Long-term Outcome of Deep Brain Stimulation of the Ventral Part of the Anterior Limb of the Internal Capsule in a Cohort of 50 Patients With Treatment-Refractory Obsessive-Compulsive Disorder

Ilse Graat, Roel Mocking, Martijn Figuee, Nienke Vulink, Pelle de Koning, Pieter Ooms, Mariska Mantione, Pepijn van den Munckhof, Rick Schuurman, and Damiaan Denys

ABSTRACT

BACKGROUND: Deep brain stimulation (DBS) is an effective intervention for patients with severe treatment-refractory obsessive-compulsive disorder (OCD). Our aim was to examine long-term effectiveness and tolerability of DBS and its impact on functioning and well-being.

METHODS: Fifty patients with severe treatment-refractory OCD received DBS of the ventral part of the anterior limb of the internal capsule and were followed for at least 3 years following implantation (mean 6.8 ± 3 years). Primary effectiveness was assessed by change in Yale-Brown Obsessive Compulsive Scale scores. Secondary effectiveness measures included Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale, World Health Organization Quality of Life Scale–Brief Version, Global Assessment of Functioning, and a scale assessing functioning in work, family, and social life. Adverse effects of DBS were examined with a structured interview (n = 38).

RESULTS: At long-term follow-up, OCD symptoms decreased by 39% (p < .001), and half of the patients were responders (≥35% decrease of Yale-Brown Obsessive Compulsive Scale score). Anxiety and depressive symptoms decreased significantly, with reductions of 48% and 50%, respectively. The World Health Organization Quality of Life Scale–Brief Version general score improved significantly, as did 3 of 4 subdomains. Both clinician- and patient-rated functioning improved substantially (p < .001). The unemployment rate decreased from 78% at baseline to 58% at last follow-up (z = −1.90, p = .058), and 21 patients stopped or decreased psychotropic medication (z = −2.887, p = .004). Long-term adverse effects included cognitive complaints and fatigue. Serious adverse events included 1 suicide attempt, related to comorbid depression.

CONCLUSIONS: Our results provide evidence that DBS of the ventral part of the anterior limb of the internal capsule is effective and tolerable for treatment-refractory OCD in the long term and improves functioning and overall well-being.

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Obsessive-compulsive disorder (OCD) is a chronic disease with a 2.3% lifetime prevalence (1). Cognitive behavioral therapy (CBT) and pharmacotherapy provide 40% to 60% symptom reduction in half of patients. However, 10% of OCD patients have treatment-refractory cases and are often remain unable to work, interact socially, or live independently (2).

Deep brain stimulation (DBS) is a treatment for severe treatment-refractory OCD. Several open-label studies and some randomized controlled trials have demonstrated efficacy of DBS (3–6). DBS results in 45% reduction of OCD symptoms with a 60% response rate (7). However, follow-ups of DBS studies in OCD are short, ranging between 3 and 36 months (7). Only 3 small studies and 1 larger study examined whether DBS remains effective beyond 3-year follow-up (8–11). Moreover, clinically relevant outcomes of prolonged treatment including social and global functioning, employment status, medication usage, and side effects are not always reported.

The present study reports on a cohort of 50 consecutive patients with treatment-refractory OCD that received DBS of the ventral part of the anterior limb of the internal capsule (vALIC) that were followed for ≥3 years but up to 13 years. First, we assessed whether short-term effectiveness of DBS for OCD remains beyond a 3-year follow-up. Second, we investigated DBS effects on quality of life (QoL) and overall functioning, including side effects, employment rates, relationship status, and medication usage.

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Long-term Outcome of DBS for Treatment-Refractory OCD

METHODS AND MATERIALS

Patients

Fifty consecutive patients with severe treatment-refractory OCD underwent DBS surgery at the Amsterdam University Medical Center and were followed for ≥3 years. Data were collected from April 2005 to July 2018. The inclusion criterion was a primary diagnosis of severe treatment-refractory OCD (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] score ≥28) (12) causing severe functional impairments. Treatment refractoriness was defined as nonresponse to CBT, two selective serotonin reuptake inhibitors, one serotonin reuptake inhibitor with an additional antipsychotic, and clomipramine, all at maximum dosage and for ≥12 weeks. Primary psychotic disorder, instable multiple sclerosis, or general contraindications for surgery were exclusion criteria.

Treatment Protocol

Patients underwent implantation of DBS electrodes (model 3389; Medtronic) bilaterally targeted at the vALIC (13) and an implantable pulse generator (IPG) under general anesthesia. Electrodes were implanted in the ALIC, with an anterior angle of approximately 75° to the intercommissural line, and the ventral end contact placed anterior to the anterior commissure. In the first 28 patients, the lower two contact points were placed in the nucleus accumbens, and the upper two contact points were placed in the vALIC. In patients 29 to 50, the upper three contact points were placed in the vALIC, and the lower contact point was placed in the nucleus accumbens. All active contact points were positioned in the white matter ventral in the ALIC. Therefore, the vALIC is a more appropriate description of the target than nucleus accumbens (13). The vALIC is almost identical to the ventral capsule/ventral striatum, a target that has Food and Drug Administration approval in the United States; however, the vALIC lies more anterior and ventral in the ALIC. Initially, two Soletra IPGs (Medtronic) were implanted bilaterally. From 2010, one nonrechargeable IPG (Activa PC; Medtronic) was placed unilaterally in the right infraclavicular pocket. IPGs needed replacement approximately every 14 months (14). Rechargeable Activa RC IPGs became available in 2012.

Two weeks after implantation, patients entered an optimization phase, optimizing symptom suppression while controlling side effects (15). As soon as DBS resulted in adequate Y-BOCS decrease, trained CBT therapists provided a CBT program of ≥24 sessions. The first 16 patients received CBT when Y-BOCS scores had decreased by ≥6 points, symptoms decreased no further, and patients avoided situations that caused obsessions or continued their compulsions. After the first trial with 16 patients, CBT was gradually initiated earlier, overlapping with the optimization phase. Small exposure and response-prevention exercises were given in the optimization phase to let patients experience how DBS supported them in resisting compulsions, as it was observed that patients underestimated initial DBS effects. Six patients did not receive additional CBT, either because of insufficient response to DBS (n = 1) that made it impossible to do CBT or because they had a good response to DBS and hence did not need or lacked motivation for CBT (n = 5). After CBT, patients were seen at least annually for follow-up at our outpatient clinic. Denys et al. (15) provide more detailed information about the treatment protocol.

Study Procedure

Psychometric rating scales were administered by unblinded clinicians at baseline, 6 months after DBS surgery, and annually until last follow-up. Follow-up length ranged between 3 and 13 years, depending on DBS surgery date. Medical charts were reviewed and questionnaires were administered at last follow-up. The Amsterdam University Medical Center ethical committee concluded that no ethical approval was needed. Patients consented for participation and data usage.

Outcome Measures

Clinical Symptoms. We rated OCD symptoms using the Y-BOCS, a clinician-rated 10-item scale with scores ranging from 0 to 40. Patients were considered responders if their Y-BOCS score decreased by ≥35%, partial responders if their Y-BOCS score decreased by ≥25%, or nonresponders if their Y-BOCS score decreased by <25% (6). We rated anxiety using the Hamilton Anxiety Rating 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 (17,18).

Because the primary study aim was to assess whether DBS effects remain at long-term follow-up, we predefined clinically significant changes on symptom scales. We predefined Y-BOCS score increases ≥3 points/year, HAM-A score increases ≥2 points/year, and HAM-D score increases ≥2 points/year as clinically significant changes (19–22).

QoL and Functional Outcomes. The World Health Organization Quality of Life Scale–Brief Version (WHOQOL-BREF) assessed QoL, comprehending a general score and 4 subdomains: physical health, psychological health, social relationships, and environment (23).

We assessed global functioning and disability at baseline and last follow-up using the clinician-rated Global Assessment of Functioning (GAF) scale (24) and the Sheehan Disability Scale (SDS) (25). The SDS consists of 3 patient-rated Likert-type scales (work, social functioning, and family life) ranging from 0 (no impairment) to 10 (severe impairment). Furthermore, we evaluated marital and working status and psychotropic medication use.

Side Effects. Side effects were monitored using a checklist, containing the most common predefined DBS side effects and a field for other unclassified side effects. We asked patients about the start of symptoms (before, right after, or during the course of treatment), whether symptoms depended on stimulation parameter changes, comorbid illnesses, and medication usage. Based on this information, symptoms were classified as likely DBS related, unlikely DBS related, or unknown. Side effects were classified as “lasting” if they were present at the time of the interview and as “transient” if they were present only during a certain period or disappeared spontaneously, or following adjustments in medication or stimulation settings.
Table 1. Demographic and Symptom Information at Baseline

| Comorbidity                          | n (%)     |
|-------------------------------------|-----------|
| Major depressive disorder           | 23 (46%)  |
| Dysthymic disorder                  | 2 (4%)    |
| Panic disorder with or without agoraphobia | 2 (4%)    |
| Social phobia                       | 2 (4%)    |
| Posttraumatic stress disorder       | 1 (2%)    |
| Eating disorder                     | 1 (2%)    |
| Bipolar I disorder                  | 2 (4%)    |
| Hoarding disorder                   | 1 (2%)    |
| Somatization disorder               | 1 (2%)    |
| Autism spectrum disorder            | 1 (2%)    |
| Obsessive-compulsive personality disorder | 5 (10%)  |
| Borderline personality disorder     | 1 (2%)    |
| Avoidant personality disorder       | 2 (4%)    |
| Unspecified personality disorder    | 1 (2%)    |

**Symptom Severity, Mean (SD)**

| Measure                      | Mean (SD) |
|------------------------------|-----------|
| Y-BOCS score                 | 33.3 (3.8) |
| HAM-A score                  | 24.8 (7.7) |
| HAM-D score                  | 20.6 (5.7) |

**Results**

**Demographic and Clinical Characteristics**

Average baseline age was 42 ± 11 years and average illness duration 25 ± 11 years (Table 1). Three of 50 patients died during follow-up. One patient died from cancer 9 years after electrode implantation, and 2 nonresponding patients requested euthanasia. In both cases, the euthanasia was well considered and was granted according to the Dutch medical-legal criteria by an external specialist (27). One patient was male and one was female, and time between implantation and euthanasia was 6 and 3 years, respectively. The DBS had been off for 7 years in the first patient, and in the other patient had been off for 3 months. Both patients were complete nonresponders and had no history of suicide attempt. None of the patients included in the present study died by suicide. Five patients no longer received active stimulation at last follow-up: three patients had no response, and one patient requested explantation of electrodes because she did not benefit from DBS and had subjective experiences of character changes (more egocentric) and neck pain. One patient stopped recharging his IPG because he noticed that he remained free of OCD symptoms without active stimulation.

Thirty-eight patients consented to participate in assessment of social functioning and side effects. For other patients, data were not available prospectively due to death (n = 3) or to noncooperation (n = 9), and data were collected from medical charts. Of these 12 patients, 7 were (partial) responders and 5 were nonresponders. Baseline and long-term follow-up WHOQOL questionnaires were available for 28 patients (17 responders, 2 partial responders, and 9 nonresponders). During follow-up, 3 patients switched to rechargeable neurostimulators (42 Activa RC [Medtronic], 1 Soletra). Mean voltage at long-term follow-up was 4.8 ± 1 V (range, 2–7 V), median pulse width was 90 μs (interquartile range, 90–130 μs; range, 60–180 μs), and median frequency was 130 Hz (interquartile range, 130–146.25 Hz; range, 130–185 Hz).

**Clinical Outcome**

A linear mixed model analysis was fitted for Y-BOCS, HAM-A, and HAM-D scores. Average follow-up length was 6.8 ± 3 years. A main stimulation effect was found on the Y-BOCS (β = −15.2; 95% confidence interval [CI], −17.6 to −12.7; p < .001), HAM-A (β = −12.9; 95% CI, −14.9 to −10.9; p < .001), and HAM-D (β = −10.8; 95% CI, −12.6 to −8.9; p < .001) (Figure 1). Average Y-BOCS scores decreased from 33.6 ± 3 at baseline to 20.5 ± 9.9 at last follow-up (39% reduction).
Average HAM-A scores decreased from 24.8 ± 7.7 to 13.2 ± 10.3 (48% reduction). Average HAM-D scores decreased from 20.6 ± 5.7 to 10.4 ± 7.9 (50% reduction). OCD remission was always accompanied by improvement of affective symptoms, but in 5 OCD nonresponders, we observed a positive effect of DBS on depressive and anxiety symptoms without improvement of OCD symptoms. Seven (14%) patients achieved full remission at long-term follow-up, with ≥75% experiencing Y-BOCS score decrease.

Y-BOCS, HAM-A, and HAM-D scores increased slightly between 1-year follow-up and the last follow-up (3–13 years); average Y-BOCS scores increased on average by 1.8 points, HAM-A scores increased on average by 1.2 points, and HAM-D scores increased on average by 0.8 points. These values remain far from crossing the predefined cutoffs for clinical significance. In addition, the main effects of time were nonsignificant (Y-BOCS: β = −0.014; 95% CI, −0.030 to 0.002; p = .099; HAM-A: β = −0.003; 95% CI, −0.035 to 0.029; p = .857; HAM-D: β = −0.019; 95% CI, −0.047 to −0.008; p = .161).

OCD symptoms fluctuated within patients over time (Figure 2). Most of the patients that were responders responded to DBS in the first year. Eight patients that were nonresponders at last follow-up had been responders, and 5 additional nonresponders had been partial responders between baseline and last follow-up. However, we found no significant difference in the number of (partial) responders and nonresponders at the different time points ($\chi^2 = 3.00, p = .261$).

QoL and Functional Outcomes

WHOQOL-BREF, GAF, and SDS scores improved significantly between baseline and last follow-up (Figure 3). General QoL scores and physical, psychological, and environmental domains of WHOQOL-BREF all improved. The general QoL score increased 85% ($t_{27} = -6.699, p < .001$), the physical domain score by 27% ($t_{27} = -4.443, p < .001$), the psychological domain score by 26% ($t_{27} = -5.506, p < .001$), and the environmental domain score by 17% ($t_{27} = -5.102, p < .001$). The social domain showed a borderline significant improvement between baseline and last follow-up ($t_{27} = -2.047, p = .05$) (Table 2).

Average GAF score increased from 44 ± 5.3 to 57 ± 12.0 ($z = -5.489, p < .001$). The average score on the SDS work subscale decreased 42%, from 9 ± 1.2 to 5 ± 3.4 ($z = -5.029, p < .001$). The SDS social life subscale decreased 39%, from 9 ± 1.3 to 5 ± 3.1 ($z = -5.070, p < .001$), and the SDS family life subscale decreased 43%, from 8 ± 1.5 to 5 ± 3.2 ($z = -4.839, p < .001$). Furthermore, unemployment rate in our group decreased from 78% at baseline to 58% at last follow-up ($z = -1.90, p = .058$). Some examples of jobs that patients had following DBS included work at an elementary school, nurse, janitor, and real estate agent.

Fewer patients used psychotropic medication at long-term follow-up than at baseline ($z = -2.887, p = .004$). Eleven of 50 patients stopped antidepressants and/or antipsychotics during follow-up (9 responders and 2 nonresponders). Another 10 patients lowered medication dosages, and 8 patients switched medication. Sixteen patients used the same medication at long-term follow-up as before DBS. Four patients increased medication dosage, and 1 patient started using a selective serotonin reuptake inhibitor between baseline and last follow-up.

Side Effects

Transient stimulation-induced hypomanic symptoms occurred shortly after DBS initiation or following stimulation parameter changes in 18 of 38 patients. Hypomanic symptoms usually disappeared within a week and never required treatment with mood stabilizers or psychiatric ward admission. Fourier patients reported transient impulsivity, like impulsive speech or actions. Sixteen patients reported weight gain (19% transient). However, this might be due to improved mood and not necessarily reflect impulsivity. Five patients reported both impulsivity and weight gain (Table S1).

Twenty-one patients reported ≥1 cognitive problems that developed gradually during DBS treatment. Cognitive complaints were subjective and not confirmed by neuropsychological assessment, which was not included in the present study. Twenty patients described fatigue. Often, fatigue was present prior to DBS, so it was hard to conclude whether fatigue could be attributed to stimulation. In 1 patient, the fatigue...
was directly linked to sleep disturbances caused by DBS. In 2 patients, fatigue occurred right after DBS initiation. A direct relationship between fatigue and DBS in these cases was deemed likely.

During DBS treatment, 7 patients had passive suicidal thoughts. Worsening of suicidal thoughts was not linked to stimulation changes, and suicidal thoughts were present prior to DBS. Therefore, we deem it unlikely that suicidal thoughts were directly DBS related. One patient attempted suicide after 2 years of DBS treatment, which was related to medication changes (selective serotonin reuptake inhibitor) and severe comorbid major depressive disorder.

Six patients reported an urge to press their left hand against their right chest, nearby the IPG. In 4 patients, this side effect was mild, but in 2 patients the urge was so severe that they experienced a great tension when having to change the position of their hand. As a result, all daily activities had to be performed with their right hand. Turning off the stimulator or significantly lowering its voltage diminished the side effect but was not enough to completely resolve the unwanted behavior and the other patient was much better able to control it.

Two of the 46 patients that switched from a nonrechargeable to a rechargeable IPG had temporary diminished effects of DBS afterward. A depleted IPG prior to the switch was considered the cause of the temporary relapse in both cases.

A total of 22 patients required psychiatric ward admission during follow-up (Table S3). The total number of admissions was 43, of which 6 were due to side effects. Major reasons of admissions were worsening of OCD and/or depressive symptoms and pharmacologic or psychotherapeutic treatment. Seven patients were admitted to change DBS settings: 4 patients because of side effects (2 patients because of the urge to press their hand to their chest, 1 patient because of restless legs syndrome, and 1 patient because of impulsivity), 1 patient with comorbid bipolar disorder to monitor possible symptoms of hypomania, and 2 patients because of nonresponse to improve stimulation optimization.

**Postsurgical Complications**

Six patients underwent reimplantation of the electrodes because the electrodes were not optimally rooted in the vALIC. In 2 patients, the malposition was caused by shifting of the leads, and in 4 patients the electrodes were implanted too deeply in the nucleus accumbens and not in the vALIC. Infection of the leads occurred in 1 patient, which required explantation and reimplantation of the electrodes (Table S2).

**DISCUSSION**

The present study reports long-term results (3–13 years) of the largest cohort of OCD patients receiving long-term DBS. Results provide support for effectiveness and safety of long-term vALIC DBS for treatment-refractory OCD. Following 1 year of

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**Table 2. Medication Usage and Functioning at Baseline and Last Follow-up (3–13 Years) (N = 50)**

| Psychotropic Medication, n (%) | Baseline | Last Follow-up |
|--------------------------------|----------|----------------|
| No medication                 | 6 (12%)  | 16 (32%)       |
| SSRI                          | 13 (26%) | 13 (26%)       |
| SSRI + antipsychotic          | 13 (26%) | 8 (16%)        |
| Clomipramine                  | 3 (6%)   | 1 (2%)         |
| Clomipramine + antipsychotic  | 13 (26%) | 10 (20%)       |
| Other                         | 2 (4%)   | 2 (4%)         |

| Functioning, Mean (SD)        |          |                |
|-------------------------------|----------|----------------|
| Global Assessment of Functioning | 43.8 (5.3) | 56.8 (12.0)   |
| SDS work subscale             | 8.8 (1.2) | 5.1 (3.4)     |
| SDS social life subscale      | 8.5 (1.3) | 5.2 (3.1)     |
| SDS family life subscale      | 8.0 (1.5) | 4.6 (3.2)     |

| Employment Situation, n (%)   |          |                |
|-------------------------------|----------|----------------|
| Single                        | 15 (30%) | 11 (22%)       |
| Married                       | 17 (34%) | 18 (36%)       |
| Living together               | 6 (12%)  | 7 (14%)        |
| Living apart together         | 8 (16%)  | 10 (20%)       |
| Unknown                       | 4 (8%)   | 3 (6%)         |

| Psychiatric Medication, n (%) | Baseline | Last Follow-up |
|-----------------------------|----------|----------------|
| Antipsychotic               | 13 (26%) | 10 (20%)       |
| SSRI                        | 13 (26%) | 13 (26%)       |
| Clomipramine                | 3 (6%)   | 1 (2%)         |
| Clomipramine + antipsychotic| 13 (26%) | 10 (20%)       |
| Other                       | 2 (4%)   | 2 (4%)         |

**SDS, Sheehan Disability Scale; SSRI, selective serotonin reuptake inhibitor.**

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**Figure 3.** Scores on the World Health Organization Quality of Life Scale—Brief Version (WHOQOL-BREF) (n = 42) and Sheehan Disability Scale (SDS) (n = 42) at baseline and last follow-up (after 3–13 years of active stimulation). The WHOQOL-BREF general score ranged from 2 to 10 and the domain scores ranged from 4 to 20, and higher scores indicate better quality of life. The SDS score ranged from 1 to 10, and higher scores indicate more dysfunction. *p < .001. Error bars indicate 95% confidence interval.
DBS, OCD symptoms had decreased by 45%. At long-term follow-up, 39% reduction of OCD symptoms was still observed. Anxiety and depression decreased by approximately 50% after 1 year. This effect remained stable at long-term follow-up. Generally, we observed an overall pattern of improvement in symptoms of OCD, anxiety, and depression following DBS.

Our results are consistent with previous studies examining long-term effects of DBS for treatment-refractory OCD, with long-term responder rates ranging between 50% and 67% (8,9,11). Although average DBS effects were constant over time, symptom suppression within individual patients fluctuated. Worsening of symptoms typically corresponded with environmental stress factors such as the loss of a family member. The majority of responses started in the first year of DBS, which was usually during the optimization period and CBT. In this first year, it often became clear to what extent a patient would profit from DBS. Unfortunately, not all patients profited from DBS. At long-term follow-up, 19 of 50 patients still experienced <25% response. Some of these patients benefitted from DBS in other ways (antidepressant or anxiolytic effects). However, 7 (14%) patients did not benefit at all (<25% decrease on Y-BOCS, HAM-A, or HAM-D scores). Four patients discontinued stimulation because of nonresponse. The other patients continued stimulation because cessation of the stimulation was associated with worsening of depressive and anxiety symptoms.

We found substantial long-term improvements in QoL on physical, psychological, and environmental domains. This corresponds with our earlier work, in a smaller sample over a shorter period of time (9). The finding that the social domain showed a borderline significant improvement in this study and not in the previous one might indicate that the social QoL also improves but that the effect is smaller and might take longer. At long-term follow-up, nearly twice as many patients (42%) were able to work or study than after 1 year of DBS (22%).

Previously, we observed that only 2 of 17 (12%) OCD patients were able to work or have a volunteering job following 1 year DBS (14). Together, these results suggest that the positive effects of DBS on working ability still increase after several years.

Patients reported several symptoms that might be related to DBS, including transient hypomanic symptoms, cognitive complaints, and fatigue. Transient hypomanic symptoms induced by DBS are frequently reported in other studies (7,11). Cognitive complaints, like problems in memory and executive functioning, were also described previously (7,11). Yet, double-blind neuropsychological evaluation has not provided evidence for stimulation-induced cognitive impairments (11), and a limitation of the present study was that it did not include objective neuropsychological assessments before and after DBS. Longitudinal trials, including neuropsychological assessments, should give more insight in DBS side effects (28).

At long-term follow-up, the majority of patients (n = 43) had switched to rechargeable IPGs. The most important advantage of rechargeable IPGs is the diminished need for IPG replacements. Two patients reported temporary relapse of OCD symptoms after switching from nonrechargeable to rechargeable. Most likely, the relapse was associated with an empty IPG prior to the switch. Usually, no weakened effect of DBS with rechargeable IPGs was observed, in line with a recent study (29).

A previous study from our group suggested that clinical improvement of DBS could be enhanced by addition of CBT (30). Therefore, a majority of patients (n = 44) from the present cohort received CBT. Of the 44 patients who received CBT, 20 patient were responders, 6 were partial responders, and 18 were nonresponders. CBT encouraged patients to stop habitual compulsions and to note that the anxiety they experienced during exposure and response prevention was not as intolerable as before DBS. In addition, patients with treatment-refractory OCD are often unemployed, socially isolated, and have no leisure activities (31), and a large part of the psychological treatment also focused on reintegrating toward normal life, rebuilding healthy activities and re-establishing social relationships.

We are aware that our research has several limitations. Importantly, this was a noncontrolled cohort study, so results should be interpreted with caution. Clinicians administering questionnaires were trained and data were reviewed to improve reliability. However, lack of blinding and absence of a control group might have induced systematic bias. Also, data were not available of all patients; self-reported disability scales were available for 42 patients and QoL data for 28 patients, which might have caused selection bias. During the study, patients changed medication, and some patients received additional psychological treatment at other institutes, for example, for comorbid personality disorder. Therefore, changes in symptoms cannot be attributed to DBS only. In addition, we did not examine beneficial effects of CBT specifically. However, patients did not respond to CBT prior to DBS, making it likely that additional benefits of CBT during DBS are mostly due to the effects of DBS (30). In addition, outcomes following DBS might be different for certain OCD subgroups, e.g., OCD subtypes or good/poor insight (6), which is a main question for follow-up research. Nonetheless, our study also has several strengths. We report the results of the largest sample of patients treated with long-term DBS for OCD worldwide, with a follow-up of ≤13 years. In addition, the current study was completely independent and not sponsored by any medical company.

In conclusion, in the long term, DBS is effective and tolerable with robust effect on OCD, depression, and anxiety. The response profile shows two extremes: 14% of patients can be considered cured (>75% decrease in scores), and an equal percentage of patients did not respond (<25% decrease in scores). Predicting response prior to DBS is therefore paramount. In addition, DBS improves QoL and overall functioning and reduces psychotropic medication use at long-term follow-up. Results from the current study provide further support for the clinical effectiveness and general implementation of DBS for treatment-refractory OCD.

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RS acts as advisor for Medtronic and Boston. The other authors report no biomedical financial interests or potential conflicts of interest.
ARTICLE INFORMATION
From the Departments of Psychiatry (IG, RM, NV, PdK, PO, DD) and Neurosurgery (PvdM, RS), Amsterdam University Medical Centre, University of Amsterdam, Amsterdam; the Department of Neurology and Neurosurgery (MM), University Medical Center Utrecht, Utrecht, the Netherlands; and the Department of Psychiatry (MF), Mount Sinai Hospital, New York, New York.

Address correspondence to Ilse Graat, M.D., at i.graat@amsterdamumc.nl.

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REFERENCES
1. Ruscio AM, Stein DJ, Chiu WT, Kessler RC (2010): The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry 15:53–63.
2. Denys D (2006): Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. Psychiatr Clin North Am 29:553–584, xi.
3. Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, et al. (2005): Deep brain stimulation for refractory obsessive-compulsive disorder. Biol Psychiatry 57:510–516.
4. Mallet L, Polosan M, Jaafar N, Baup W, Welter M–L, Fontaine D, et al. (2008): Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 359:2121–2134.
5. Greenberg BD, Gabriels LA, Malone DA, Rezai AR, Friehs GM, Okun MS, et al. (2010): Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: Worldwide experience. Mol Psychiatry 15:64–79.
6. Denys D, Mantione M, Figeé M, van den Munckhof P, Koerselman F, Westenberg H, et al. (2010): Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 67:1061–1068.
7. Alonso P, Cuadras D, Gabriels L, Denys D, Goodman W, Greenberg BD, et al. (2015): Deep brain stimulation for obsessive-compulsive disorder: A meta-analysis of treatment outcome and predictors of response. PLoS One 10:e0133591.
8. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, et al. (2006): Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology 31:2384–2393.
9. Ooms P, Mantione M, Figeé M, Schuurman PR, van den Munckhof P, Denys D (2014): Deep brain stimulation for obsessive-compulsive disorders: Long-term analysis of quality of life. J Neurol Neurosurg Psychiatry 85:153–158.
10. Fayad SM, Guizick AG, Reid AM, Mason DM, Bertone A, Foote KD, et al. (2016): Six-nine year follow-up of deep brain stimulation for obsessive-compulsive disorder. PLoS One 11:e0167875.
11. Luyten L, Hendrickx S, Raymaekers S, Gabriels L, Nuttin B (2016): Electrical stimulation in the bed nucleus of the stria terminals alleviates severe obsessive-compulsive disorder. Mol Psychiatry 21:1272–1280.
12. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. (1989): The Yale–Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 46:1006–1011.
13. van den Munckhof P, Bosch DA, Mantione MHM, Figeé M, Denys DAJP, Schuurman PR (2013): Active stimulation site of nucleus accumbens deep brain stimulation in obsessive-compulsive disorder is localized in the ventral internal capsule. Acta Neurochir Suppl 117:53–59.
14. Ooms P, Blankers M, Figeé M, Bergfeld IO, van den Munckhof P, Schuurman PR, Denys D (2017): Cost-effectiveness of deep brain stimulation versus treatment as usual for obsessive-compulsive disorder. Brain Stimul 10:836–842.
15. Denys D, Graat I, Mocking R, de Koning P, Vulink N, Figeé M, et al. (2020): Efficacy of deep brain stimulation of the ventral anterior limb of the internal capsule for refractory obsessive-compulsive disorder: A clinical cohort of 70 cases. Am J Psychiatry 177:265–271.
16. Hamilton M (1959): The assessment of anxiety states by rating. Br J Med Psychol 32:50–55.
17. Hamilton M (1960): A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.
18. Trajković G, Starčevec V, Latas M, Leštarević M, Ille T, Bukumirić Z, Marinković J (2011): Reliability of the Hamilton Rating Scale for Depression: A meta-analysis over a period of 49 years. Psychiatry Res 189:1–9.
19. Fisher PL, Wells A (2005): How effective are cognitive and behavioral treatments for obsessive-compulsive disorder? A clinical significance analysis. Behav Res Ther 43:1543–1558.
20. Lovell K, Cox D, Haddock G, Jones C, Raines D, Garvey R, et al. (2006): Telephone administered cognitive behaviour therapy for treatment of obsessive compulsive disorder: Randomised controlled non-inferiority trial. BMJ 333:883.
21. Semkovska M, Landau S, Dunne R, Kolshus E, Kavanagh A, Jelovac A, et al. (2016): Bitemporal Versus High-Dose Unilateral Twice-Weekly Electroconvulsive Therapy for Depression (EFFECT-Dep): A pragmatic, randomized, non-inferiority trial. Am J Psychiatry 173:408–417.
22. Stein DJ, Khoo J-P, Ahokas A, Jarema M, Van Ameringen M, Vavrusova L, et al. (2018): 12-week double-blind randomized multi-center study of efficacy and safety of agomelatine (25–50 mg/day) versus escitalopram (10–20 mg/day) in out-patients with severe generalized anxiety disorder. Eur Neuropsychopharmacol 28:970–979.
23. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. (1998): Psychol Med 28:551–558.
24. Hall RCW (1995): Global Assessment of Functioning: a modified scale. Psychosomatics 36:267–275.
25. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV (1997): Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med 27:93–105.
26. Gueorguieva R, Krystal JH (2004): Move over ANOVA: Progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen Psychiatry 61:310–317.
27. Denys D (2018): Is euthanasia psychiatric treatment? The struggle with death on request in the Netherlands. Am J Psychiatry 175:822–823.
28. Bergfeld IO, Mantione M, Hoogendoorn ML, Denys D (2013): Cognitive functioning in psychiatric disorders following deep brain stimulation. Brain Stimul 6:532–537.
29. De Voo P, Raymaekers S, van Kuyck K, Luyten L, Gabriels L, Nuttin B (2018): Rechargeable stimulators in deep brain stimulation for obsessive-compulsive disorder: A prospective interventional cohort study. Neuromodulation 21:203–210.
30. Mantione M, Nieman DH, Figeé M, Denys D (2014): Cognitive-behavioural therapy augments the effects of deep brain stimulation in obsessive-compulsive disorder. Psychol Med 44:3515–3522.
31. Ferrao YA, Shavitt RG, Bedin NR, de Mathis ME, Carlos Lopes A, Fonteneille LF, et al. (2006): Clinical features associated to refractory obsessive-compulsive disorder. J Affect Disord 94:199–209.