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Long-term comparative effectiveness of deep brain stimulation in severe obsessive-compulsive disorder

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ABSTRACT

Background: Twenty years after the first use of Deep Brain Stimulation (DBS) in obsessive-compulsive disorder (OCD), our knowledge of the long-term effects of this therapeutic option remains very limited.
Objective: Our study aims to assess the long-term effectiveness and tolerability of DBS in OCD patients and to look for possible predictors of long-term response to this treatment.
Methods: We studied the course of 25 patients with severe refractory OCD treated with DBS over an average follow-up period of 6.4 years (±3.2) and compared them with a control group of 25 patients with severe OCD who refused DBS and maintained their usual treatment. DBS was implanted at the ventral anterior limb of the internal capsule and nucleus accumbens (vALIC-Nacc) in the first six patients and later at the bed nucleus of stria terminalis (BNST) in the rest of patients. Main outcome was change in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score between the two groups assessed using mixed models. Secondary effectiveness outcomes included Hamilton Depression Rating Scale (HDRS) and Global Assessment of Functioning (GAF) scores.
Results: Obsessive symptoms fell by 42.5% (Y-BOCS score) in patients treated with DBS and by 4.8% in the control group. Fifty-six per cent of DBS-treated patients could be considered responders at the end of follow-up and 28% partial responders. Two patients among those who rejected DBS were partial responders (8%), but none of the non-DBS group achieved criteria for complete response. HDRS and GAF scores improved significantly in 39.2% and 43.6% among DBS-treated patients, while did not significantly change in those who rejected DBS (improvement limited to 6.2% in HDRS and 4.2% in GAF scores). No statistically significant predictors of response were found. Mixed models presented very large comparative effect sizes for DBS (4.29 for Y-BOCS, 1.15 for HDRS and 2.54 for GAF). Few patients experienced adverse effects and most of these effects were mild and transitory.
Conclusions: The long-term comparative effectiveness and safety of DBS confirm it as a valid option for the treatment of severe refractory OCD.

1. Introduction

Obsessive compulsive disorder (OCD) is characterized by the presence of obsessions (unwanted and distressing thoughts, images

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or impulses) and compulsions (repetitive overt or mental behaviours performed to reduce anxiety) [1]. Between 60% and 75% of patients with OCD respond well to the standard combination of psychopharmacological treatment, which includes first-line therapy with cognitive-behavioural therapy and serotonin reuptake inhibitors and possible augmentation with atypical antipsychotics [2]. However, around 10% of patients are refractory to all available anti-obsessive therapies and present severe impairment in functioning in multiple areas that is accompanied by great suffering in both patients and families [3–5]. During recent decades, new treatment options have been proposed for these patients, including deep brain stimulation (DBS) [6].

DBS was first proposed as an alternative to surgical treatment for patients with severe refractory OCD by Nuttin et al., in 1999 [6,7]. However, DBS for OCD was not approved by the United States Food and Drug Administration until 2009, through the Humanitarian Device Exemption Program [8]. Since the first description by Nuttin et al., the literature on DBS for OCD in the main international databases has grown considerably [9–12]. According to recent reviews, around 300 DBS devices have been implanted in various targets of the cortico-striato-thalamo-cortical circuit (ventral capsule/ventral striatum, anterior limb of the internal capsule, subthalamic nucleus, and bed nucleus of the stria terminalis, among others) [10,13]. The meta-analyses carried out to date indicate that 60% of patients achieve a reduction of more than 35% in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score, and are thus considered responders [10,11,13,14].

Despite the attention that DBS has received in recent years, knowledge of its effectiveness is limited due to the study designs used [10,12]. Specifically, most studies are characterized by the lack of a control group, given that it was deemed ethically unacceptable not to provide treatment to suffering patients. Furthermore, the sample size of most studies is lower than five patients, making it extremely difficult to obtain statistically significant results. As a consequence, the search for predictors of response to DBS has so far been disappointing [15]. The same is true for the selection of the optimal stimulation parameters and the optimal "target site", and while most adverse effects (AEs) are mild and transient, more serious ones may also appear [16]. Finally, although DBS has been used in severe refractory OCD patients for the last 20 years, information on patients' long-term response remains limited [11,12].

In a recent systematic review of response to DBS, we observed a similar reduction in Y-BOCS scores of around 47% in patients treated with DBS in the short- (less than 36 months) and long-term outcome (more than 36 months). Nonetheless, significantly more patients satisfied the response criteria (reduction of Y-BOCS scores $\geq$35%) in the long-term follow-up (70.7% vs. 60.6%), suggesting that a progressive slow improvement in response to DBS may occur over the years [10]. However, different patterns of long-term response have been observed.

The objective of this study was to assess the effectiveness, tolerability and long-term course in a sample of 25 patients with severe refractory OCD treated with DBS for a period of 1–13 years and to compare them with a group of patients with severe resistant OCD who were offered DBS but refused it and maintained their usual treatment over the same period of time.

2. Methods and materials

2.1. Study design

We conducted a prospective observational study based on clinical practice data (real-world data) [17], comparing samples of severe refractory OCD patients who were treated or not treated with DBS. The study protocol was approved by the Bellvitge Clinical Research Ethics Committee (registration number AC007/14).

2.2. Patient selection

At the Department of Psychiatry of Hospital de Bellvitge (Barcelona, Spain), 25 patients with severe to extreme OCD attending the OCD Clinical and Research Unit were recruited between 2007 and 2020, and followed up until 2021. Diagnosis was assigned by two psychiatrists with extensive clinical experience in OCD, following DSM-IV (from 2007 to 2013) and subsequently DSM-5 criteria for OCD, using the Spanish version of the Mini International Neuropsychiatric Interview (MINI) 6.0 and 7.0.2 versions. Patients were required to meet the following inclusion criteria: 1. diagnosis of severe to extreme OCD, understood as a total Y-BOCS [18] score of at least 30/40; 2. resistance to standard OCD treatment defined as (a) no response to a minimum of six attempts with first- and/or second-line medications, including at least three selective serotonin reuptake inhibitors (SSRIs), clomipramine and the addition of two different antipsychotics, at antiobsessive doses according to therapeutic guidelines, for a minimum period of 16 weeks at the maximum tolerated doses for each trial, and (b) lack of response to an adequate trial of cognitive-behavioural therapy (20 1-h sessions of in vivo exposure and response prevention); 3. serious impairment of daily functioning with a Global Assessment of Functioning (GAF) [19] score <45%; 4. diagnosis of disabling OCD documented in their medical record more than 5 years earlier; 5. age older than 18; and 6. ability to understand and follow instructions and provide written informed consent to be included in the study.

The following exclusion criteria were applied: 1. a current axis I disorder that was primary to the OCD; 2. a neurological condition affecting cognitive skills; 3. substance abuse or dependence according to DSM-IV or DSM-5 criteria in the six months prior to the screening test; 4. a suicide attempt requiring medical treatment less than three months prior to the screening test; or 5. a comorbid diagnosis of a cluster A or B personality disorder; or 6. failure to provide informed consent.

In order to assess the comparative effectiveness, we considered a control group comprising 25 patients diagnosed with severe refractory OCD and also followed up at the OCD unit who, after meeting the selection criteria, were offered DBS during the same period but refused it and maintained their usual treatment and visit schedule. The main reason for rejecting DBS was fear of the risks associated with surgery or the possible adverse effects of stimulation. Thus, the design did not include random assignment of patients to the DBS or control groups.

2.3. Surgical procedure and stimulation protocol

In the first six patients, and taking as a reference the lesions carried out in stereotactic ablative surgery, two bilateral 3389 DBS leads [Medtronic, Inc., Minneapolis, MN, USA] were implanted in the region of the ventral anterior limb of the internal capsule and nucleus accumbens (vALIC-Nacc). Implanted 3389 electrodes featured 1.5-mm-long contacts 0.5 mm apart, spanning a total length of 7.5 mm. Target was placed 2 mm anterior, 6 mm lateral and 4 mm inferior with respect to the anterior comissure (AC). Our clinical experience and that of other groups [20], suggesting a better outcome with a slightly more posterior target, led us to shift the target of stimulation in the next 19 patients to the bed nucleus of the stria terminalis (BNST), an area classically associated with sustained anxiety responses and threat monitoring, which has shown abnormally increased functional connectivity with the prefrontal cortex in OCD patients [21]. The stimulation of the BNST,

a fronto-subcortical white matter fiber bundle as the ALIC itself or the inferior thalamic peduncle, has been shown to be able to reduce obsessive symptoms by rebalancing abnormal dorsal anterior cingulate cortex (dACC) hyperactivity disrupting aberrant frontostriatal connectivity [22]. In this second group of patients, two bilateral 3391 DBS Medtronic leads [Medtronic, Inc., Minneapolis, MN, USA] were implanted featuring 3-mm-long contacts 4 mm apart, spanning a total length of 24 mm. Initial target was selected 5–6 mm lateral to the posterior border of AC. Trajectory was designed to cover the length of the ALIC. The inferior contact was placed below the select target point in a position inferior and posterior with respect to AC. The leads were connected subcutaneously to an implantable pulse generator (IPG) (Activa PC or RC, Medtronic). Fig. 1 shows examples of the final position of the electrodes and the region where the stimulation has been centered in both groups. Postoperative computed tomography was performed to confirm lead location and check for bleeding complications. On the following day, when fully recovered from the anaesthesia, patients underwent DBS parameter selection to identify optimal parameter settings. This first stimulation session, as well as all the subsequent adjustments in the stimulation parameters, was carried out by three of the psychiatrists at the OCD Unit of Bellvitge Hospital who have extensive experience in the management of DBS. As starting parameters, the target region was stimulated via the DBS lead using monopolar stimulation (contacts 0−/C+) with a constant pulse width of 210 μs, a frequency of 130 Hz and an increasing intensity from 1 V to 3.5 V. Subsequently, the next two upper contacts (1-/C+,2-/C+) were explored, starting with the same frequency and pulse width, and progressively increasing intensity. The same process was performed to assess bipolar stimulation (0-/1+, 1-/2+, 2-/3+). Clinical changes related to obsessive thoughts, anxiety level and mood that appeared during the stimulation process, as well as any secondary effects, were borne in mind in the attempts to optimize the stimulation parameters for each patient. After this initial session, stimulation parameters were adjusted in follow-up visits according to the clinical course of each patient. All patients received bilateral stimulation, with a frequency that ranged between 100 and 130 Hz, and a pulse duration between 90 and 210 μs depending on tolerance. Monopolar or bipolar stimulation was chosen, as well as the active contact(s), and the amplitude of stimulation (between 3 and 5.5 V) according to the response and tolerance of each patient. The optimization protocol throughout the trial prioritized monopolar stimulation with an active contact on each electrode, with a progressive increase in stimulation amplitude up to 5.5 V. In the absence of response, bipolar or monopolar stimulation was tried with more than one active contact on each electrode (see Supplementary Material Table SM1 for a detailed description of the most effective contacts for each patient). In 14 of the 25 patients, the best response was obtained by activating not the deepest contact, implanted in the grey-matter target region, but higher contacts, which stimulate white matter fibers of the internal capsule.

2.4. Clinical assessment

With the aim of replicating previous studies on clinical predictors of response [15], we collected information on the following variables for each patient: age at DBS device implantation, age at OCD onset, sex, psychiatric comorbidities and OCD symptom dimensions. The latter were assessed using the Y-BOCS Symptom Checklist, considering six dimensions: 1. Aggressive; 2. Sexual/Religious; 3. Ordering/symmetry; 4. Contamination/cleaning; 5. Hoarding; and 6. Miscellaneous, and scoring the presence or absence of symptoms in each dimension for all patients.

The main outcome measure was the Y-BOCS score, but two additional measures were also considered to complete the assessment with data on functional and mood dimensions (the GAF and HDRS scores respectively) [19,23]. The questionnaires were administered at the beginning of the study, at 3, 6, 9 and 12 months after implantation and annually thereafter by three trained psychiatrists with extensive experience in the treatment and evaluation of OCD (PA, CS, ER), who were the clinical referents of each of the patients and were responsible for optimizing the neurostimulation parameters based on clinical response. Each patient was always evaluated and treated by the same psychiatrist throughout the entire follow-up period. At each medical visit, clinical and functional symptoms and adverse effects (AEs) were assessed, and psychopharmacological changes and stimulation parameter adjustments made if necessary.

The Spanish version of the Y-BOCS was used to assess the severity of obsessive-compulsive symptoms throughout the follow-up (score range: 0 to 40) [18]. Following standardized criteria [24], patients were considered responders if their Y-BOCS score fell by more than 35%, partial responders if it fell by between 25% and 35%, and non-responders if it fell by less than 25%. Although no clear criterion for remission in OCD exists, patient with a Y-BOCS reduction $\geq$75% and a final Y-BOCS score $\leq$8 were considered cured. Depressive disorders are the most frequent comorbidity in patients with OCD treated with DBS [13,25], and therefore, the 17-item Hamilton Depression Rating Scale (HDRS) [23] was used to quantitatively assess the severity of depressive symptoms (score range: 0 to 54) and to monitor changes therein during follow-up [23]. Global functioning was evaluated at each visit using the GAF [26,27]. This tool measures social, occupational and psychological functioning (score range: 1 to 100).

Psychotropic medication usage during the follow-up period was recorded for all patients. Finally, AEs associated with the DBS treatment were systematically recorded during the interviews carried out with patients at 3, 6, 9 and 12 months after device implantation and annually thereafter. AEs were classified as surgery- and device-related, neurological or somatic, and psychiatric.

2.5. Statistical analysis

The statistical significance of the differences in characteristics between groups was assessed using Student's *t*-test for normally distributed data and the non-parametric Wilcoxon test for non-normally distributed and ordinal data. The level of significance was set at $p = 0.05$. Chi-squared tests were used to analyse contingency tables. Statistical analysis was carried out using R v3.6.1.

YBOCS, HDRS and GAF trajectories were modelled using mixed models [28], which are a variant of regression models that include not only fixed effects but also patient-specific random effects. First, we adjusted the mixed models to reproduce the changes in each group of patients separately. Second, we applied them to compare outcomes in the two groups. Given the extent of change in the three scales in the first year, the natural logarithm of time was included in the model. The model's goodness of fit was assessed in terms of the percentage of random effects explained [28].

To analyse whether the magnitudes of the observed changes were clinically significant, effect sizes were calculated [29] by dividing the difference between the means in both groups (DBS and control) by the pooled standard deviation of their baseline values [30]. To take into account the repeated measurements, the coefficients of the group in the mixed models were used as the numerator [31]. Cohen defined an effect size of less than 0.2 as non-significant, between 0.2 and 0.5 as small, between 0.5 and 0.8 as moderate, and greater than 0.8 as large [32].

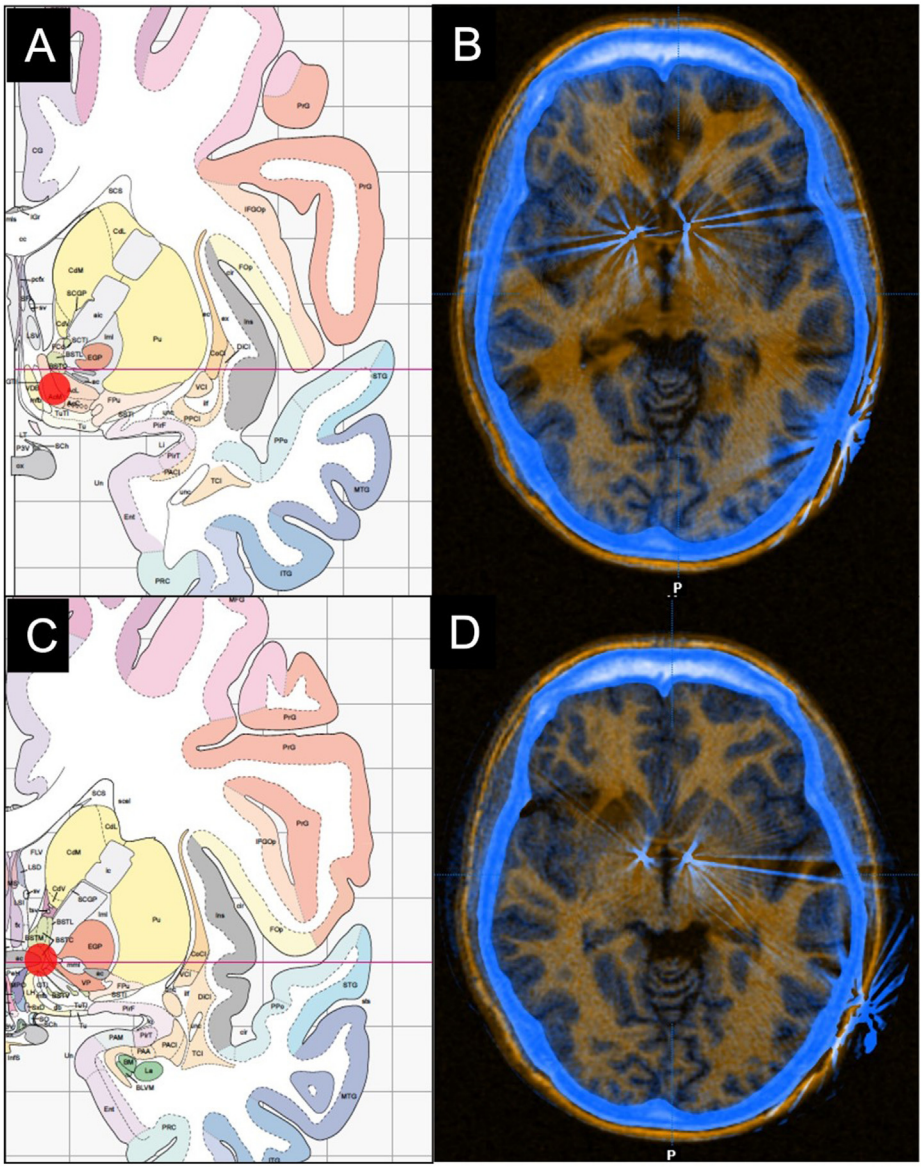

Fig. 1. Anatomical location of the stimulation points and postoperative location of the electrodes on both groups. A-B correspond to the first group. C-D correspond to the second group. Red dots reflect the region stimulated superimposed in Mai atlas*†. A. Coronal section of the Mai atlas 2,7 mm anterior to AC B. Postoperative CT fused with MRI showing the radiological position of the electrodes with respect to AC in the firt group. C Coronal section of the Mai atlas at the level of AC. D. Postoperative CT fused with MRI showing the radiological position of the electrodes with respect to AC in the second group.
* Images on both sides correspond to frontal sections of left hemispheres of the human brain in Mai atlas. Frontal sections most closely related with anatomical location of the stimulation point have been chosen for the figure. † Mai et al. Atlas of the Human Brain, 3ed Elsevier Ltd. (ISBN 9780123736031).. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Potential clinical predictors of response were explored through univariate analysis considering the following variables: age at OCD onset, age at implantation, gender and OCD symptom dimensions.

3. Results

3.1. Clinical and demographic characteristics

We recruited 50 patients with severe OCD diagnosed and treated at Bellvitge University Hospital from July 2007 to December 2020. All patients were offered DBS for severe refractory OCD. Of these, 25 agreed and had a DBS device implanted. The mean lengths of follow-up were 6.4 years (±3.4, range 1–13 years) and 7.0 years (±2.4, range 3–9 years) in the intervention and control groups respectively. The mean age at DBS device implantation was 41.1 years in the intervention group, while the control group was slightly older at the time DBS was proposed and rejected (44.8 years). There were no other statistically significant differences between the groups in baseline sociodemographic or clinical characteristics (see Table 1).

Considered as a whole, the sample comprised 27 male and 23 females, with a mean age of 42.2 years (SD = 11.3) and a mean duration of illness of 29.5 years (SD = 11). The most common OCD dimensions were aggressive/checking (43%) and contamination/cleaning (28%). The average baseline scores on the Y-BOCS and HDRS were 34.4 (SD = 2.7) and 17.2 (SD = 4.6) respectively. The most prevalent comorbidity was major depressive disorder (36%).

At baseline, 96% of patients (48/50) were receiving pharmacotherapy.

3.2. Clinical outcomes

The initial Y-BOCS score was similar in the two groups (35.4 in cases and 33.4 in controls). In the DBS-treated group, mean Y-BOCS scores fell from 35.4 at baseline to 20.7 at the last follow-up (42.5% reduction). In this group, 56% of the patients (14/25) were considered long-term responders (i.e., with a reduction in Y–BOCs score of more than 35%), while 28% (7/25) were partial responders (25–34% reduction) and 16% (4/25) were non-responders [18,33]. Four patients (16%) from the long-term responders were considered cured since they showed a Y-BOCS reduction $\geq$75% and a final Y-BOCS score $\leq$8. In contrast, in the control group, the initial YBOCS score of 33.48 only fell to 31.7 (a 4.8% reduction). Two patients in this group were considered partial responders (Y-BOCS reduction 25–34%) in the long-term follow-up, while none met the criteria for response.

Fig. 2 and **Table SM2** (supplementary material) show the changes in Y-BOCS scores in both groups. The main reduction in the DBS group was observed during the first year after starting the intervention, and the mean score remained stable with slight fluctuations during follow-up. In all, 76.45% of those who achieved the criterion of response after the first year of stimulation (13/17) showed a sustained response to DBS on the long-term follow-up. Nevertheless, 23.5% of responding patients experienced relapses during follow-up, in some patients on more than one occasion. These relapses were related to various causes, including device-associated events (e.g., battery depletion or broken electrodes or extension wires in five patients), comorbid conditions (manic episodes in four patients) or stressful personal events (e.g., divorce or loss of a family member in two patients). Throughout the years of follow-up, some patients presented partial transient clinical worsening without an apparent cause, which improved with readjustment of the stimulation parameters.

None of the patients requested the removal of the electrodes during the follow-up, but a patient with partial response after one year requested the interruption of the stimulation, due to complaints of persistent paraesthesia in the scalp that only subsided when turning off the DBS. Although the patient worsened by interrupting the stimulation, she continues to prefer at the present time, two years later, not to restart it.

To assess the possible influence of the DBS target on our results, we compared the response between the first six patients in the study who received vALIC-Nacc stimulation and the 19 subsequent patients who were implanted at the BNST (Table 2). Patients receiving vALIC-Nacc stimulation were implanted between 2007 and 2011 and were therefore followed up for a longer period than those implanted at the BNST from 2011 to 2019 (9.3 years $\pm$4.3 vs 5.4 years $\pm$2.4, $t = 2.8$, $p = 0.01$). The Y-BOCS scores of the first six patients were slightly more severe than those of the second group implanted in the BNST (37.3 vs 35.3, $t = 2.4$; $p = 0.02$) We observed no other significant differences in either preoperative clinical variables, measures of severity before or after surgery, or response rates between the groups. Although the Y-BOCS reduction was slightly greater among those implanted at the BNST, the difference was not statistically significant (36% vs 44.2%).

Fig. 3**, Figure SM1** and **Table SM3** represent the different response groups according to Y-BOCS reductions (responders, partial responders, and non-responders) during the follow-up period. Between 50% and 60% of patients could be considered responders in each assessment period. Besides Y-BOCS scores, the HDRS and GAF scores also improved significantly from baseline to the last follow-up assessment in patients treated with DBS (Fig. 4 and **Table SM2**), with mean falls of 39.2% (from 17.2 to 10.3) in the HDRS scores and increases of 43.6% (from 37.9 to 68.6) in GAF scores. As with the Y-BOCS, in both these scales, the largest improvements were observed during the first year. This improvement was maintained over time. There was no significant change in the HDRS and GAF scores in the control group.

Medication usage at baseline and last follow-up is displayed in Table 3. In the patients treated with DBS, a reduction in overall

Table 1
Characteristics of the intervention and control samples of patients with obsessive-compulsive disorder.

	Deep brain stimulation group (n = 25)			Treatment as usual group (n = 25)		
	Mean	SD	Range	Mean	SD	Range
Female gender, n (%)	12 (48)			11 (44)		
Age, years	41.1	10.6	40–54	44.8	8.7	40–47
Age of onset of OCD, years	16.2	5.5	13–17	23.6	9.2	16–28
Duration of illness, years	31.2	8.7	24–36	27.8	8.7	20–36
Study follow-up, years	5.8	3.2	1–13	7.0	2.4	3–9
Unemployment rate, %	100			100		
School, years	11.76	2.8	8–13	12.0	2.2	12–13
Comorbid major depressive disorder, n (%)	10 (40)			8 (32)		
Comorbid bipolar disorder, n (%)	2 (8)			1 (4)		
Comorbid dysthymia, n (%)	1 (4)			1 (4)		
Comorbid panic disorder, n(%)	1 (4)			0		
Comorbid social phobia, n (%)	2 (8)			0		
Comorbid generalized anxiety disorder, n (%)	1 (4)			1 (4)		
Comorbid eating disorder, n (%)	1 ($)			0		
Main type of OCD symptom, n (%)						
Aggressive obsessions	11 (44)			5 (20)		
Religious and sexual obsessions	2 (8)			2 (8)		
Perfectionism, symmetry, and rituals	4 (16)			5 (20)		
Fear of contamination and cleaning	7 (28)			8 (32)		
Miscellaneous	1 (4)			5 (20)		
Symptom severity						
Baseline Y-BOCS score	35.4	3.03	35–37	33.4	2.4	32–36
Baseline HDRS score	17.2	4.99	14–21	17.3	4.3	14–19
Baseline GAF score	37.9	7.24	30–40	42.8	9.8	30–50

GAF: Global Assessment of Functioning; HDRS: Hamilton Depressive Rating Scale; OCD: Obsessive-Compulsive Disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

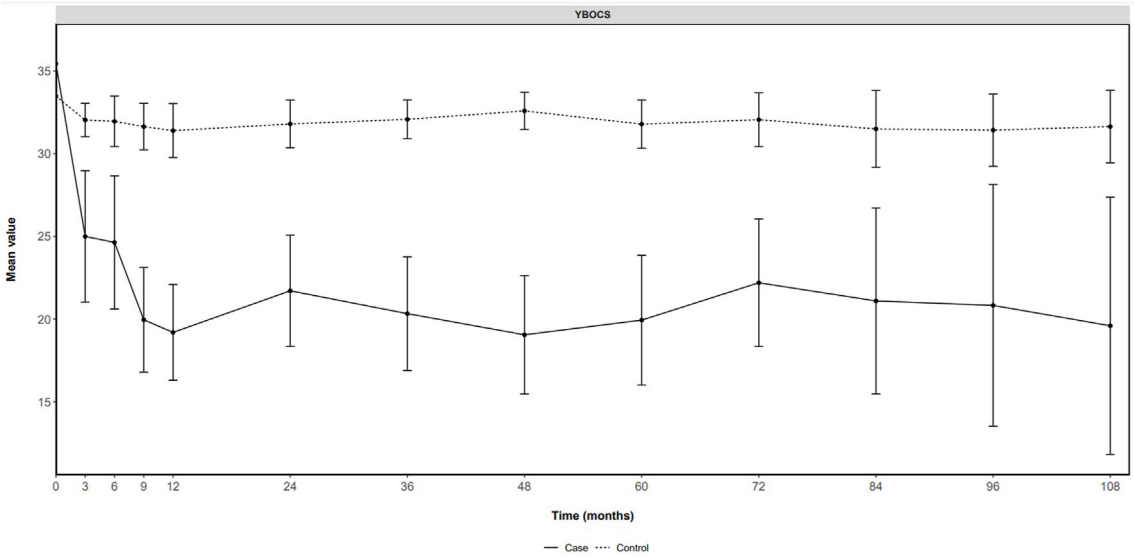

Fig. 2. Mean Yale-Brown Obsessive-Compulsive Scale scores during the follow-up in the intervention (deep brain stimulation) and control groups.
YBOCS: Yale-Brown Obsessive-Compulsive Scale.

psychotropic medication was observed (from 2.7 drugs per patient to 2.1 at the last follow-up). At the end of the follow-up, four DBS-treated patients no longer needed any medication (16%) and nine patients (36%) required only low doses of benzodiazepines as hypnotics, whereas among the controls, only one patient was on no medication (4%); since he had shown no response to any of the previously tested treatments, pharmacological therapy was stopped on proposing DBS. Among DBS- treated patients, antipsychotics, used as potentiation agents, could be withdrawn in eight of the 13 patients who had required them, and clorimipramine or SSRIs were stopped in three more patients. In the control group, only small adjustments were made in the pharmacological treatment during follow-up (trials of some previously untested SSRI or increases in the dose of benzodiazepines as anxiolytics) since patients had already shown resistance to all antiobsessive treatments before DBS was offered to them. At the end of the follow-up, most patients in the control group (14/25) were taking clorimipramine along with an SSRI or/and an antipsychotic, a complex pharmacological combination reserved for severe resistant cases of OCD.

Four patients in the DBS-treated group and eight patients in the control group continued to undergo cognitive-behavioural therapy through exposure with response prevention during the years of follow-up. Although continued CBT was offered to all patients in the study, nine in the DBS group did not consider it necessary after experiencing a clear improvement with the stimulation, and 12 were not motivated to try it again as it had not been effective before surgery. The remaining 17 patients in the control group had tried CBT unsuccessfully and did not want to resume treatment.

Table 4 lists the AEs. The most frequently reported device and/or surgery-related AEs were tightness in the passage regions of the wiring, mainly in the neck and ear area (60%), post-surgical headache (32%), and wound infection (12%). In two of the three patients who suffered wound infection, it affected the retroauricular incision while in the other one the infection affected the abdominal incision in the area of implantation of the battery. Intravenous antibiotic treatment was initiated in all these patients but given the difficulty in controlling the infection and the risk of extension to an intracranial infection, the stimulation system was removed and reimplanted again after a few months. Two of the three patients who suffered wound infections had severe weight problems and diabetes prior to the intervention which could have contributed to an increased risk of skin infections. So, extreme pre- and post-surgical hygiene measures are essential in all patients, but especially in those with associated risk factors such as diabetes. During the follow-up period, five patients required reintervention because of a broken electrode or extension wire. In all cases, the electrode or wiring break was detected after the patients described a sharp worsening of their obsessive symptoms. All patients requested to be reoperated and reimplanted. After the second surgery, they all recovered the clinical improvement obtained after the first intervention.

Regarding neurological and somatic AEs, the most common were forgetfulness, anomie, and other memory complaints (44%), headache (40%), insomnia (32%) and weight gain (24%). Cognitive complaints were transient and mild, without any functional interference and could not be objectively confirmed or quantified since

Table 2
Comparison between patients receiving DBS at ventral anterior limb of the internal capsule and nucleus accumbens (vALIC-Nacc) and bed nucleus of stria terminalis (BNST).

	vALIC DBS		BNST DBS (n = 6) (n = 19)			
	Mean	SD	Mean	SD	X^2/t	p
Female gender, n (%)	4 (66.6)		8 (42.1)		1.1	0.2
Age, years	49.8	10.0	46.7	11.0	0.6	0.5
Age of onset of OCD, years	17.1	4.9	15.9	5.7	0.4	0.6
Duration of illness, years	32.6	9.0	30.8	8.9	0.4	0.6
Study follow-up, years	9.3	4.3	5.4	2.4	2.8	0.01
Baseline Y-BOCS score	37.3	1.6	35.3	1.7	2.4	0.02
Last follow-up Y-BOCS score	23.8	4.4	19.7	8.7	1.0	0.2
Baseline HDRS score	17.3	5.3	17.2	5.0	0.05	0.9
Last follow-up HDRS score	10.5	2.7	10.3	7.1	0.06	0.9
Baseline GAF score	36.6	5.1	37.8	6.7	−0.4	0.6
Last follow-up GAF score	67.5	4.1	68.9	23.9	−0.2	0.8
Y-BOCS reduction %	36.0	11.9	44.2	23.9	−0.7	0.4
HDRS reduction %	38.2	6.6	41.5	32.9	−0.2	0.8
GAF improvement %	45.2	9.8	43.1	14.4	0.3	0.7
Responders, n (%)	3 (50%)		11 (57.8%)		0.1	0.5

vALIC: ventral anterior limb of the internal capsule; Nacc: nucleus accumbens; BNST: bed nucleus of stria terminalis; GAF: Global Assessment of Functioning; HDRS: Hamilton Depressive Rating Scale; OCD: Obsessive-Compulsive Disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

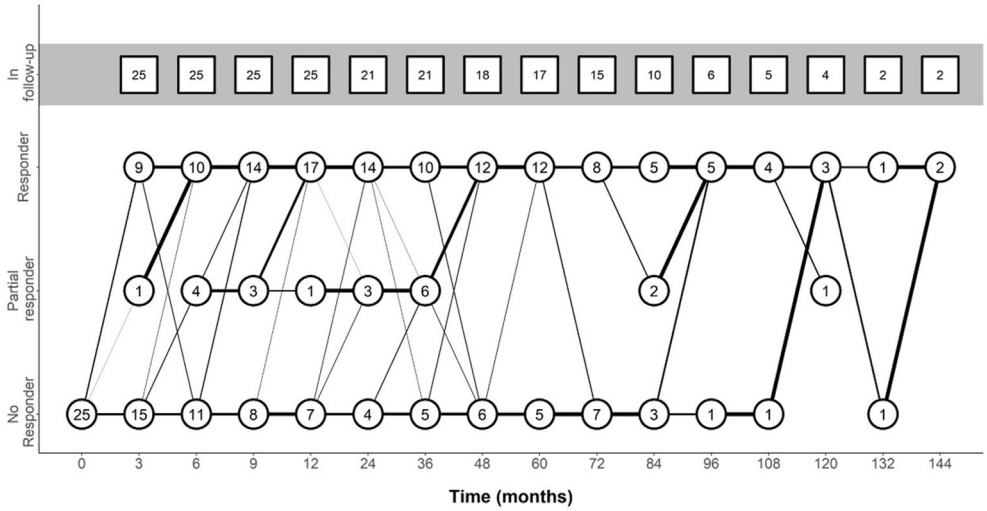

Fig. 3. Number of patients and transitions according to the level of response to deep brain stimulation treatment during the follow-up.

no neuropsychological examination was carried out within the study. The psychiatric AEs reported were mania/hypomania (44%), followed by apathy (32%) and transient worsening of anxiety (28%). Seven patients (28%) showed transient hypomanic symptoms, lasting less than a week, which disappeared with the adjustment of stimulation parameters and did not require any pharmacological treatment. Four patients (16%) experienced a manic episode that required hospital admission with a mean stay of 31.3 days. Two of them were patients with a previous comorbid diagnosis of bipolar disorder on mood stabilizer treatment with lithium carbonate. All manic episodes resolved completely with pharmacological treatment (risperidone or olanzapine) and adjustment of stimulation parameters, and did not recur with new stimulation trials. Antipsychotic treatment in these four patients was discontinued less than four weeks after discharge and it was not considered necessary to initiate a mood stabilizer in the two patients who were not previously taking one. Another patient presented a psychotic episode that also required hospitalization and remitted completely with antipsychotic treatment (risperidone). Complaints of apathy were transient and disappeared with the adjustment of the stimulation parameters, except in two patients who reported apathy prior to the implantation of DBS and who had comorbid diagnoses of Major Depression and Dysthymia respectively.

Five patients in the DBS and four in the control group described passive suicidal ideation during the follow-up period. These passive suicide thoughts had been present before DBS was implanted or offered and rejected, and in the case of the patients who received DBS, they were not linked to changes in stimulation. Two patients in the DBS group and four in the control group committed at least one suicide attempt, all of them drug overdoses, a percentage that did not differ significantly between the two groups ($X^2 = 0.7$, $p = 0.6$). Nor did the mean number of attempted suicides differ between the two groups (DBS group: 1.08 ± 3.95 vs control group: 0.2 ± 0.73, $t = 0.9$, $p = 0.8$), although the number of suicide attempts was higher in the group that received DBS, in which two patients with comorbid Bipolar Disorder had taken up to 27 drug

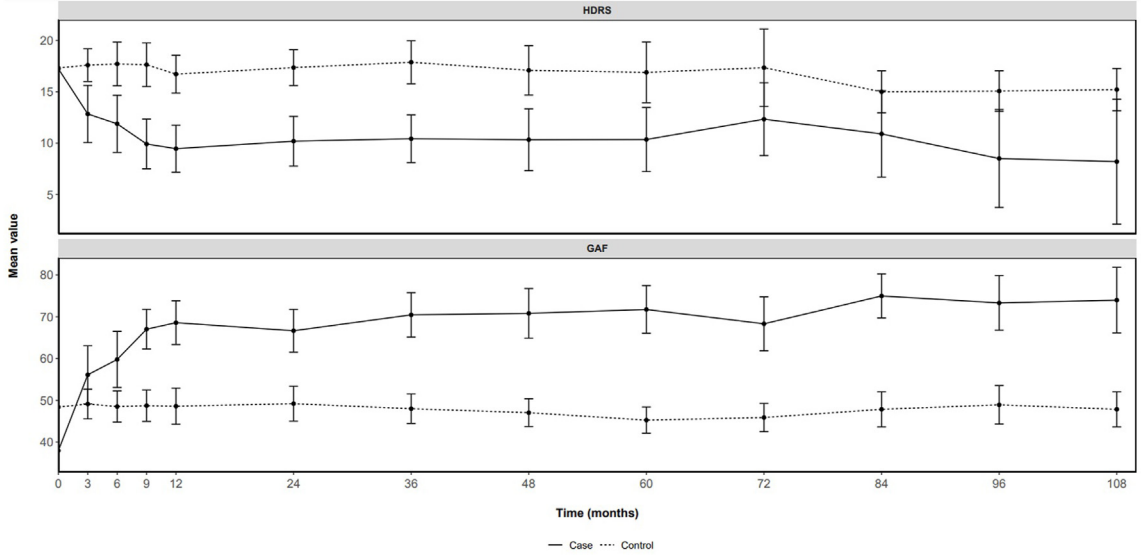

Fig. 4. Mean Hamilton Depression Rating Scale and Global Assessment of Functioning scores during the follow-up in the intervention (deep brain stimulation) and control groups. HDRS: Hamilton Depression Rating Scale; GAF: Global Assessment of Functioning.

Table 3
Medication usage at baseline and last follow-up.

	Deep brain stimulation group (n = 25)		Treatment as usual group (n = 25)	
	Baseline	Last Follow-up	Baseline	Last Follow-up
No medications, n (%)	1 (4)	4 (16)	1 (4)	1 (4)
SSRI, n (%)	3 (12)	3 (12)	3 (12)	4 (16)
SSRI + antipsychotic, n (%)	5 (20)	3 (12)	1 (4)	1 (4)
Clomipramine, n (%)	2 (8)	2 (8)	2 (8)	2 (8)
Clomipramine + antipsychotic, n (%)	3 (12)	1 (4)	2 (8)	1 (4)
Clomipramine + SSRI, n (%)	5 (20)	2 (8)	6 (24)	4 (16)
Clomipramine + SSRI + antipsychotic, n (%)	5 (20)	1 (4)	9 (36)	9 (36)
Others, n (%)	1 (4)	9 (36)	1 (4)	3 (12)

SSRI: selective serotonin reuptake inhibitor. Others: pregabalin, valproic acid, lithium, benzodiazepine.

overdoses in the last 14 years, compared to seven overdoses in the four patients from the control group. All patients who attempted suicide during the follow-up period had a previous history of suicidal behaviour before the start of the study (drug overdoses) and the two patients in the DBS group had been previously hospitalized for suicidal gestures. These two patients attributed their self-injuring before and during the study to affective fluctuations in the context of their Bipolar Disorder and did not relate them to obsessive symptoms or changes in the neurostimulator.

During DBS treatment, 24 patients switched from a non-rechargeable to a rechargeable battery.

3.3. Multivariate analysis and predictors of response

The comparative effect of the DBS versus the control group treatment measured through mixed models for each scale (Y-BOCS, HDRS and GAF) is presented in Table 5, which contains the coefficients for each parameter included in the multivariate analysis. The model for the Y-BOCS explained 55.6%, the HDRS 62.8% and the GAF 58.5% of the random effects. The coefficient showing the mean difference between the DBS group and the control group was 10.6 points for the Y-BOCS, 5.3 points for the HDRS and −18.5 for the GAF, all of which were statistically significant. The estimated effect sizes were 4.29 for the Y-BOCS, 1.15 for the HDRS and 2.54 for the GAF, all of them well above the 0.8 threshold for a large effect size proposed by Cohen [32] (**Table SM4**).

Univariate analysis was performed of potential clinical predictors (age at OCD onset, age at implantation, gender and main OCD symptom dimension) but none of them were found to be significant. There were differences according to gender, since 76.9% of the men (10/13) responded to DBS compared to just 33.3% of the women (4/12), but the difference did not reach statistical significance.

Table 4
Adverse effects in deep brain stimulation group during the follow-up.

Adverse effects	N (%)
Device and/or surgery-related	
Wound infection	3 (12%)
Post-surgical headache	8 (32%)
Tightness at extension leads	15(60%)
Neurological and somatic	
Memory complaints	11 (44%)
Weight gain	6 (24%)
Insomnia	8 (32%)
Headache	10 (40%)
Fatigue	9 (36%)
Nausea and epigastric pain	3 (12%)
Enuresis	2 (8%)
Diarrhoea	1 (4%)
Psychiatric	
Hypomania	11 (44%)
Apathy	8 (32%)
Anxiety worsening	7 (28%)

4. Discussion

Our study significantly expands the limited information on the long-term effects of DBS in OCD, comparing for the first time this last-resort therapeutic option with maintenance of the usual treatment in a comparable sample of severe and refractory obsessive patients who rejected DBS. Our main finding was that DBS is highly effective at reducing symptoms of severe OCD and that changes in HDRS and GAF scores also indicated clear improvements in depressive symptoms and global functioning. The regression models used to measure outcomes estimated a comparative effectiveness of 32% (Y-BOCS), 39% (HDRS) and 67% (GAF) over the initial mean values in the DBS group. The changes were statistically significant according to the mixed models and also clinically significant given the large effect sizes [32,34]. The magnitude of the change in the intervention group is large enough to state that the treatment with DBS was worthwhile for severe OCD patients, even taking into account the risk of adverse effects. Moreover, the patients in the control group did not show significant improvements in either obsessive-compulsive or depressive symptoms or global functioning during the years of follow-up, despite continued medication. These results are consistent with the data in the international literature indicating that OCD patients' quality of life, in terms of functional limitations and discomfort, is correlated with Y-BOCS score [15,35,36].

The effectiveness of DBS was already apparent at 12 months of follow-up, when 18 patients (72%) were classified as responders. The reduction in symptoms remained stable over time, the final number of responders being 17 (68%). These results are comparable to those of a long-term study by Graat et al., which found that 74% of patients followed for at least three years (mean 6.8 ± 3 years) were responders to DBS treatment at one year and 62% were responders at the end of the follow-up [35]. When there is a lack of response at 1 year, clinicians face the decision of whether to remove the DBS device, based on a benefit-risk analysis. If the patient is not going to improve, eliminating the device and its connections with the brain might be the option selected in order to prevent complications. However, the removal of the electrodes also entails a risk, as it has been associated with a significant likelihood of postoperative small superficial haemorrhages [37]. Although most of the improvement in OCD symptoms in our patients was achieved in the first year of stimulation, some subjects who did not respond one year after surgery were eventually late responders. These results agree with those reported by Luyten et al., who described a 37% reduction in Y-BOCS scores in an initial on/off phase lasting six months, a figure that rose to 66% at four years of follow-up [20]. Based on these results and given the severity of OCD in the target

Table 5
Mixed model results for Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Depression Rating Scale (HDRS) and Global Assessment of Functioning (GAF) scores comparing the treated and untreated groups.

	Y-BOCS score				HDRS score				GAF score			
	Estimate	CI(2.5)	CI(97.5	Sig	Estimate	CI(L)	CI(U)	Sig	Estimate	CI(2.5)	CI(97.5	Sig
(Intercept)	2.226	−18.230	22.601		−2.379	−8.530	3.809		36.593	20.907	52.312	*
log(time)	−0.684	−1.003	−0.359	*	−0.095	−0.345	0.148		1.744	1.204	2.288	*
Initial YBOCS	0.560	0.020	1.102	*	–	–	–	–	–	–	–	–
Initial HDRS	–	–	–	–	0.773	0.518	1.025	*	–	–	–	–
Initial GAF	–	–	–	–	–	–	–	–	0.597	0.277	0.916	*
Group (Control)	11.313	7.803	14.830	*	6.821	4.326	9.331	*	−25.323	−32.405	−18.245	*
Age of diagnosis	0.044	−0.154	0.241		−0.047	−0.197	0.102		0.136	−0.223	0.495	
Gender (Female)	2.098	−1.054	5.247		1.029	−1.328	3.393		−1.687	−7.476	4.089	
Type (Aggressive)	−0.194	−5.379	4.979		−0.104	−4.054	3.853		−0.048	−9.543	9.473	
Type (Religious)	0.113	−6.579	6.805		2.192	−2.937	7.336		1.553	−10.718	13.836	
Type (Symmetry)	−1.898	−7.620	3.861		0.429	−3.868	4.750		4.929	−5.540	15.364	
Type (Cleaning)	−0.135	−5.180	4.902		1.615	−2.157	5.376		−1.579	−10.814	7.690	

Type: main dimension.
GAF: Global Assessment of Functioning; HDRS: Hamilton Depressive Rating Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale. CI: Confidence Intervals. (L): lower; (U): Upper.

population, our recommendation is to maintain the stimulation in the case of partial response during the first year and to continue exploring new stimulation parameters. Moreover, some of the patients who did not show improvement in their obsessive symptoms (8/25) reported other benefits during treatment, such as a reduction in depressive symptoms, better functioning and the feeling of being more accompanied. Despite the small sample size, these results support the maintenance of DBS because improvement may be observed in various areas after years of stimulation. as previous studies have shown [15,35],

The reduction in obsessive symptoms was accompanied by improvements in both depressive symptoms and functioning, with large effect sizes according to Cohen's criteria [32]. The same pattern of improvement showing overall reductions in OCD, anxiety and depression was reported in the only other long-term study to date, namely, that of Graat et al. [35]. The correlation of the trends in Y-BOCS with HDRS and GAF scores indicates that DBS transformed responders' lives. In our sample, after years of stimulation, two very severe patients who had been admitted to long-stay units for years were discharged home as their independence in activities of daily living improved thanks to the marked reduction in their obsessive symptoms.

Sociodemographic and clinical factors were analyzed as possible predictors of response but no associations were found [15]. The identification of predictors is hindered by the small sample size and would require pooling samples from different studies in order to achieve sufficient statistical power. Clinical features that have previously been associated with better clinical outcomes after DBS include older age at OCD onset and presence of sexual/religious obsessions and compulsions according to Alonso et al.'s meta-analysis [11], and later age at onset, comorbid personality disorder and insight into illness in Graat et al.'s study [15]. Nevertheless, the evidence is not sufficient to establish clear clinical guidelines. In a recent pioneering study, Barcia et al. obtained a high response rate (in six out of seven OCD patients) by individualizing the anatomical locus of the best contact through an index derived by combining functional MRI responses to specific symptom provocation for each patient and prefrontocortico-striatal projections defined by probabilistic tractography [38]. These results suggest that we should move from the classical search for a single target valid for all patients to an individualized target based on clinical manifestations and functional and brain connectivity biomarkers.

Most DBS-induced side effects were mild and readily reversible by adjusting stimulation parameters, and in most patients the treatment was well tolerated. However, there are certain risks associated with DBS that cannot be ignored and may be serious. In our series of cases, we did not report any haemorrhages or epileptic seizures after implantation, but we did record three infections that obliged the removal of the stimulator. This rate is slightly higher than that of other studies and may be related to certain medical conditions in some of our patients (e.g., diabetes and comorbid obesity), to which special attention should be paid.

Our study had several limitations. Although we included a control group, the patients were not randomized and the study was not double blinded. Both of these circumstances may have biased our findings. Given that patients were recruited over more than a decade, the variable follow-up period and the different target sites also limit the scope of our findings. Finally, although our sample size was relatively large given the number of patients with OCD who receive DBS worldwide [39], it did not provide sufficient statistical power to identify predictors of response.

Our study confirms that DBS is an effective and safe treatment option in patients with severe refractory OCD, in both the short and the long term. Nonetheless, since it is associated with certain severe AEs, its risks and benefits must be assessed on a case-by-case basis. As a neurosurgical procedure, it must be performed at specialized centres with multidisciplinary teams. To conclude, given the small target population worldwide, multicentre studies should be carried out to establish common guidelines based on a shared stimulation protocol, to study predictive factors, and to define the best target sites.

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Availability of data and materials

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Lorea Mar-Barrutia: Conceptualization, Investigation, Writing – original draft. **Oliver Ibarrondo:** Methodology, Software, Formal analysis, Writing – review & editing. **Javier Mar:** Methodology, Formal analysis, Writing – original draft. **Eva Real:** Investigation, Validation, Writing – review & editing. **Cinto Segalàs:** Investigation, Validation, Writing – review & editing. **Sara Bertolín:** Investigation, Validation, Writing – review & editing. **Marco Alberto Aparicio:** Investigation, Validation, Writing – review & editing. **Gerard Plans:** Investigation, Validation, Writing – review & editing. **José Manuel Menchón:** Investigation, Validation, Writing – review & editing. **Pino Alonso:** Conceptualization, Investigation, Writing – original draft, All authors revised the manuscript for important intellectual content and approved the final version. Further, they all had full access to all the data used in the study and accepted responsibility to submit the paper for publication.

Declaration of competing interest

PA, ER, CS, MAA, GP and JMM participated in a clinical trial sponsored by Medtronic to monitor the safety and performance of electrical stimulation of the AIC in patients with chronic, severe, treatment-resistant OCD from 2014 to 2017 (ClinicalTrial.gov identifier: NCT01135745). The authors report no other biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.07.050.

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