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Rebound of Affective Symptoms Following Acute Cessation of Deep Brain Stimulation in Obsessive-compulsive Disorder

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ABSTRACT

Background: Deep brain stimulation (DBS) is regarded as an effective way to treat refractory obsessive-compulsive disorder (OCD). Little is known about the effects of DBS cessation following a longer period of stimulation.

Objective: To determine the relapse and rebound effects of psychiatric symptoms, and their impact on Quality of Life (QoL) following acute cessation of DBS in OCD patients.

Methods: We included 16 out of 32 patients who were treated with DBS between April 2005 and January 2011 at the Academic Medical Center, Amsterdam. After treatment for at least one year, patients entered a 1-week phase in which DBS was switched off. We evaluated psychiatric symptoms and QoL at three time points: before DBS surgery (pre-DBS), following at least one year of DBS treatment (DBS-on) and following 1 week of DBS off (DBS-off). Psychiatric symptoms were assessed with the Yale-Brown obsessive-compulsive disorder scale (Y-BOCS), the Hamilton anxiety rating scale (HAM-A) and the Hamilton depression rating scale (HAM-D). QoL was assessed using the World Health Organization QOL scale (WHOQOL-Bref).

Results: Switching from DBS-on to DBS-off, Y-BOCS scores increased with 50%, HAM-A scores with 80% and HAM-D scores with 83%. In the DBS-off period, HAM-A and HAM-D scores exceeded pre-surgery levels with approximately 40%, suggesting a rebound phenomenon. Furthermore, a deterioration of physical and psychological QoL to levels comparable with pre-surgery was found during DBS-off.

Conclusion: Acute DBS cessation causes a relapse of obsessions and compulsions and a rebound of anxiety and depression. Additionally, improvements on QoL disappear.

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Introduction

Deep brain stimulation (DBS) is a safe and effective treatment strategy for therapy-refractory obsessive-compulsive disorder (OCD). Studies report overall responder rates of approximately 50%, limited side effects, and a positive influence on functioning and quality of life (QoL) [1]. However, maintaining these positive effects most likely requires chronic and likely life-long application of DBS.

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Given this permanent reliance on DBS, it is important to consider that unintended cessation occurs on a regular base. Videnovic and Metman reported a hardware complication rates of 8.4%–10.3% per electrode year [2], which often causes unintended temporary cessation of DBS. Moreover, especially in OCD treatment, high currents are used, which causes battery depletion every 1–2 years. The advent of rechargeable batteries has reduced this problem considerably. However, to function properly these batteries have to be recharged often, on average ranging from once a day to once in five days, dependent on stimulation setting. Therefore unintended cessation of DBS is nowadays often related to recharging issues.

Despite the frequent interruption of active stimulation, little is known about its impact on clinical symptoms and general wellbeing of the patients. Case-series [3–5] and efficacy studies with DBS on-off design [6,7] generally report an acute worsening of psychiatric

Table 1
Demographic and clinical characteristics.

	Patients (n = 16)	
	Mean (range)	SD
Gender (Males/females)	9/7	
Age (years)	45 (27–59)	9.73
Age at onset (year)	16.12 (5–35)	8.15
Age at DBS surgery (year)	42 (22–55)	9.75
Y-BOCS before DBS surgery	33.88 (28–40)	3.32
HAM-A before DBS surgery	21.89 (12–42)	7.66
HAM-D before DBS surgery	19.75 (5–30)	6.97
Duration of DBS treatment (months)	33.19 (12–56)	18.05
Percentage decrease on Y-BOCS	41% (0–84)	19.72

symptoms when batteries are depleted or stimulation is abruptly stopped. Typically, though individually highly variable, a worsening of mood and anxiety is observed immediately after DBS cessation, followed by a more gradual and less marked relapse of OCD symptoms [3,8]. In a previous DBS efficacy study of our group [6], we found indications for worsening of symptoms even exceeding baseline levels, so called rebound phenomena. Recently, Vora et al., described such a rebound in one patient consisting of increased severity of OCD symptoms compared to pre-surgery levels following battery depletion [9]. In none of these studies however, anxiety or depressive symptoms were systematically compared between pre-surgery and DBS-off, making it uncertain whether depressive and anxiety symptoms also rebound after DBS cessation. Furthermore, none of these studies assessed the patient perspective, leaving it unclear how patients experience DBS cessation, and whether cessation influences their QoL. This information is important to obtain a more complete understanding of the clinical impact of DBS cessation.

In the current study we determine the effects of acute DBS cessation with validated scales for OCD, anxiety, depressive symptoms and QoL. We aim to determine whether (1) patients experience a relapse (severity higher than with DBS-on, but at a lower or similar level than before surgery) or rebound (severity higher than with DBS-on and higher than before surgery) of symptoms following cessation of DBS and (2) if and to what extent QoL is affected during DBS cessation. These results will help us understand the impact of DBS cessation in OCD patients, which will be crucial for good patient education and follow-up care, especially considering the growing number of patients treated with this technique.

Methods

Subjects

From April 2005 until January 2011, 32 patients were treated with DBS at the Academic Medical Center (AMC) Amsterdam. Details of the surgical technique are described elsewhere [6,10]. Inclusion criteria for the current study were (1): Time since surgery had to be at least 1 year and (2) patients had to have a stable pattern of OCD, mood and anxiety symptoms for at least 5 months. Table 1 summarizes the clinical and demographic characteristics of 16 out of the 32 patients who met both inclusion criteria. Six of the 16 patients who were excluded from the study did not meet the first inclusion criterion, four were considered to have an instable pattern of psychiatric symptoms, and six others did not want to participate because of fear of turning DBS off.

Study design

The current study was part of a larger experiment investigating the neural mechanisms of DBS in a one week DBS-off design, of which parts have been published earlier [11]. At the beginning of

the study, symptom severity and QoL were assessed while DBS was still on (DBS-on). The next day DBS was turned off and remained off for the next seven days. At the seventh day of the off-period, patients were again assessed (DBS-off). One day later DBS was turned back on. Patients and clinicians were aware of the DBS condition during the whole period. The responsible psychiatrist (MF) assessed all symptoms scales. The results were compared to pre-surgery data which were obtained one month before DBS surgery (pre-DBS). The study was approved by the medical ethics committee of the Academic Medical Center (AMC) Amsterdam.

Outcome measures

Severity of OCD symptoms was measured using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) [12], a 10-item semi-structured, clinician-administered scale. Each item is scored on a 5-point Likert scale ranging from 0 to 4. Depressive symptoms were rated with the 17-item Hamilton Depression Rating Scale (HAM-D) [13], scores ranging from 0 to 54. Anxiety was evaluated with the Hamilton Anxiety Scale (HAM-A) [14], a 14-item scale with a range of 0–56 points. All three scales are widely used and have well-established psychometrics [15–17]. For all three measures, higher scores indicate more severe symptoms.

Quality of life was assessed using the abbreviated version of the World Health Organization quality of life questionnaire (WHOQOL-BREF) [18]. This instrument measures the individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It comprises 26 questions summarized in four domain scores: physical, psychological, social and environmental. All questions are rated on a 5-point Likert scale. An example item is: *How satisfied are you with your health?* 1 = very dissatisfied, 5 = very satisfied. The scores of the four domains range from 4 to 20. Higher scores indicate a higher perceived quality of life. The Dutch translation of the WHOQOL-bref displays a good content and construct validity and test-retest reliability in a psychiatric population [19]. The recall period was adjusted to one week for the purpose of this study (two weeks in the original version).

Statistical analysis

Repeated-measures analysis of variance (ANOVA) with the three time points (pre-DBS, DBS-on and DBS-off) as within-subject factors were used to examine if the mean scores on the different time points were statistically different. To control for the influence of baseline variables, age, gender and length of follow up were entered in the model as covariates. However, in none of the analysis they proved to be significant, so only main effects were reported. Significant main effects were explored using post-hoc *t*-test between DBS-on and DBS-off, and pre-DBS and DBS-off. To adjust for multiple testing, Bonferroni correction ($\alpha = 0.05/2 = 0.025$) was used. Cohen's *d* effect sizes were calculated to estimate effect size. To identify relapse or rebound of symptoms, the scores of each subject at DBS-off were compared with their own scores at DBS-on and pre-surgery. Relapse was defined as an increase in score between DBS-on and DBS-off. Rebound as an increase in score between pre-surgery and DBS-off. All statistical analyses were performed using commercially available statistical software (SPSS, version 20.0; SPSS Inc, Chicago, Illinois).

Results

Clinical symptoms

Repeated measures ANOVA showed a significant effect of time between the three time points on the Y-BOCS ($F(2,15) = 33.074$,

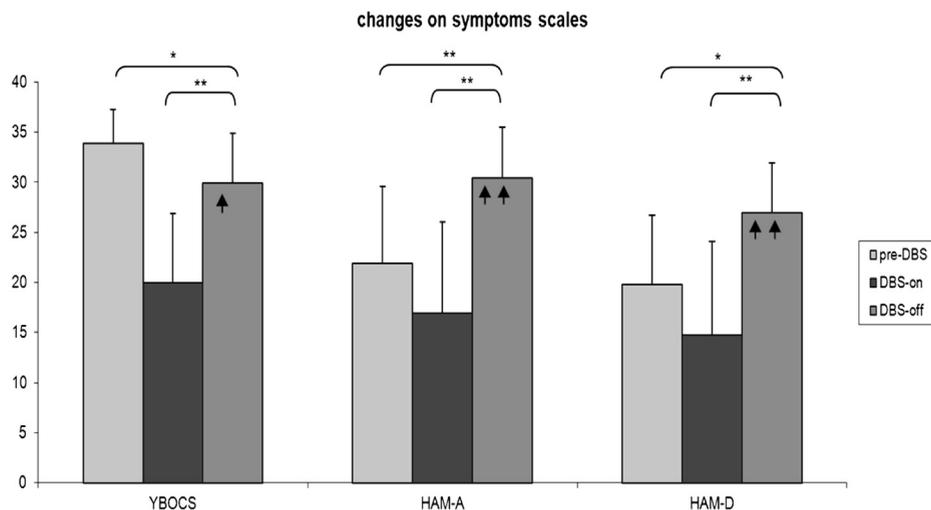


Figure 1. Change in clinical symptoms between DBS-on and DBS-off, and between pre-DBS and DBS-off. Abbreviations: Y-BOCS = Yale-Brown Obsessive-Compulsive scale; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Scale; DBS: Pre-DBS = 1 month before DBS surgery, DBS-on = at least one year of active stimulation, DBS-off = one week without stimulation. (*) paired sample *t*-test significant at $P < 0.05$, (**) paired sample *t*-test significant at $P < 0.01$, (▲) = relapse of symptoms, (▲▲) = rebound of symptoms.

$P < 0.01$, on the HAM-A ($F(2,15) = 15.088$, $P < 0.01$), and on the HAM-D ($F(2,15) = 11.743$, $P < 0.01$) (Fig. 1).

Post hoc *t*-tests between DBS-on and DBS-off showed a significant increase on all symptom scales between DBS-on and DBS-off, indicating worsening of all clinical symptoms in the absence of DBS stimulation. The Y-BOCS score increased on average 50%, from 19.94 (SD = 6.92) to 29.90 (SD = 5.74) points ($t(15) = -5.150$, $P < 0.01$, $d = 1.57$). The HAM-A increased with 80%, from 16.94 (SD = 9.10) to 30.44 (SD = 10.26) points ($t(15) = -4.624$, $P < 0.01$, $d = 1.39$) and the HAM-D increased 83%, from 14.69 (SD = 9.41) to 26.94 (SD = 8.69) points ($t(15) = -5.107$, $P < 0.01$, $d = 1.35$). On the individual level an increase in psychiatric symptoms was found in 15 of the 16 patients on the Y-BOCS and HAM-D, and in 13 patients on anxiety. Nine of 16 patients reported a subjective worsening of OCD symptoms and 11 of anxiety and depression symptoms after 1 day of DBS off.

Post-hoc *t*-tests between pre-DBS and DBS-off revealed that the Y-BOCS score remained on average 12% lower, during DBS-off (29.90 points, SD = 5.74) than before DBS surgery (33.88 points, SD = 3.32), ($t(15) = 2.823$, $P = 0.013$). The effect size was found to be high ($d = 0.85$). On the individual level, of the 15 patients who experienced an increase in OCD symptoms, two were found to have

a rebound of OCD. Notably, HAM-A scores at DBS-off (30.44 points, SD = 10.26) were found to be on average 39% higher than before surgery (21.88 points, SD = 7.66), ($t(15) = -4.129$, $P < 0.01$, effect size: $d = -0.95$), and this anxiety rebound was observed in 11 of the 13 patients who had a increase of anxiety between DBS-on and DBS-off. Similarly, HAM-D scores at DBS-off (26.94 points, SD = 8.69) were on average 36% higher compared to the pre-surgery scores (19.75 points, SD = 6.97), ($t(15) = -2.783$, $P = 0.014$, effect size: $d = -0.91$), with a rebound of depressive symptoms in 11 of the 15 patients who had a increase in depressive symptoms when stimulation was stopped.

Quality of life

Quality of life as measured by the WHOQOL-bref showed a significant effect of time, on the physical ($F(2,15) = 4.346$, $P = 0.022$) psychological ($F(2,15) = 10.808$, $P < 0.01$) and environmental domain ($F(2,15) = 3.981$, $P = 0.029$). The social domain ($F(2,15) = 1.559$, $P = 0.227$) showed no significant change. Figure 2 shows a graphical presentation of the QoL scores during the different time points and a comparison with a Dutch norm

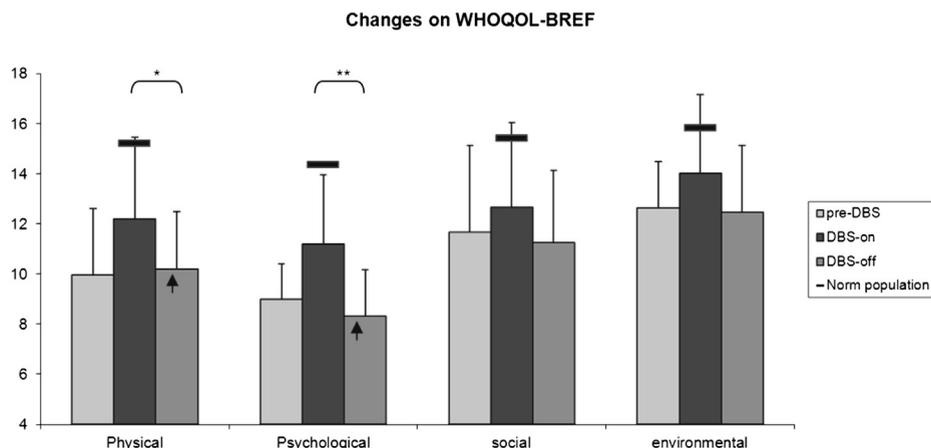


Figure 2. Comparison of WHOQOL-bref scores of the DBS group and a healthy population. Abbreviations: WHOQOL-BREF: World Health Quality of life scale – Range: domain scores 4–20. Higher scores indicating better quality of life brief version; Pre-DBS = 1 month before DBS surgery, DBS-on = at least one year of active stimulation, DBS-off = one week without stimulation; Error bars indicate one standard deviation; (*) paired sample *t*-test significant at $P < 0.05$, (**) paired sample *t*-test significant at $P < 0.01$, (▲) = relapse of QoL.

population [20], indicating that during DBS-on the scores on the WHOQOL-bref approach the scores of the norm population for all but the Psychological subscale.

Post-hoc *t*-test (Table 2) showed that the physical and psychological domain of the WHOQOL-bref decreased significantly between DBS-on and DBS-off. The physical domain score dropped on average 16%, while the psychological domain decreased with 26%. The environmental domain score showed a decrease of 11%, but this did not remain significant after correction. The change on the social domain was not significant. When comparing DBS-off scores with pre-DBS scores none of the domain scores showed a significant difference.

Discussion

Our results indicate that acute DBS cessation in stabilized OCD-patients causes a relapse of OCD symptoms and a rebound of anxiety and depression. Furthermore, seven days of DBS cessation causes an immediate deterioration of physical and psychological QoL.

The symptomatic relapse corresponds with observations from previous DBS on/off efficacy studies and case-series [3,6,9]. It confirms the necessity of continuous, long-term stimulation in OCD patients. Although OCD, anxiety and depression all increased significantly, the increase of anxiety and depression was the most pronounced. This is in line with previous findings [3,8] and indicates a strong and direct relation between stimulation and affective symptoms.

The finding that the increase of anxiety and depression following DBS cessation exceeds pre-surgery levels is important and potentially worrisome. This finding confirms the indication of an affective rebound following acute DBS found in our previous efficacy study [6]. Apart from an anecdotal report of rebound in one patient [9], this is the first study to show that psychiatric symptoms increase above pre-surgery levels when stimulation is abruptly stopped.

A potential explanation for the affective rebound might be that the increase of anxiety and depression reflect autonomic withdrawal symptoms, similar to the withdrawal seen during the first weeks of discontinuation of psychiatric medication like serotonin reuptake inhibitors or benzodiazepines [21]. The increase of cortisol found during DBS cessation in the same patient population [22] supports this hypothesis, since deregulation of the hypothalamic-pituitary-adrenal axis is likely to be involved in withdrawal-induced depression [23]. Alternatively, it could be that affective rebound symptoms reflect feelings of craving for DBS. We have recently demonstrated that effective DBS in these patients restores reward responses in the nucleus accumbens and induces dopamine release in the striatum [11,24]. A sudden interruption of these processes may induce feelings of distress that can be compared to craving phenomena. Finally, patients may have become used to a lower burden of disease and this may have changed how they evaluate themselves and interpret events. A sudden reoccurrence of symptoms may therefore be experienced as being more severe than

before, because patients have raised the standards of what is normal to them.

The deterioration of physical and psychological QoL along with the relapse of OCD and the rebound of anxiety and depression indicates that the impact of cessation is not limited to symptom changes alone. It implies that DBS cessation has a direct impact on patients' wellbeing and the perception of their position in life. The decrease of QoL to pre-surgical levels suggests that despite all the benefit patients have encountered in the years living with DBS and the knowledge that DBS is discontinued for only a short period of time, all QoL improvements disappear when stimulation is stopped. This underlines the severity of DBS cessation and translates the changes on symptoms scales to a more practical understanding. Interestingly, QoL scores during DBS cessation were not significantly lower than pre-surgery. Which nuances the clinical significance of the affective rebound somewhat. It indicates that although patients are more anxious and depressed than before surgery, this does not lead to lower QoL than before surgery. However, it is important to consider that the baseline QoL scores in this sample were very low, so our results could also be influenced by floor effects of the WHOQOL-bref scale.

Our findings raise several questions. First, it is unclear whether and when rebound symptoms disappear over time. Second, it is uncertain whether these rebound symptoms also occur when stimulation would be tapered off slowly. These questions are important from a clinical point of view, for example for patients and clinicians who are confronted with a longer period of DBS cessation, such as following explantation of infected DBS hardware, or explantation because of non-response. To address these questions future studies should apply a longer DBS-off period and include a tapering off group. A third issue arising from our results concerns the validity of on/off designs in DBS trials. Our results indicate that such a study design carries the risk of measuring rebound/withdrawal symptoms. Information on length of withdrawal periods will be important for determining the optimal length of on/off phases in future sham controlled studies toward effectiveness.

Limitations of the current study are that patients were aware of stimulation settings which may have caused patient bias. Future research with a double blind design may eliminate this. However we believe that our design really reflects the daily clinical practice: almost all of the patients who experience DBS cessation are acutely aware of this happening because of the limited placebo effect [11] and the possibility to check the DBS condition with the personal patient controller. Another limitation is the small sample size. However, the fact that we found a rebound in almost two third of this sample suggests that affective rebound is a common effect, making this finding worrisome. Last, because people tend to use their current affective state to judge how happy and satisfied they are with their lives [25], it is likely that they will judge their QoL of this period lower when stimulation is off than when stimulation would be back on and their mood would be stabilized. However assessing QoL in this period reflects how patients evaluate their QoL

Table 2

Paired sample *t*-test of change on WHOQOL-bref between DBS-on and DBS-off, and between pre-DBS and DBS-off.

	Pre-DBS		DBS-on		DBS-off		Change DBS-on – DBS-off				Change pre-DBS – DBS-off				
	M	SD	M	SD	M	SD	<i>t</i>	df	<i>P</i>	<i>d</i>	<i>t</i>	df	<i>P</i>	<i>d</i>	
WHOQOL-bref															
Physical	9.96	2.65	12.21	3.25	10.21	2.27	2.789	15	0.014*	−0.71	0.286	15	0.779	0.1	
Psychological	9	1.4	11.21	2.75	8.33	1.85	3.874	15	0.001*	−1.23	1.247	15	0.232	−0.41	
Social	11.67	3.46	12.67	3.37	11.3	2.88	1.982	15	0.066	−0.45	0.426	15	0.676	−0.13	
Environmental	12.63	1.85	14.03	3.14	12.47	2.68	2.478	15	0.026	−0.54	0.273	15	0.788	−0.07	

WHOQOL-bref: World Health Quality of life scale – brief version; Physical = physical domain of the WHOQOL-bref; Psychological = psychological domain of the WHOQOL-bref; Social = social domain of the WHOQOL-bref; Environmental = environmental domain of the WHOQOL-bref; (*) significant after Bonferroni correction.

during the DBS cessation period and therefore gives valuable information of how they experience DBS cessation.

In conclusion, DBS cessation causes a relapse of OCD symptoms and a rebound of affective symptoms, which has a direct impact on the QoL of patients. Information on the length of rebound and whether this rebound could be overcome by slowly tapering of stimulation are important questions that need to be answered. Prevention of DBS cessation should be a goal for clinicians and DBS manufacturers. Recent developments such as battery life estimators to ensure timely battery replacements [26] and rechargeable batteries may reduce the risk of DBS cessation. Notwithstanding, the risk of cessation remains and therefore it is important to inform patients and family members on the possible effects, and how to react when this happens.

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