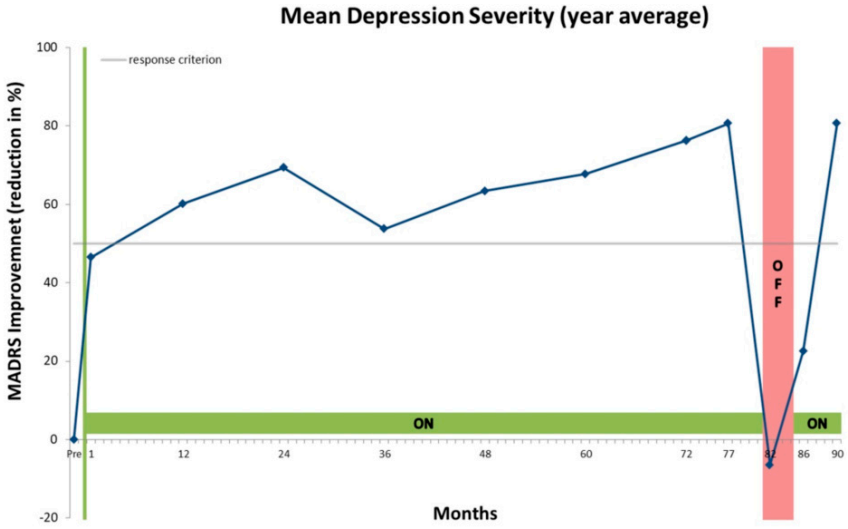

Figure 1. Montgomery–Åsberg Depression Rating Scale (MADRS) reduction over seven years and during the period of discontinued stimulation. Blue line indicates the MADRS scores (reduction in % compared to baseline) of the single patient. Grey line indicates the response criterion (MADRS reduction ≥ 50%). Figure 1 shows the mean scores for each year.

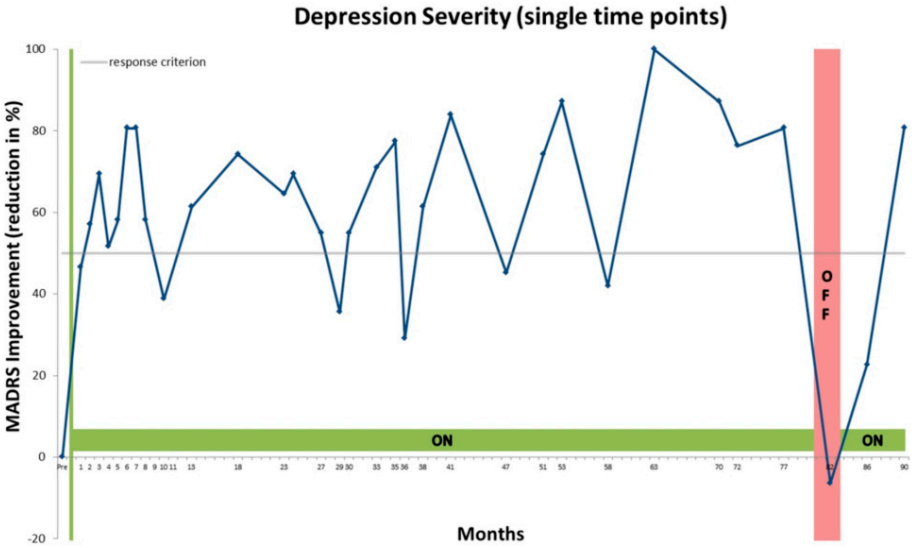

Figure 2. Montgomery–Åsberg Depression Rating Scale (MADRS) reduction over seven years and during the period of discontinued stimulation. Blue line indicates the MADRS scores (reduction in % compared to baseline) of the single patient. Grey line indicates the response criterion (MADRS reduction ≥ 50%). Figure 2 shows every single data point that was collected during the seven years of DBS treatment. This impressively demonstrates that patients responding to DBS still have normal affective reactions to life events.

The reduction of depressive symptoms was so significant that he was able to resume his normal life functions, including his professional occupation as a police officer. He was again able to be socially active and engage in interaction with his son. Motivation and energy were improved. DBS improved the quality of his life significantly. In 2019, he took up sports again and was able to voluntarily lose weight consecutively. Depressive symptoms were sustainably reduced for seven years, and the patient did very well. Nonetheless, he still experienced a reduction of emotions as a residual symptom. He indicated that he was not able to feel real pleasure or sadness. The patient was very motivated and convinced of the treatment as such.

In September 2019, the patient called because he experienced severe symptoms of depression (MADRS sum = 33 points). He described his state comparable to the situation before implantation. He was very anxious and did not want to tell his wife how bad he was feeling. He tried very hard to keep up his normal life so that nobody would notice. At this time, he was very hopeless, frustrated and desperate; he lost his appetite, was easily irritated and experienced suicidal thoughts without any intention to act. After learning about this, we tried to convince him to make an appointment, but he saw himself unable to make the trip to our clinic. In November, he checked his device randomly and it turned out that the stimulation had been discontinued without being noticed by the patient. The stimulation was discontinued due to battery depletion and was not automatically switched on again by charging the battery.

After noticing the inactive stimulation status, the patient turned on the stimulation. After the re-onset of stimulation, depressive symptoms improved slightly but were still significantly worse compared to April 2019. For this reason, we made an appointment with the patient in January 2020 to adjust the stimulation parameters. In this case, the parameter adjustment was necessary in order to resume the pre-discontinuation level of the antidepressant response. Several months later, in May 2020, symptoms were fully remitted again (MADRS sum = 6 points) (see Figures 1 and 2).

5. Discussion

Here, we report a case with a successful complete recovery from depression over seven years following the onset of DBS, in which a full relapse of depressive symptoms after unintended stimulation

interruption and finally the return to treatment efficacy after re-initiation of DBS and parameter adjustment was experienced. This single case is reported together with a literature review of other case reports of DBS discontinuation in TRD and OCD as well as studies investigating effects of an intended DBS interruption. The course of the current case report is in line with a case series of slMFB DBS discontinuation presented before [38] and underlines the need for chronic, long-term DBS with constant electrical stimulation.

Reviewing the literature and summarizing the cases, a discontinuation of DBS in psychiatric disorders seems to be associated with a high risk of worsening of psychiatric symptoms. In some patients, even rebound symptoms exceeding baseline levels are described. In the case of OCD, DBS discontinuation has been associated with the reemergence of OCD symptoms as well as the (re-) occurrence of symptoms of depression, anxiety and suicidality. In patients with TRD, an increase of depressive symptoms is demonstrated following the discontinuation of DBS. This is important in light of the fact that this seems to happen even after long periods of clinically stable improvement. In the current case, a worsening of symptoms occurred rapidly after the discontinuation although DBS sustainably reduced depressive symptoms for more than seven years previously. A discontinuation after such a long follow-up has not been reported in the literature yet. Regarding the reviewed literature, only a few articles describe a small number of three (out of nine) [24] and two (out of four) [29] OCD patients as well as two (out of five) [40] TRD patients that seem to experience no clinical change after the cessation of stimulation. Here, two of the seven patients were classified as DBS non-responders before, experiencing no clinically significant improvement with active stimulation as well as no clinically meaningful effects of DBS discontinuation [24].

Until today, there have been no variables known that can predict in which patients antidepressant effects will be maintained or in which a worsening of symptoms will occur. Neither is known why some patients show a stable response even after DBS discontinuation. The duration of continuous stimulation before the cessation does not seem to explain the differences, as even patients with permanent DBS for several years and a sustained response or remission do not seem to be protected from a relapse following interruption of DBS. Future studies or cases are needed to study behavioral as well as biological changes in patients with stable response after DBS cessation. Furthermore, psychological factors, such as vulnerability of the depression network, ability of emotion regulation, availability of stabilizing resources (caregivers, social environment, work, hobbies, etc.) as well as self-efficacy expectations need to be explored regarding the reactions to DBS cessation.

Altogether, the reported literature strongly underlines the need for chronic DBS in psychiatric disorders, as is well-known from the DBS treatment in PD [9]. Patients with sustained responses after DBS discontinuation seem to be in the minority. Despite the above-mentioned double-blind studies investigating DBS discontinuation in OCD [28–31] and TRD [40,41], scientific evidence for the need of continuous DBS is still lacking. This is because effects of discontinuation of stimulation are mostly reported in form of anecdotes. Further studies with blinded cross-over designs in larger patient samples are needed for a better understanding of the effects of DBS discontinuation. Nevertheless, the need for double-blind studies must be balanced against the risk of a DBS switch-off described here. The definition of criteria to rescue patients experiencing a rapid worsening in the DBS off phase as well as the possibility to prematurely end the discontinuation of stimulation are important for ethical considerations.

In future studies, the role of nocebo effects and negative expectations as well as the fear of facing a discontinuation of DBS need to be critically investigated as contributing factors. Negative expectations may have had an impact in studies where patients were aware of the moment of discontinuation or randomization to the OFF-phase [31,40]. Uncertainty and doubt about entering the blinded discontinuation of stimulation led to a minor increase in OCD symptoms as well as depression severity. Here, symptoms worsened just because patients faced the risk of a DBS discontinuation. One OCD patient refused to participate in the cross-over phase because he was frightened to face the risk of losing the experienced improvement [31]. In the DBS treatment of PD, same effects of negative

expectations have been demonstrated [45,46]. Benedetti et al. (2003) showed a nocebo effect describing a worsening of symptoms when researchers only pretended to turn off the stimulation in ten patients with PD. Although nocebo effects and effects of negative expectations are likely, cases of unintended discontinuation due to battery depletion speak against that explanation, because patients were unaware of stimulation status and did not expect any clinical change [38].

Furthermore, studies investigating changes in brain metabolism following DBS discontinuation can contribute to this discussion and to the understanding of possible underlying mechanisms of discontinuation effects. Regarding the mode of action in PD, DBS seems to induce only transient changes of brain functioning, indicating a functional and temporary phenomenon [47,48]. During active DBS, metabolism in the subthalamic region is increased compared to inactive DBS in 14 PD patients [47]. The abnormal parkinsonian network can be restored as long as the stimulation is actively applied. This is in line with the clinical worsening of motor symptoms in PD during the non-stimulation phase. Effects of DBS represent a reversible phenomenon regarding the clinical as well as biological changes [48].

Similar results have been described in the DBS treatment for psychiatric disorders. In OCD, NAcc activity was decreased during the DBS OFF phase and showed lower activity compared to controls, while the discrepancy disappeared with active DBS [49]. Therefore, it can be assumed that NAcc-DBS may normalize the activity of the NAcc and restores the intrinsic frontostriatal network dynamics only as long as the stimulation is active. In TRD, acute changes in brain metabolism have been observed within 48 hours of inactive stimulation [50]. In this study, regional glucose metabolism decreases occurred in the dorsal anterior cingulate (BA24), the premotor region (BA6) and in the putamen prior to clinical changes. Brain metabolism changes could constitute a precursor of re-occurrence of depressive symptoms after DBS interruption. Additionally, DBS discontinuation is associated with a stress response. In OCD, cortisol levels increased by 53% in eight patients when stimulation was switched off for one week after chronic NAcc DBS [51]. The increased cortisol levels correlated with the re-occurrence of OCD symptoms as well as depressive symptoms. During active stimulation, cortisol excretion was within the reference of healthy individuals. These results show that symptom improvement with DBS could be related to a normalization of hypercortisolism and that this effect may diminish with a discontinuation of DBS even after a year of continuous stimulation. No conclusion regarding the causality between the changes in clinical symptoms and biological changes can be reached from this study. Altogether, it is very likely that the interruption of DBS results in biological changes that might precede clinical changes. Nonetheless, future studies need to investigate whether DBS discontinuation itself or the relapse of symptoms causes biological changes.

The described biological changes can also be discussed as an explanation for the described rebound phenomenon reflecting an autonomic withdrawal symptom [26]. Nonetheless, no additional symptoms besides symptoms underlying the psychiatric disease have been described [43]. Furthermore, a discontinuation of antidepressants sometimes is associated with a lack of further efficacy in the same patient. Interestingly, this seems not to be the case in DBS treatment. Antidepressant effects were recaptured within one day to several weeks independently of the time of DBS treatment and the duration of discontinuation.

The occurrence of DBS discontinuation should be regarded as an important safety aspect, because the rapid (re-) occurrence of symptoms could constitute a medical emergency. Suicidality, suicidal ideation and non-compliance to the treatment are the most worrisome aspects in the described scenarios [37]. Battery depletion as well as IPG replacements must be monitored carefully and patients need to be informed about such incidents. In OCD, battery replacements are reported frequently [20] and patients need to recharge the device normally once a day to once in five days [26]. Compared to patients treated with slMFB-DBS for OCD and TRD, recharging is only necessary on average every two to four weeks. Regarding the effects that a discontinuation of stimulation by battery depletion can cause, lower charging frequency as well as longer battery life are important issues for the DBS long-term treatment in context of the safety concerns described above. The extension of battery life

should be an important goal for the further development of the medical DBS devices and patients should be aware of the importance to charge the battery regularly to prevent an unintended cessation of stimulation due to battery depletion. Additionally, it would be helpful for the patients if a notice would appear, for example, during the charging process of the device that informs about the inactive status of the stimulation. For now, close and regular follow-up visits are highly important to prevent such incidents. Furthermore, it is important that psychiatrists are involved in the aftercare and the follow-up of these patients.

Another important aspect of DBS discontinuation in TRD and OCD is the stimulated brain target. No differences of cessation effects could be seen between the different stimulation targets for OCD or TRD possibly due to small sample sizes. Worsening of symptoms seems to be independent from stimulation target, although these effects have been researched more thoroughly in some targets than others. In OCD, discontinuation effects have been described for DBS of the VC [23,24], the ALIC [20,25,27–29], the NAcc [26,31] and the STN [30]. Most studies as well as cases describing DBS cessation in TRD are reported for the stimulation of the SCG [16,33,34,37,39,40,43]. Discontinuation of stimulation of the ALIC and VC has been reported in four articles [17,32,36,41], while there is only one article briefly mentioning the cessation of NAcc-DBS [42] and a case series about slMFB-DBS in TRD [38]. Discrepancies in the discontinuation effects seem to differ rather individually than between the varying brain targets. For a systematic comparison of differences between the varying brain targets, further studies are needed.

6. Conclusions

DBS interruption constitutes an important safety aspect in the treatment of psychiatric patients. Here, we describe the course of depression of a single patient experiencing a sustained recovery with continuous slMFB stimulation over seven years and a rapid and full relapse into depression after the unintended cessation of stimulation. Symptoms are now fully recovered four months after the adjustment of stimulation parameters. The re-activation of stimulation itself did not lead to a return to symptom levels before discontinuation. Regarding this case together with the reviewed literature, the unintended discontinuation of DBS is associated with important safety aspects. Patients experience a rapid and severe worsening of symptoms (even rebound of symptoms) without noticing that the stimulation has stopped. In some cases, it is more difficult to recapture the antidepressant response; meanwhile, worsening of symptoms as well as symptoms of suicidality can occur immediately. We believe that this two-way change reflects efficacy of DBS, and cannot be explained by mere placebo response or solely by negative or positive expectations. Nonetheless, there are some patients with a sustained treatment response even after DBS cessation. Biological as well as psychological factors following DBS and DBS cessation need to be investigated in future studies, and predictors for a sustained efficacy after DBS discontinuation need to be explored. In conclusion, patients and clinicians need to be aware of possible discontinuation effects regarding the described risks of a worsening of symptoms.

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