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Cyclic versus continuous deep brain stimulation in patients with obsessive compulsive disorder: A randomized controlled trial

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ABSTRACT

Background: Deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule (vALIC) is effective for refractory obsessive-compulsive disorder (OCD), but patients typically require high stimulation voltages and DBS comes with a risk for adverse events (AE).
Objective: The aim of the present study was to advance DBS for OCD by optimizing energy efficiency and minimize adverse events using a cyclic form of stimulation
Methods: This double blind, randomized crossover trial compares 2 weeks of continuous versus cyclic DBS (0.1 s ON, 0.2 s OFF) in 16 patients with OCD. We compared OCD symptoms (Yale-Brown Obsessive-Compulsive Scale, Y-BOCS), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), AEs, battery life, cognitive performance and quality of life.
Results: Average Y-BOCS scores at baseline increased significantly with 5.5 points ($p = 0.006$) in the cyclic condition. Average HAM-D and HAM-A scores increased with 2.2 ($p = 0.088$) and 2.8 points ($p = 0.018$). The overall health scale of quality of life worsened during cyclic DBS ($p = 0.044$). Patients reported on average 3.3 AEs during continuous stimulation and 4.4 AEs during cyclic stimulation ($p = 0.175$), though stimulation-related AEs such as headache and concentration problems reduced during cyclic DBS. Battery usage during continuous DBS was 0.021 V per hour compared to 0.008 V per hour during cyclic DBS.
Conclusion: Though specific stimulation-related AEs improved, cyclic stimulation (0.1 s ON, 0.2 s OFF) comes with a high relapse risk in patients with DBS for OCD. Cyclic DBS is no alternative for standard DBS treatment, but applicable in case of debilitating AEs.

1. Introduction

Deep brain stimulation (DBS) is a treatment for patients with refractory obsessive-compulsive disorder (OCD) that involves the implantation of two electrodes that are connected to a subcutaneously implanted pulse generator (IPG). Several studies have demonstrated effectiveness of DBS in the ventral limb of the internal capsule (vALIC) for refractory OCD, reducing symptoms on average by 40% with an effect size of 1.5 [1]. A recent meta-analysis showed that the pooled response rate of patients with DBS for refractory OCD is 76% [2].

DBS for psychiatry comes with a risk between 2 and 30% for adverse events (AEs), such as insomnia, impulsivity, mood swings, movement disorders, and potentially negative effects on cognitive performance [3–5]. Although side-effects often depend on voltage or stimulation localization, adjusting these stimulation settings may reverse the beneficial effects of DBS. In addition, effective DBS for OCD requires a relatively high average voltage of 4.8 V [4]. Because of the higher currents used for DBS in OCD, the mean life span of the non-rechargeable IPG-battery lies around 14 months, which implies frequent, costly and burdensome surgical IPG replacements [6]. Though the use of rechargeable stimulators has lowered the total number of replacements, the time spent on recharging may have a negative effect on the patient's quality of life since patients experience this as time-consuming [7]. Minimizing side effects and optimizing energy efficiency could significantly improve the quality of life of patients with DBS for OCD.

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In general, DBS is delivered in a continuous 'tonic' fashion, but the device can be programmed to intermittent cycles of on and off stimulation, called cyclic DBS. Studies on cyclic DBS in patients with neurological disorders and computational models suggested that clinical effects of DBS can be retained and improved with cyclic compared to continuous DBS [8–11]. Two previous studies showed that cyclic stimulation may be as effective as regular stimulation in patients with Parkinson's disease (PD) [12] and tremor [13]. Moreover, cyclic versus regular stimulation of the subthalamic nucleus (STN) improved motor performance in eight patients with PD [14]. This effect was significantly associated with suppression of simulated beta frequency oscillations and stronger desynchronizing in a computational model derived from intraoperative microelectrode recordings [14].

Potential advantages of cyclic DBS are reduced side effects and more efficient battery usage. Cyclic vALIC DBS has previously been applied in 3 OCD patients in order to reduce side effects [4]. These patients suffered from a continuous urge to compulsively press their left hand against their right chest at the implantation site of the IPG. They experienced a great tension when having to change this position, and as a consequence all daily activities had to be performed with their right hand. Turning off the stimulator or lowering voltage improved this specific compulsive behavior, at the expense of relapsing their general OCD-symptoms. However, after a week of cyclic DBS (0.1 s on, 0.2 s off), one patient reported complete resolution of this compulsive behavior, and two patients were much better able to control it. The effect of DBS on symptoms of OCD remained stable during cyclic DBS. In addition, the patients reported less battery charging time (own clinical data).

Motivated by these promising preliminary findings, we performed a double blind, randomized, crossover trial to examine whether cyclic DBS reduces side effects and improves battery life. Because cognitive side effects like memory and concentration problems are often reported by patients with DBS for OCD [4], we specifically examine the effects of continuous and cyclic DBS on cognitive functioning. We investigate whether cyclic DBS is as effective as continuous DBS in reducing symptoms of OCD, applying a non-inferiority design.

2. Methods

2.1. Patients

Patients were recruited from the psychiatric outpatient clinic at the Amsterdam University Medical Centers (Amsterdam UMC) between 2018 and 2021. Inclusion criteria were a primary diagnosis of OCD treated with DBS, with stable stimulation settings (i.e., period of optimization of stimulation settings completed). DBS was either implanted in the vALIC using anatomical landmarks on a structural MRI, or in the medial forebrain bundle (a white matter bundle running through the vALIC) using diffusion weighted imaging. For inclusion in the present study, patients had to have a minimal response to DBS of 25% reduction on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) compared to the pre-operative Y-BOCS score. Exclusion criteria were alcohol or substance abuse during the last six months (excluding tobacco use). Patients either had a non-rechargeable IPG (Activa PC) or a rechargeable IPG (Activa RC). All patients provided written informed consent to participate in the study. This study was approved by the Medical Ethical Committee of the Academic Medical Center (AMC) and pre-registered in the Dutch Trial Register (trialregister.nl, NTR7394).

2.2. Randomization

Patients were randomized according to variable block randomization. Each block (size 2 and 4) consisted of two sequences, which contained one sequence of cyclic first and one of continuous first. An independent unblinded researcher generated the randomization list using a software package (Castor EDC) based on a validated variable block randomization model. All patients, raters and treating physicians were blinded for the condition of the subjects. Afterwards, both patients and raters were asked to guess the order of the treatments to calculate the guess rate.

2.3. Procedure

After providing informed consent, patients were randomly allocated to one of two sequences: first cyclic DBS followed by continuous DBS, or vice versa (Fig. 1). After 2 weeks, the patients crossed over to the next 2-week block. Individual stimulation parameters such as active contacts, voltage, frequency and pulse width were kept stable in both conditions. Continuous DBS consisted of regular stimulation. For cyclic DBS, the IPG was programmed to a 0.1/0.2 s on-off frequency based on our experience in the three beforementioned patients. The programming was done by the unblinded physician and concealed for the patient and rater. Clinical symptom questionnaires were assessed at baseline (week 0), after the first block (T1, week 2) and after the second block (T2, week 4). At time-point T1 and T2, we assessed AEs, QoL, battery usage and patients completed a cognitive assessment battery. An escape protocol was included in the study, stating that patients could move on to the next block in case of severe relapse of OCD.

2.4. Outcome measures

The primary outcome measure was severity of OCD symptoms as measured by the Y-BOCS, a clinician-rated scale with scores ranging from 0 to 40 [15]. Secondary, we rated anxiety symptoms using the Hamilton Anxiety Scale (HAM-A), a 14-item scale with scores ranging from 0 to 56 [16]. We used the 17-item Hamilton Depression Rating Scale (HAM-D), ranging from 0 to 54, to evaluate depressive symptoms [17]. Higher scores on all three symptom scales reflect more severe symptoms.

The WHO QoL Scale-Brief Version (WHOQOL-BREF) and the EuroQol 5 (EQ-5D) were used to assess QoL. The WHOQOL-BREF consists of 26 Likert items (range 1–5) on 5 domains: physical (7 items), psychological (6 items), social (3 items), environmental (8 items) and general (2 items) [18]. Domain scores are calculated as the mean score of the items multiplied by four (range 4–20), except for the general domain, which is the sum score of the 2 items (range 2–10). Higher scores represent better QoL. The EQ-5D defines health in terms of 5 dimensions that are each scored on a 5-point Likert scale with lower scores representing a better QoL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and 1 item for overall health that is scored on a visual analog scale ranging from 0 to 100 with higher scores representing a higher QoL [19].

Cognitive functioning was tested using subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB); a standardized computerized neuropsychological battery widely used in research involving OCD patients, that has showed to be sensitive for cognitive change [20,21]. Patients were assessed on 4 CANTAB instruments: 1) Verbal Recognition Memory-immediate (VRM) assessing immediate free recall memory for verbal information with the total number of distinct words correctly recalled as outcome, 2) Paired Associates Learning (PAL) assessing episodic memory with the total number of errors adjusted for number of trials completed as outcome, 3) Spatial Working Memory (SWM) assessing working memory and strategy use with the number of times the subject begins a new search as outcome, and 4) Verbal Recognition Memory (VRM-delayed) assessing delayed recognition

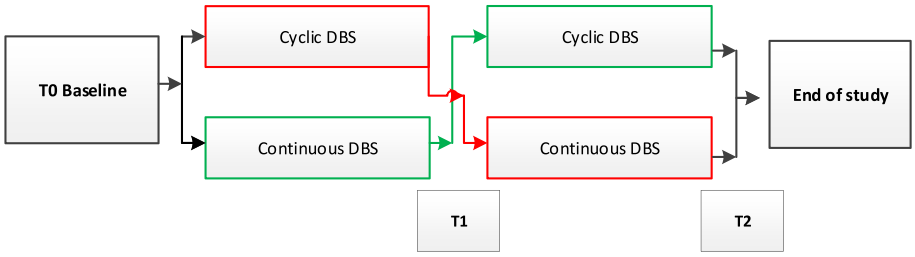

Fig. 1. Flowchart study design.

memory for verbal information with the total number of words that the subject correctly recognizes as outcome.

In patients with a rechargeable IPG, data from the last 6 charging sessions was obtained from the IPG to estimate battery usage between charging sessions. By using the amount of operational capacity between charging sessions, we could calculate the battery usage. For non-rechargeable IPG's, the decrease in battery life over 2 weeks was not sensitive enough.

2.5. Power calculation

A previous non-inferiority trial on OCD used Y-BOCS as primary outcome variable [22] and specified that the experimental treatment was not inferior to the control treatment if the upper boundary of the 95% confidence interval of the difference between the treatments was below a pre-specified margin of 5 Y-BOCS points. Based on this previous study and our clinical experience, we chose a conservative non-inferiority margin of 4 Y-BOCS points. We observed a standard deviation of Y-BOCS change between two measurements one year apart of 5.8 points in our own clinical data including 58 OCD patients with good response to DBS. Since we measured the Y-BOCS with only two weeks in between, we expected the standard deviation to be smaller. However, in order to maintain a conservative estimate, we used a standard deviation of change in Y-BOCS score of 5 points.

According to our power analysis for a two-by-two crossover design with an equal number of patients in each sequence, a total sample size of 16 patients would achieve 80% power to detect non-inferiority using a one-sided *t*-test when the margin of non-inferiority is 4 Y-BOCS points, the true mean difference is 0 Y-BOCS points, the significance level is 0.025, and the standard deviation of the paired differences is 5. Considering a potential drop-out of 20%, we aimed for 20 patients.

2.6. Statistical analysis

Y-BOCS scores were analyzed using a linear mixed model with Y-BOCS scores as criterion and order of blocks (first, second) and treatment (cyclic, continuous) as fixed effects. The order × treatment interaction was included to test for carry-over effects. We tested non-inferiority of cyclic vs. continuous DBS with a 95% confidence interval. Similar models were estimated for HAM-D and HAM-A scores. WHOQOL-BREF scores were analyzed using repeated measures ANOVAs, controlling for carry-over effects. EQ-5D scores were analyzed using Wilcoxon signed rank tests.

AEs were presented in contingency tables with cyclic and continuous DBS as columns. A difference in total number of reported AEs during continuous and cyclic DBS was formally tested with a repeated measures ANOVA. CANTAB data were analyzed using repeated measures ANOVAs. For all analyses, we tested for an interaction with order of blocks.

Analyses of battery life were dependent on battery type. A repeated measures ANOVA was used to compare battery usage between continuous and cyclic DBS. We tested for normality using Shapiro-Wilk tests. Data was presented as the mean (SD) and significance was set at a 2-tailed level of 0.05. Statistical analyses were conducted using IBM SPSS Statistics v26.

3. Results

Sixteen patients were included in the present study (Fig. 2). Demographical characteristics of patients are presented in Table 1. None of the patients withdrew from the study and therefore we

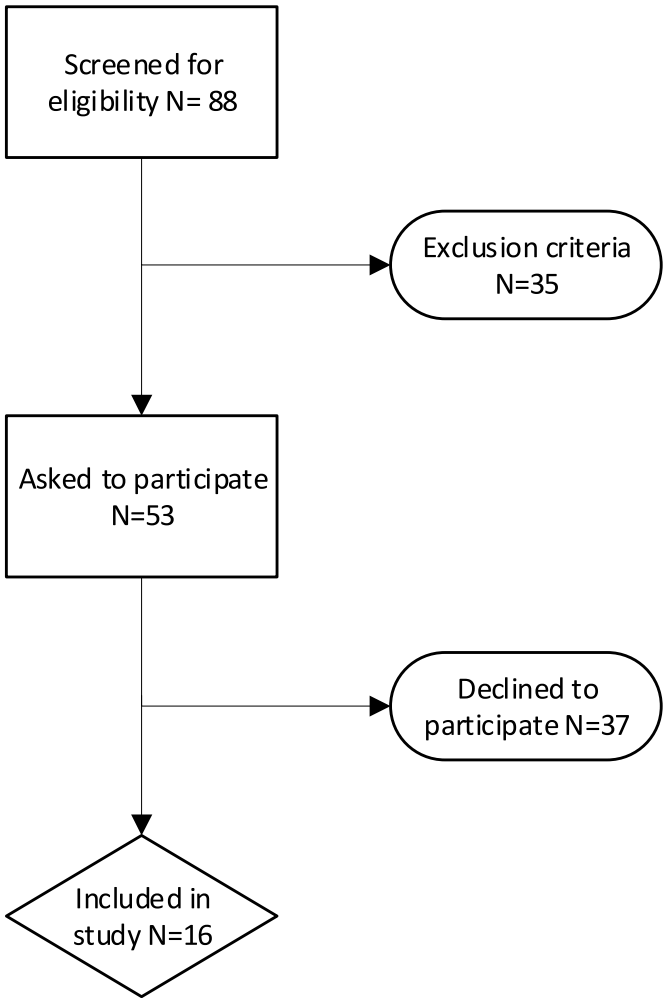

Fig. 2. Inclusion of patients with deep brain stimulation for obsessive compulsive disorder to participate in the study on cyclic deep brain stimulation.

included 16 patients. In three patients, the cyclic phase was shortened due to an increase of obsessive compulsive and/or affective symptoms, which was in accordance with the escape protocol. QoL scores following both continuous and cyclic DBS were available of 15 patients and CANTAB scores of 11 patients, due to the shortened study phase in 3 patients and technical issues in 2 patients. Data on rechargeable battery usage was available of 9 patients. The correct guess rate in patients was 81.3% and in raters 75%.

3.1. Effectiveness and QoL

The mean Y-BOCS score at baseline was 17.1 (SD 10.4), during continuous stimulation 17.3 (SD 10.1) and 22.8 (SD 9.8) during cyclic stimulation (Fig. 3). The mixed model showed a significant effect of treatment (continuous vs cyclic) on Y-BOCS scores ($F(2) = 6.679$; $p = 0.004$). The average increase in Y-BOCS scores following cyclic DBS exceeded the preset limit of clinical significance. Eight out of 16 patients experienced a clinically significant increase in Y-BOCS scores of at least 4 points. The mean HAM-D score at baseline was 7.6 (SD 6.0); after continuous stimulation 8.0 (SD 6.0) and after cyclic stimulation 9.8 (SD 5.6; $F(2) = 2.659$; 0.088). Mean HAM-A score at baseline was 8.3 (SD 5.9), after continuous stimulation 6.9 (SD 4.9) and after cyclic stimulation 11.1 (SD 6.0; $F(2) = 6.679$; $p = 0.018$). For all models, no significant interaction effect between treatment and order was found.

There was no significant difference between continuous and cyclic DBS on the EQ-5D subscales for mobility, self care, daily activities, pain/discomfort and anxiety/depression (Supplement Table 1). Following continuous DBS patients scored significantly higher on the EQ-5D overall health subscale than following cyclic DBS (71.9 points [SD 13.5] vs 60.1 points [SD 13.1], $Z = -2.014$, $p = 0.044$). There was no significant difference between continuous and cyclic DBS on all 4 WHO-QOL-BREF domain subscores (Supplement Table 1).

3.2. Adverse events and CANTAB

There was no significant difference between average number of AEs during continuous and cyclic DBS (3.25 [SD 0.9] vs 4.44 [SD 0.85]; $F(1) = 2.041$, $p = 0.175$) and no significant interaction-effect with order (Supplement Table 2). During cyclic DBS, patients experienced more AEs such as anxiety, depression and restlessness, but less concentration problems and headache. One patient with a continuous urge to press her left hand against her right chest reported that this unwanted behavior was less during cyclic DBS, though it was still present. One patient reported symptoms of hypomania during continuous DBS, which was likely an effect from the switch from cyclic to continuous DBS since this patient was familiar with hypomanic symptoms following increases in current. No significant differences between continuous and cyclic DBS were found for scores on the CANTAB tests for recognition memory, visual memory and spatial working memory (supplement table 1). There we no significant interactions with order of treatment.

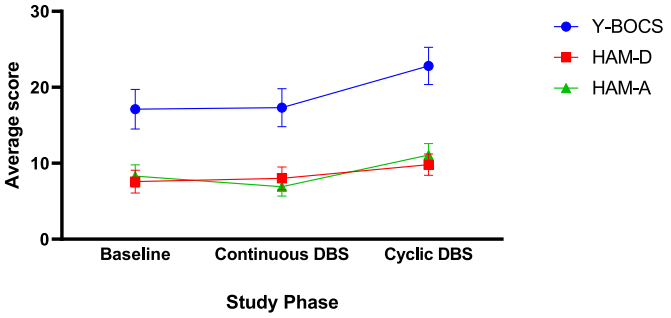

Fig. 3. Average scores and standard error of mean on the Yale- Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A) at baseline and following continuous deep brain stimulation (DBS) or cyclic DBS (0.1 s on; 0.2 s off) in 16 patients with refractory obsessive compulsive disorder. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3. Battery life

During continuous DBS, the voltage of the battery decreased with 0.021 V per hour (SD 0.033) on average. During cyclic DBS, the voltage of the battery decreased with 0.008 V per hour (SD 0.017) on average. Though cyclic DBS required less than half of the battery usage of continuous DBS, the analysis showed no significant difference in battery usage ($F(2) = 2.002$, $p = 0.198$), and no significant interaction with order of treatment.

4. Discussion

The present study is the first RCT to directly compare the effects of different DBS parameters in patients with treatment-refractory OCD. Cyclic DBS with a 0.1/0.2 s on-off paradigm increased battery life of the IPG compared to continuous DBS but cyclic DBS did not diminish AEs and was associated with a relapse of OCD symptoms in half of the patients. The relapse in OCD symptoms was temporary and effectiveness of DBS was reestablished within hours when patients received continuous stimulation.

Contrary to what was expected, cyclic DBS led to a clinically significant increase in OCD symptoms of 133% on average. In 8 out of 16 patients the Y-BOCS score increased with at least 4 points following cyclic DBS. Previous studies in patients with PD and tremor showed that a non-regular form of DBS is equally or even more effective than continuous stimulation [12]. However, these studies applied different non-regular temporal patterns of stimulation. Brocker et al. examined the effects of periodic patterns with low entropy (<1 bits/pulse) and patterns characterized by either short periods absent of pulses or the presence of short bursts of pulses occurring at 4.4 Hz in patients with PD stimulation [12]. They also examined patterns that were highly irregular, in contrast to the pattern examined in the present study. Kuncel et al. tested 12 combinations of cycling on/off times [13]. They found that cycling with stimulation on for at least 60% of the time was as effective as

Table 1
Demographics of 16 obsessive-compulsive disorder patients with continuous deep brain stimulation (DBS) first and cyclic DBS second (n = 8) or vice versa (n = 8).

	Continuous first n = 8	Cyclic first n = 8
Sex (male/female)	3/5	4/4
Age in years (mean/SD)	51.8 (14.2)	47.6 (8.2)
Voltage at start study (mean/SD)	4.8 (1.2)	4.9 (1.1)
Frequency at start study (mean/SD)	138.8 (18.1)	138.8 (18.1)
Pulse width at start study (mean/SD)	100 (32.5)	93.8 (25.0)
Battery type (rechargeable/non-rechargeable)	5/3	7/1

continuous stimulation. In the present study, the stimulation was on for one third of the time. We chose for an 0.1/0.2 s on-off paradigm since this was effective in alleviating AEs while maintaining effectiveness in 3 patients with side effects of DBS [4]. Nevertheless, the amount of active stimulation time during cyclic stimulation was likely too low. Possibly, a stimulation paradigm with more than 60% on-time may have been effective in reducing AEs while remaining effectiveness.

A previous computational modeling study showed that intermittent DBS yielded significantly stronger desynchronizing effect on neuronal activity compared to continuous DBS in OCD, corresponding with a stronger effect on OCD symptoms [14,23]. However, this study examined DBS of the subthalamic nucleus (grey matter), not vALIC (white matter). Future studies examining irregular DBS, for example for the application of closed-loop DBS, should use data on underlying neuronal dynamics captured by real-time recordings, to define optimal stimulation pattern characteristics.

Interestingly, 50% of patients did not experience a clinically significant increase of OCD symptoms during cyclic DBS. In 4 patients there was even a small improvement of 1–3 points on the Y-BOCS. Some patients experienced a diminished effect of cyclic DBS within hours and other patients only after more than a week. This emphasizes how all patients respond different to changes in stimulation settings. Nevertheless, most patients did notice the change in stimulation settings, since we found that 13 out of 16 patients guessed the order of the phases correctly.

Overall, cyclic DBS caused more AEs than continuous DBS although this difference was not statistically significant. AEs that were common during cyclic DBS were psychiatric symptoms like anxiety, depression and restlessness likely related to the relapse of OCD symptoms induced by the cyclic stimulation paradigm. However, some stimulation-related AEs decreased during cyclic DBS, including headache, concentration problems, loss of inhibition and the urge to press a hand to the chest. Two patients benefited from cyclic DBS and reported a decrease in AEs without relapse of OCD. One patient chose to remain on cyclic DBS when the study was finished.

The present study has some limitations. First, only one type of cyclic stimulation (0.1/0.2 s on/off) has been investigated, so no conclusions about other types of cyclic stimulation can be drawn. In addition, the majority of patients guessed correctly what type of stimulation they were receiving. Therefore, placebo or nocebo effects may have influenced our results although it can also be argued that the effect of DBS is so strong that patients cannot be blinded for its effect. At last, data on battery usage was not available of all patients since we could only use data from rechargeable batteries so our analysis on battery usage was potentially underpowered. On the other hand, this was the first randomized double-blind controlled study to compare different stimulation paradigms. Worldwide, the number of studies on DBS for OCD are increasing, but randomized controlled trials are still a rarity. If we truly want to advance DBS, more RCT's are necessary to systematically examine how to improve the treatment.

Since cyclic DBS triggered a relapse of OCD in half of the included patients, we advise against applying cyclic DBS as a standard option of DBS treatment. However, cyclic DBS brought relief of AEs in a small number of patients while remaining effective. Therefore, clinicians may consider trying cyclic DBS in patients with severe AEs of DBS. In that case, it is advisable to closely monitor the patient for potential relapse. Moreover, the optimal way of delivering cyclic DBS needs to be determined.

Concluding, cyclic stimulation (0.1 s ON, 0.2 s OFF) comes with a high relapse risk in patients with DBS for OCD. Though some stimulation-related AEs decreased, the adverse consequences of cyclic DBS overshadowed the positive effect in most cases. Further studies on optimizing DBS are required in the search for personalized treatment strategies to establish an optimal balance between reduction of AEs while keeping effectivity. In addition, other stimulation paradigms need to be exploited before a firmer conclusion about the benefit of cyclic DBS in general can be drawn. Nevertheless, the rapid and clinically significant reversible worsening of symptoms during this RCT once again supports the effectiveness of DBS for OCD.

CRediT authorship contribution statement

Ilse Graat: Conception and design, Conceptualization, Data/literature acquisition, Data curation, Funding acquisition, Data/literature analysis and interpretation, Formal analysis, Statistical analysis, Drafting the manuscript, Writing – original draft, Critical revision of the manuscript. **Geeske van Rooijen:** Critical revision of the manuscript, Supervision. **Janine Prinsen:** Data/literature acquisition, Data curation, Funding acquisition, Critical revision of the manuscript. **Martijn Figee:** Conception and design, Conceptualization, Critical revision of the manuscript. **Damiaan Denys:** Conception and design, Conceptualization, Critical revision of the manuscript, Supervision. **Roel Mocking:** Critical revision of the manuscript, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.01.1664.

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