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Long-term effects of subthalamic stimulation in Obsessive-Compulsive Disorder: follow-up of a randomized controlled trial

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Obsessive-Compulsive Disorder (OCD) is characterized by intrusive, anxious thoughts with repetitive, ritualized behaviors, and has negative impacts on family relationships and social life. Its lifetime prevalence is estimated to be 2-3% [1]. Cognitive and behavioral therapy and selective serotonin reuptake inhibitors are the standard treatments for OCD; nevertheless, despite these treatments, between 25 and 40% of patients display persistent symptoms leading to severe functional disability [2]. Neurosurgical treatment targeting different parts of the orbito-fronto-striato-thalamo-cortical circuit has been proposed for the most severe and refractory forms, including both gamma knife non-invasive stereotactic lesions and invasive deep brain stimulation (DBS) [3] (Supplementary Information). However, the long-term efficacy (> 3 years) and safety of DBS for OCD is not fully reported. We prospectively followed 14 OCD patients treated with subthalamic DBS (STN-DBS, STOC study) for 46 months [4] (*ClinicalTrials.gov* Number: NCT00169377) (Supplementary Information). The primary outcome was the change in the total Yale Brown Obsessive Compulsive Scale (Y-BOCS) score between inclusion (baseline) and month 46 with STN-DBS, or month 34 in the case of missing data at month 46 (Supplementary Figure 1). We also assessed others psychiatric symptoms, global functioning and tolerance (Supplementary Information) [4]. Twelve patients completed the follow-up study (Supplementary Figure 1). The Y-BOCS total score between inclusion (baseline) and the end of the follow up period showed a median decrease of 15.5 points (IQR=-31 to -6), with a median change of 50% (IQR=-86.1 to -19.4%, Table 1). At the final follow-up, 11 patients (92%) were considered at least partial responders (>25% of Y-BOCS decrease) and 9 (75%) full responders (>35% of Y-BOCS decrease) (Table 1). The Y-BOCS score was also significantly improved at month 46 compared to month 16 (Table 1) and decreased by an average of 1 (SE=.04) point per year between month 16 and month 46 (Time effect p=0.027, Supplementary Figure 2). At the end

of the follow-up period (month 46), the compulsion, obsession, anxiety and depression scores, but also global functioning and social and family life subscores were significantly improved (Supplementary Table 1). We found a significant positive relationship between the severity of OCD at month 46 and the age at onset (r=0.61, *p*=0.045, Supplementary Figure 3) with early onset patients having fewer OCD symptoms with STN stimulation. During the follow-up, the medication had not changed significantly (not shown) but stimulation voltage was significantly increased (*p*=0.042, Supplementary Table 2). Twenty-three serious adverse events occurred, 5 being transient and related to STN-DBS (hypomania, impulsivity, dysarthria or fall) and 18 related to the disease (increased anxiety and obsessive and compulsive symptoms, and major depressive episodes with suicide attempts, Supplementary Table 3). Our results show that STN-DBS can effectively treat OCD symptoms in severe and refractory patients over a period more than 3 years, with a 53% decrease in OCD severity and 11 out of 12 patients being considered responders at the final assessment with improvements in global functioning and social life. The fact that DBS of other limbic structures within the cortico-basal ganglia circuitry, such as the nucleus accumbens and the bed nucleus of the Stria terminalis, induce a median decrease in Y-BOCS scores of 45%, with two thirds of responders, favors the hypothesis that modulation of the neuronal activity within the limbic basal ganglia circuitry by DBS leads to OCD reduction [5]. In our patients, we observed a continuous and progressive significant improvement with time, concomitantly with increased DBS voltage. This suggests that a certain threshold of electric charge is needed to obtain an optimal outcome, but also that chronic and continuous STN-DBS might promote brain plasticity with additional improvement over time. Such plasticity phenomena have been suggested to explain the long-term results for GKC treatment [6]. Finally, even though ablative neurosurgery such as GKC may have some advantages over DBS

and be seen as a "quick-fix", “minimal-invasiveness” and “low-cost” paradigm [7], DBS has the advantage of being able to be continuously adapted to the patients’ condition to obtain the best effects for each individual and thus based on a "adjustability" paradigm [7] (Supplementary Information). It is, however, a “high-cost” procedure, with the need for prolonged hospitalization, regular outpatient visits and neurostimulator replacements. In our study, the fact that these beneficial effects were obtained with low voltage and that no stimulator replacement was needed during the follow-up period would suggest that STN-DBS is less expensive with high cost-effectiveness compared to other DBS procedures [8]. One patient (P12) showed no OCD reduction over the course of the study, and in the two patients who withdrew during the follow-up study (P05 and P14) there was no significant improvement. This is unlikely to have been related to the electrode placement, because the therapeutic contacts were correctly located within the associative-limbic part of the STN in all patients (Supplementary Figure 4). This suggests that about 20% of our patients are unresponsive to STN-DBS, as also previously reported with other DBS targets [5]. Four of our 12 patients (33%) developed hypomania and impulsivity and 3 patients (23%) attempted suicide, with concomitant stimulation-induced impulsivity, acute alcoholism or increased anxiety, depressive signs and/or OCD. This rate of psychiatric signs is high in comparison to that previously reported for STN-DBS in Parkinson’s disease (PD) [9], but similar to that reported with DBS of the nucleus accumbens or Stria terminalis in OCD patients [5]. This suggests that the occurrence of these psychiatric signs could result from DBS of these limbic structures [10], but also from an aggravation of the disease in these severe and refractory OCD patients [1]. In conclusion, the findings from this 46-month follow-up study demonstrate that STN-DBS represents a new therapeutic option for severe and refractory OCD, with a very high response rate, good long-term outcome and improvement in global

functioning, social and familial disability, providing a multidisciplinary approach to optimize stimulation parameter settings and minimize potential side-effects. Larger studies are now needed to assess the health-economic benefits of STN-DBS and to compare this treatment with other stimulation targets, with the use of study designs taking into account the advantages of DBS's adaptability.

Conflicts of interest

Dr. Mallet reports grants from Fondation pour la recherche médicale (FRM), grants from Agence Nationale de la Recherche, grants from Fondation Privée des HUG, grants from Fondation ICM, grants from Halphen Foundation, outside the submitted work; Dr. Bardinet reports grants from Medtronic, during the conduct of the study; Dr. Chabardes reports personal fees from Medtronic, personal fees from Boston Scientific, outside the submitted work; Dr. Fontaine reports grants and personal fees from Medtronic, outside the submitted work; Dr. Houeto reports personal fees from Medtronic, outside the submitted work; Dr. Krack reports grants and other from Medtronic during the conduct of the study; grants and personal fees from Medtronic, grants and personal fees from Boston Scientific, grants from St Jude Medical France, grants from Edmond J & Lily Safra Foundation, grants and personal fees from Movement Disorder Society, grants from French Ministry of Health (PHRC), grants from INSERM (French National Institute of Health and Research in Medicine), grants from France Parkinson, grants from Swiss National Science Foundation, grants from Roger de Spoelberch Foundation, grants from Centre National Recherche Scientifique, personal fees from European Society Stereotactic Functional Neurosurgery, grants and personal fees from UCB, grants from Orkyn, grants from Homeperf, outside the submitted work; Dr. Millet reports grants and personal fees from Medtronic, grants and personal fees from Syneïka,

personal fees from Lundbeeck, personal fees from Astra Zeneca, personal fees from Celgene, personal fees from Janssen, outside the submitted work; Dr. Polosan reports personal fees from Medtronic, grants from Boston Scientific, grants from Agence Nationale de la Recherche, outside the submitted work; Dr. Tezenas du Montcel reports personal fees from Boston Scientific, outside the submitted work; Dr. Welter reports personal fees from Medtronic, grants from Michael J Fox Foundation for Parkinson's Disease, grants from Agence Nationale de la Recherche, outside the submitted work. The other authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

References

[1] Ruscio A, Stein D, Chiu W, Kessler R. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry 2010;15:53–63. doi:10.1038/mp.2008.94.

[2] Skapinakis P, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, et al. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. The Lancet Psychiatry 2016;3:730–9.

[3] Nuttin B, Wu H, Mayberg H, Hariz M, Gabriels L, Galert T, et al. Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. J Neurol Neurosurg Psychiatry 2014:1–7.

[4] Mallet L, Polosan M, Jaafari N, Baup N, Welter M-LM-LL, Fontaine D, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 2008;359:2121–34. doi:10.1056/NEJMoa0708514.

[5] Luyten L, Hendrickx S, Raymaekers S, Ls LG euml, Nuttin B. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol Psychiatry 2015;21:1272–80.

[6] Sheth SA. Commentary Stereotactic Radiosurgical Capsulotomy for the Treatment of Refractory Obsessive-Compulsive Disorder. Biol Psychiatry 2018;84:320–1. doi:10.1016/j.biopsych.2018.06.013.

[7] Müller S, Riedmüller R, van Oosterhout A. Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness. Front Integr Neurosci 2015;9:27. doi:10.3389/fnint.2015.00027.

[8] Moon W, Kim SN, Park S, Paek SH, Kwon JS. The cost-effectiveness of deep brain stimulation for patients with treatment-resistant obsessive-compulsive disorder. Med (United States) 2017;96:1–8. doi:10.1097/MD.0000000000007397.

[9] Schuepbach WMM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610–22.

[10] Mallet L, Schüpbach M, N'Diaye K, Remy P, Bardinet E, Czernecki V al, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci U S A 2007;104:10661–6.

doi:10.1073/pnas.0610849104.

Table 1. Changes in OCD severity (Y-BOCS) after STN-DBS in 14 patients.

				Y-BOCS Score			Difference in Y-BOCS scores			
Patient No.	**Center No.**	**Sex**	**Age**	**Baseline**	**Month 16**	**Month 46**	**month 46 vs baseline**		**month 46 vs month 16**	
								(%)		(%)
01	1-1	M	36	31	13	7	-24	(-77%)	-6	(-46%)
02	1-2	F	37	34	15	11	-23	(-67%)	-4	(-27%)
03	1-3	M	56	31	9	9	-22	(-71%)	0	(0%)
05	2-2	F	49	28	31	_	_		_	
07[a]	6-2	M	34	35	29	25[a]	-10	(-29%)[a]	-4	(-14%)
08	7-1	M	29	27	15	12	-15	(-56%)	-3	(-20%)
09	8-1	M	53	37	28	22	-15	(-41%)	-6	(-21%)
10	9-1	F	45	30	13	15	-15	(-50%)	2	(+15%)
11	9-2	M	50	35	26	26	-9	(-26%)	0	(0%)
12	9-3	F	47	31	25	25	-6	(-19%)	0	(0%)
13	10-1	M	39	38	23	22	-16	(-42%)	-1	(-4%)
14	10-2	M	51	35	35	_	_		_	
15	10-3	F	43	36	7	5	-31	(-86%)	-2	(-29%)
16	10-4	F	42	32	20	16	-16	(-50%)	-4	(-20%)
Mean			**43.8**	**32.4**	**20.9**	**15.4**	**-16.8**	**(-51.2%)**	**-2.3**	**(-13.8%)**
SD			**7.6**	**3.6**	**8.5**	**7.0**	**7.1**	**(21.2%)**	**2.6**	**(16.7%)**

Y-BOCS total score on a scale of 0 to 40, higher scores indicate greater severity. Difference and percentage of changes (%) between month 46 and baseline (inclusion); and between month 46 and month 16. Negative value indicates improvement. Y-BOCS: Yale Global and Brown Obsessive Compulsive Score. [a] This patient was assessed at month 34. P04 (2-1) and P06 (5-1) were not included in the long-term follow-up study.

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Appendix A. Supplementary material

Supplementary Information

Methods

Participants

Fourteen patients with severe and refractory OCD were included in this long-term study (Supplementary Figure 1). They had previously been enrolled in the double-blind phase of a research program (STOC study) between January 2005 and April 2006 which aimed to assess the effects of 3 months of STN-DBS on OCD severity [1]. Inclusion criteria were the presence of OCD, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, revised text (DSM IV-TR),[2] with a score on the Yale-Brown Obsession and Compulsion Scale (Y-BOCS)[3] of more than 25 (on a scale from 0 to 40 - with lower scores indicating less severe symptoms), a disease duration of over 5 years, a score on the Global Assessment of Function (GAF)[4] score of less than 40 (on a scale from 1 to 90 with higher scores indicating higher levels of functioning), a score for illness severity on the Clinical Global Impression (CGI)[5] scale of more than 4 (on a scale of 1 to 7, with higher scores indicating greater disease severity), and a lack of response to both drug therapy after adequate administration of at least three serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy; normal cognitive status (a score of > 130 on the Mattis Dementia Rating Scale-MDRS, range 0 to 144, with lower scores indicating more severe dementia) [6]; normal findings on the magnetic resonance brain imaging (MRI) and no contraindications to surgery or anesthesia [1]. Exclusion criteria were the presence of any comorbid psychiatric disorder in axes I and II of the DSM IV-TR, current severe major depressive episode with a Montgomery and Asberg Depression Scale (MADRS)[7] score of more than 20 (on a scale from 0 to 60, with higher scores indicating greater severity of depressive symptoms) and a risk of suicide (a score >2 on MADRS item 10).

Study design

The initial study used a randomized, double-blind, cross-over design with two 3-month phases (active *versus* sham stimulation) separated by a one month washout period (Supplementary Figure 1) [1]. At the end of the randomized crossover period (month 10), stimulation was initiated in all patients (month 10 –

Supplementary Figure 1). All of these were offered the opportunity to be included in a prospective open design study after at least 6 months with active stimulation (month 16, Supplementary Figure 1). Full clinical assessments were performed at months 16, 22, 34 and 46 (Supplementary Figure 1). The trial was conducted at 10 academic centers in France in accordance with the Declaration of Helsinki ethical rules and was approved by the ethics committee of Paris Ile-de-France (*ClinicalTrials.gov* Number: NCT00169377). All patients provided written informed consent before enrolment. A clinical assessment was performed at each visit, as per trial protocol, by a psychiatrist, a neuropsychologist and a neurologist. Any new symptom or worsening of a pre-existing symptom was classified as an adverse event.

Outcomes

The percentage of full responders was evaluated, and defined as a decrease in the YBOCS score of more than 35% between inclusion and month 46 (or the last assessment), a decrease of 25% being considered a partial response [8].

The secondary outcomes were the changes on the following scales (see below): obsessions and compulsions YBOCS subscales, GAF, CGI, MADRS, Brief Anxiety Scale (BAS) [9], Hospital Anxiety and Depression Scale (HADS) [10], Maudsley Obsession Compulsion Inventory (MOCI) [11], Social Adjustment Scale Self-Reported (SAS-SR) [12], Short-Form Health Survey (SF-36 physical and mental subscales) [13], Sheehan Disability Scale (SDS work, social life and family life subscales) [14], Stroop interference scale, verbal fluency, Trail making test (A, B, A-B) [15], Starkstein [16] and Robert [17] apathy scales, facial emotion recognition [18] at the end of the follow-up period (month 46 or last assessment) in comparison to inclusion, and at the end of the follow-up period in comparison to the start of the open-label period (month 16). The change in the total Y-BOCS score and in the stimulation settings (pulse width, frequency, voltage) between the start (month 16) and the final assessment of the follow-up period were also evaluated.

The Yale Brown Obsessive Compulsive Scale (YBOCS) indicates the severity of obsessive-compulsive symptoms with ten sub-items; five for obsessive thoughts and five for compulsions, with the total score ranging from 0 to 40 [3]. The Global functioning evaluation scale (GAF) assesses the level of psychological, social and professional functioning on a hypothetical continuum ranging from 1 (representing the most seriously ill individual) to 90 (representing an individual who is virtually free of symptoms or with very minimal symptoms and who functions satisfactorily within their social environment or family) [4]. The scale is divided into 9 equal

intervals ranging from 1 to 10, 11 to 20, 21 to 30, etc.… The Global Clinical Impression Scale (CGI) provides an initial overall severity score from 0 to 7, at baseline, and the overall improvement obtained from the patient throughout the study [5]. The Comprehensive Psychopathological Rating Scale (CPRS) [19], a 67-item scale, provides quantitative assessment of the whole psychopathology. Two sub-scores are extracted: the Montgomery and Asberg Depression Rating Scale (MADRS)[7] that explores depressive symptomatology with scores ranging from 0 to 60 and the Brief Anxiety Scale (BAS)[9] that represents a dimensional measure of generalized anxiety with scores ranging from 0 to 70. The Hospital Anxiety and Depression scale (HADS) is a self-assessment questionnaire for monitoring anxiety and depressive symptom occurrences from the patient's perspective [10]. HADS is a fourteen-item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression. The Maudsley Obsessional Inventory (MOCI) is a self-assessment questionnaire for monitoring obsession and compulsion symptoms that comprises 30 items using a true/false format with 4 subscales for checking compulsions, washing/cleaning compulsions, slowness and doubting [11]. The social adaptation scale (SAS) evaluates social adjustment, with 51 items, classified into five sections: work, social life and leisure, conjugal life, interaction with children [12]. Each item is rated from 1 to 5 (excellent to poor) allowing an estimate of efficiency. The self-administered version was used (SAS-SR) [20]. The Short Form Health Survey (SF-36) is a 36-item, patient-reported survey of patient health [13]. It consists of eight scaled scores, which are the weighted sums of the questions in their section [21]. Each scale is directly transformed onto a 0-100 scale on the assumption that each question carries equal weight. The lower the score the greater the disability. The higher the score the lower the disability i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The Sheehan Disability Scale (SDS) is a 5 item self-report tool that assesses functional impairment in work/school, social life, and family life [14]. Each domain is assessed using a modified visual analog scale from 0 (no disability) to 10 (severe disability). The neuropsychological assessment included the STROOP interference test, a neuropsychological test that measures the effect on reaction time of incongruence between words and printed colors. It was used to examine impulsiveness, being considered as a lack of ability to inhibit interference between words and printed colors. We also examined semantic verbal fluency and the Trail making test [15]. Apathy was assessed using the Starkstein fourteen-item scale, (range 0 to 42) with higher scores indicating greater apathy and a score of 14 used as the pathological cut-off [16], and the Apathy Inventory (for global assessment of apathy and separate assessment of emotional blunting, lack of initiative, and lack of interest) [17] scales. Lastly, the facial emotion recognition test was performed including

eight facial emotions: happiness, sadness, fear, anger, surprise, disgust, neutral; each being rated from 0 to 100 [18].

Imaging data processing

The position of the electrode was confirmed by post-operative CT-scanning or MRI and visualized with atlas-based neuroimaging [22,23]. For this purpose, the post-operative images were superimposed on the stereotactic preoperative MRI. The MR images were resliced along the AC-PC plane together with the contours of atlas structures in 3 orthogonal standard planes (sagittal, coronal, and axial). The electrodes and stimulating contact artefacts were visible on the CT-scan images and individually reconstructed within the basal ganglia atlas space (Supplementary Figure 4).

Results

Of the 16 patients that performed the double-blind randomized phase of the study, two patients withdrew before the beginning of the follow-up study and 14 patients were enrolled in the long-term follow-up study (Supplementary Figure 1). Three of the 14 patients could not be evaluated at 46 months: one patient (P07) missed the assessment with last follow-up at 34 months; one patient was explanted at his request due to absence of effect (P14, month 20); one patient (P05) was lost to follow-up at month 22 after stimulation had been switched off with no evidence of improvement (Supplementary Figure 1). Finally, assessments with subthalamic stimulation were obtained in 11 out of 14 patients (79%) at month 46, and 12 out of 14 patients (86%) at months 16, 22 and 34.

We found a significant positive relationship between the severity of OCD at month 46 and the age at onset (r=0.61, *p*=0.045, Fig. S3) with early onset patients having fewer OCD symptoms with STN-DBS. No significant relationship was found between the severity of OCD at month 46 and age at time of surgery, MADRS and BAS at month 46.

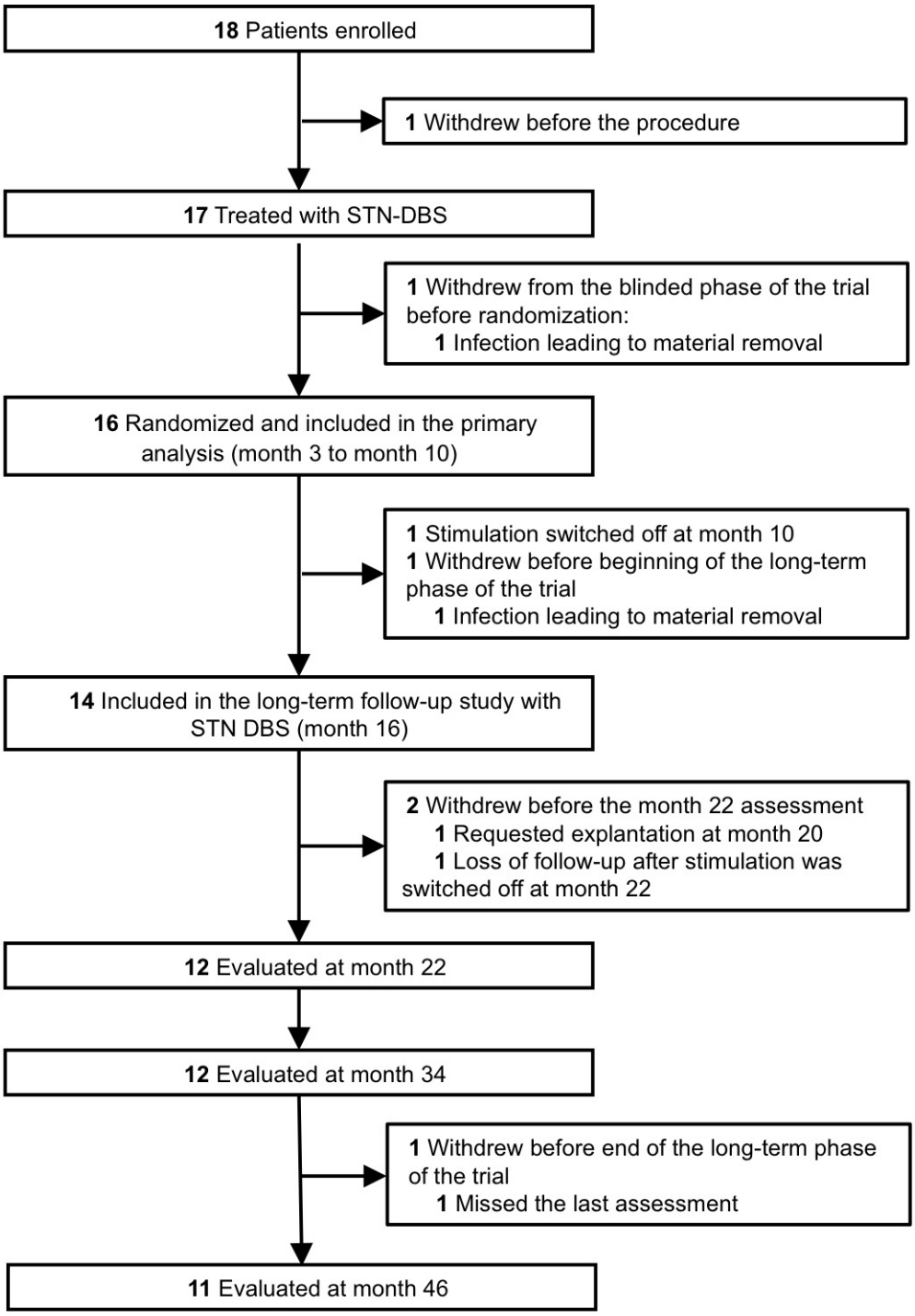
Discussion

Gamma knife capsulotomy (GKC) was employed from the 1970s and showed OCD symptom improvement but with major side effects including executive impairments [24,25] which led to its abandonment. More recently, GKC has been employed to target the anterior limb of the internal capsule (ALIC) with a significant

50% decrease in OCD severity found in 55 patients 3 years after surgery, with 37 patients being considered full responders (>35% improvement). This procedure was well tolerated with no significant neuropsychological side effects [26]. However, a legitimate concern persists regarding the ethical basis, acceptability and potential impact of ablative neurosurgery on psychiatric patients [27].

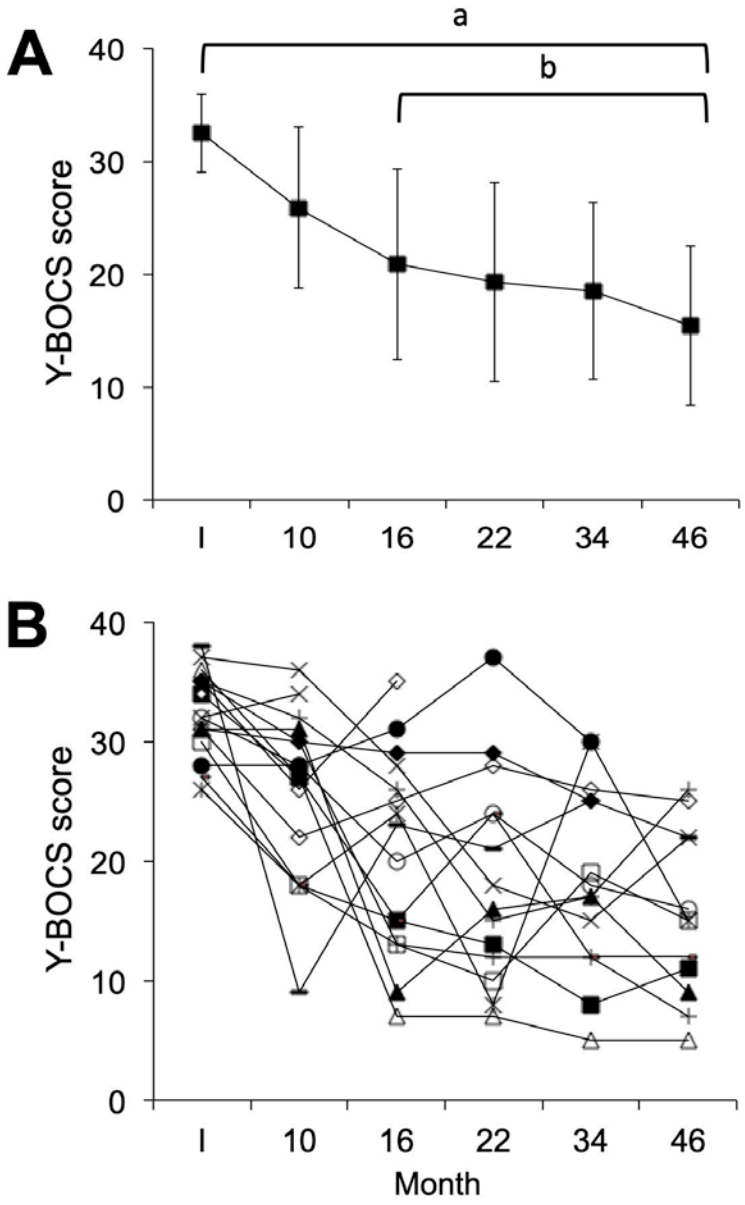
In our patients, we also observed a continuous and progressive significant improvement with time, with a larger effect of STN-DBS on OCD symptoms 46 months after surgery as compared to 16 months. This might indicate that chronic and continuous STN-DBS promotes brain plasticity thus leading to additional improvements over time. In accordance with this hypothesis, a progressive improvement over time after STN-DBS with no significant increase in electric charge has been recently reported in patients with dystonia [28]. Such plasticity phenomena have also been suggested to explain the long-term results for GKC treatment [25]. Interestingly, concomitant with this progressive decrease in OCD severity we needed to significantly increase the DBS voltage. This would imply that a certain threshold of electric charge is needed to obtain an optimal outcome. Again, this highlights the major advantage of DBS, i.e. the possibility of continuously modifying the stimulation parameters over time in accordance with patients' condition to obtain the best effects for each individual. The reversibility of the procedure is also of great importance, clinically in case of major side effects, but also scientifically to explore the relevance of different targets [29] and the physiology basis of the disease [30]. Finally, even though ablative neurosurgery such as GKC may have some advantages over DBS as a general method of treatment for some psychiatric patients, particularly those who may not be able to commit to long-term follow-up. This might be seen as a "quick-fix", "minimal-invasiveness" and "low-cost" paradigm [31], whereas DBS is understood as being based on a "adjustability" paradigm [31] but is a "high-cost" procedure, with the need from prolonged hospitalization, regular outpatient visits and neurostimulator replacements [24]. In our study, the fact that these beneficial effects were obtained with low voltage and that no stimulator replacement was needed during the follow-up period could suggest that STN-DBS is less expensive with high cost-effectiveness compared to other DBS procedures [32]. Finally, up to now and with the current stage of our knowledge, each paradigm seems associated with a different set of costs and benefits for a particular patient [31]. However, the improvement of DBS procedures, including directional stimulation to improve anatomical accuracy of the stimulation with therapeutic window widening [33], rechargeable batteries, and the development of closed-loop systems with adaptive stimulation linked to brain activity [34], will allow us to further adapt the treatment to the anatomy and physiology of an individual patient, with better cost-effectiveness in the future.

The findings from this 46-month follow-up study confirm that STN-DBS represents a new therapeutic option for severe and refractory OCD, with a very high response rate, good long-term outcome and improvement in global functioning, social and familial disability, providing a multidisciplinary approach to optimize stimulation parameter settings and minimize potential side-effects. Larger studies are now needed to assess the health-economic benefits of STN-DBS and to compare this treatment with other stimulation targets, with the use of study designs taking into account the advantages of DBS's adaptability [35].



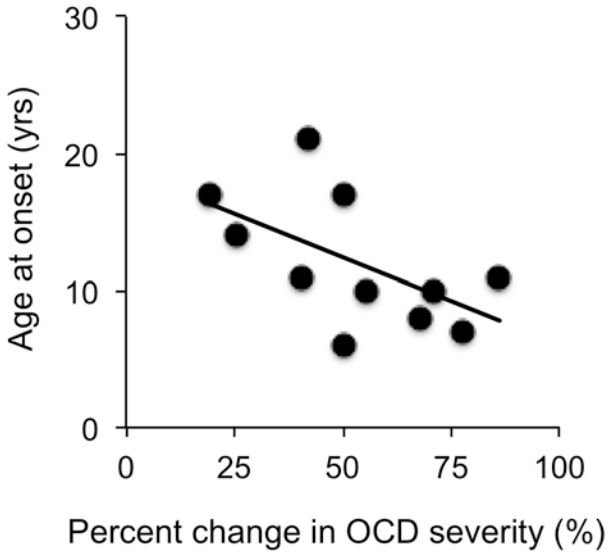
Supplementary Figure 1. Trial profile

The study included a randomized double-blind crossover design period (months 3 to 10, with two 3-month phases separated by a 1-month washout period), followed by an open-label period of 36 months. Patients were evaluated at inclusion (baseline), less than 2 months before surgery; 3 and 10 months after surgery, at the beginning and end of the double-blind period, respectively; and 16, 22, 34 and 46 months after surgery during the open-label period.



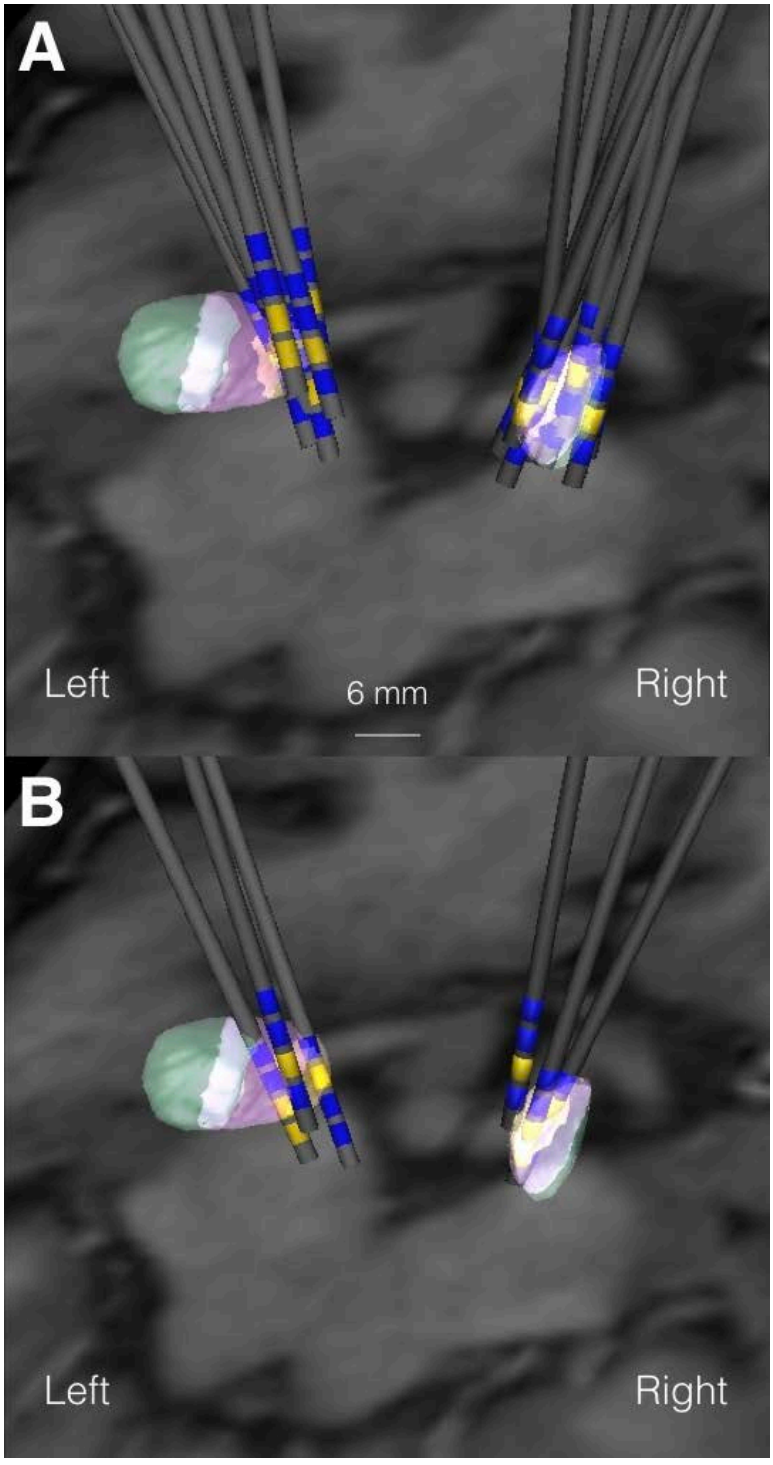
Supplementary Figure 2. Changes in OCD severity in 14 patients during the open-label follow-up period of STN-DBS.

Panel A shows the mean (±SD) scores on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Data are shown at the time of inclusion in the study (I), at months 10, 16, 22, 34 and 46 of the follow-up. Panel B shows the individual Y-BOCS scores during the follow-up period. [a] $p<.05$ compared to month 46,[b] $p=0.027$ Time effect during the 16 to 46 Month period (linear trend).



Supplementary Figure 3. Relationship between effects of subthalamic stimulation on OCD severity and age at onset.

Relationship between the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at month 46 with subthalamic stimulation and age at onset of OCD.



Supplementary Figure 4. Location of stimulating electrodes in responder and non-responder OCD patients to STN-DBS.

Panel A shows the positions of the electrodes and stimulating contacts (yellow cylinders) within the atlas space in the 11 responder patients. Panel B shows the positions for the 3 non-responder patients (P12, P05, P14). Note that in the 3 non-responder patients the stimulating contacts were bilaterally localized as in the 11 responder patients, within the anterior (associative-limbic) part of the STN.

Supplementary Table 1. Changes in OCD severity, global health functioning, anxiety, depression, quality of life, neuropsychological status and facial emotion recognition in OCD patients after long-term STN-DBS

Scale	Inclusion		Month 16		Month 46		Change between Inclusion and Month 46		*p* Value for treatment effect[a]	Change between Month 16 and Month 46		*p* Value for treatment effect[a]
Y-BOCS												
Overall score	33	[31 – 36]	18	[13 – 26]	15	[9 – 22]	-15	[-22 – -9]	<.001	-3	[-4 – 0]	0.055
Compulsion subscale	17	[15 –18]	9	[6 – 12]	8	[5 – 12]	-6	[-10 – -6]	.001	0	[-3 – 1]	.84
Obsession subscale	17	[15 – 19]	9	[7 – 14]	7	[4 – 11]	-8	[-12 – -4]	<.001	-2	[-3 – -1]	.001
GAF	35	[30 – 35]	55	[53 – 59]	65	[55 – 70]	30	[20 – -35]	<.001	12	[2 – 15]	.004
CGI	6	[6 –7]	4	[4 – 5]	4	[3 – 5]	-2	[-3 – -2]	<.001	-1	[-1 – 0]	.18
MADRS	13	[6 – 16]	7	[3 – 11]	5	[1 – 10]	-7	[-12 – -2]	.066	-1	[-5 – -1]	.027
BAS	13	[9 – 17]	8	[4 – 11]	4	[2 – 12]	-8	[-10 – -1]	.12	-2	[-5 – 1]	.18
HADS-anxiety	16	[13 – 18]	9	[7 – 12]	7	[4 – 12]	-7	[-9 – -6]	<.001	-2	[-3 – 0]	.18
HADS-depression	12	[9 – 13]	4	[1 – 8]	3	[1 – 11]	-5	[-8 – -2]	.002	-1	[-3 – 0]	.53
SAS-SR	3	[2 – 3]	2	[2 – 2]	2	[2 – 2]	0	[-1 – 0]	.041	0	[0 – 0]	.29
SF-36												
Physical health	NA[b]		54	[40 – 56]	51	[44 – 56]	-		-	-1	[-6 – 4]	.85
Mental health	NA		32	[26 – 42]	43	[32 – 49]	-		-	-3	[-17 – 2]	.34
SDS												
Work	10	[10 – 10]	6	[4 – 7]	5	[4 – 8]	-3	[-5 – -1]	.004	0	[-2 – 2]	.912
Social life	9	[8 – 10]	5	[3 – 6]	5	[2 – 8]	-4	[-7– -1]	.002	-1	[-2– 2]	.89
Family life	9	[8 – 9]	5	[2 – 7]	6	[2 – 9]	-2	[-6 – -1]	.001	0	[-2 – 3]	.75
STROOP Interference	-4	[-5 – 3]	0	[-11 – 6]	-4	[-6 – 2]	-2	[-7 – 8]	.61	-4	[-8 – 1]	.28
Verbal fluency (2 min)	52	[42 – 70]	50	[46–62]	58	[48 – 83]	5	[-2 – 9]	.34	5	[0 – 7]	.11
TMT-A	42	[34 – 55]	35	[26 – 36]	27	[20 – 41]	-13	[-18 – -6]	.016	-3	[-8 – 4]	.33
TMT-B	114	[76 – 141]	73	[57 – 104]	79	[56 – 108]	-19	[-36 – -6]	.068	-2	[-17 – 24]	.97
TMT A-B	62	[45 – 72]	39	[24 – 69]	52	[37 – 67]	-8	[-23 – 5]	.16	8	[-9 – 20]	.55
Apathy												

Starkstein scale	NA		7	[6 – 12]	8	[4 – 13]	-		-	1	[-5 – 4]	.88
Robert scale	NA		0	[0 – 15]	0	[0 – 11]	-		-	0	[-7 – 2]	.44
Facial emotion recognition												
Happy	100	[100 - 100]	100	[19 – 100]	100	[85 – 100]	0	[0 – 0]	1.00	0	[0 – 7]	.28
Sad	64	[43 – 71]	57	[8 – 86]	71	[57 – 86]	14	[0 – 15]	.22	14	[-14 – 29]	.095
Fear	57	[43 – 78]	71	[5 – 86]	57	[29 – 89]	0	[-29 – 42]	.97	14	[0 – 29]	.027
Anger	78	[57 – 86]	71	[15 – 100]	71	[42 – 100]	-1	[-28 – 14]	.58	0	[0 – 14]	.37
Surprise	93	[71 – 100]	71	[14 – 100]	85	[71 – 100]	0	[-14 – 0]	.71	4	[0 – 29]	.078
Disgust	86	[86 – 100]	86	[14 – 100]	100	[85 – 100]	7	[-1 – 15]	.45	1	[0 – 15]	.34
Neutral	86	[85 – 100]	100	[19 – 100]	89	[85 – 100]	0	[0 – 14]	.43	0	[0 – 14]	.55

Values are median [IQR 25%−75%]. Y-BOCS= Yale and Brown Obsessive Compulsive Scale, range is 0 to 40, with higher scores indicating worse function. This scale comprises obsession, compulsion and overall severity subscales; GAF= Global Assessment Functioning, range is 1 to 90, with higher scores indicating better global functional status; CGI = Clinical Global Impression, range from 1 to 7, with higher scores indicating greater severity of the disease; MADRS = Montgomery and Asberg Rating Scale, range from 0 to 60, with higher scores indicating greater severity of depressive symptoms; BAS = Brief Anxiety Scale, range from 0 to 60, with higher scores indicating greater severity of symptoms of anxiety; HADS = Hospital Anxiety Depression Scale, with anxiety and depression subscales, range from 0 to 21, with higher scores indicating greater severity of symptoms of anxiety and depression; SAS-SR= Social Adjustment Scale Self-Report with five sections: work, social life and leisure, conjugal life, interaction with children. Each item is rated from 1 to 5 (excellent to poor); SF-36 = Short Form Health Survey (35), with physical and mental health scores, range from 0 to 100, with higher scores indicating lower disability; SDS= Sheehan Disability Scale; TMT= Trail Making Test; The STROOP interference test, no range, higher scores indicate higher impulsivity. P values correspond to the statistical significance for changes between inclusion and Month 16; and between Month 16 and Month 46. [a]The change in the Y-BOCS was the primary outcome criterion. All other analyses were prespecified secondary outcomes. [b]NA: not available.

Supplementary Table 2. Parameter settings chosen during the open-label period (M16-M46).

Patient	M16				M22				M34				M46			
	Right		Left		Right		Left		Right		Left		Right		Left	
	C	V	C	V	C	V	C	V	C	V	C	V	C	V	C	V
01	2	2	1	2	2	2	1	2	2	2.05	1	2.05	2	2.05	1	2.05
02	0	2	1	2	0	2.2	1	2.2	0	2.2	1	2.2	0	2.3	1	2.3
03	1	1.3	1	1.7	1	1.35	1	1.75	1	1.35	1	1.75	1	1.3	1	1.7
07	1	3.3	2	3.3	1	3.3	2	3.3	1	3.3	2	3.3	_	_	_	_
08	3	3	NS	NS	3	3	NS	NS	1	2.3	NS	NS	1	2.3	NS	NS
09	0	1.8	0	2	1	2.2	1	2.4	1	2	0	2	0	2.3	1	2.4
10	1	2.4	0-1	2.6	1	2.3	0-1	2.6	1	2.3	0-1	2.6	1	2.3	0-1	2.6
11	0-1	1.55	1	1.8	0-1	1.6	1	1.85	0-1	1.7	1	1.95	0-1	1.7	1	1.95
12	2	2.35	2-3	2.4	0	2.7	0	2.7	0-1	2.35	0-1	2.35	0-1	2.35	0-1	2.35
13	1	1	1	1	1	1.3	1	1.3	1	1.2	1	1.2	1	1.2	1	1.2
15	2	4	2	4	2	4	2	4	2	4	2	4	2	4	2	4
16	1	1	1	1.3	1	1	1	1.3	1	1.2	1	1.5	1	1.3	1	1.5
Median (V)	**1.9**		**2.2**		**2.2**		**2.2**		**2.1**		**2.1**		**2.2**[a]		**2.3**[a]	
IQR	**1.7 to 2.5**		**1.5 to 3.0**		**1.6 to 2.8**		**1.8 to 2.7**		**1.7 to 2.3**		**1.9 to 2.5**		**1.8 to 2.4**		**1.5 to 2.3**	

C: negative contact; V: voltage (Volts). In all cases, the case was positive, the frequency of stimulation 130 Hz, and the pulse width 60 µs.

[a] the values for patient 7 obtained at month 34 were included in the statistical analysis.

Supplementary Table 3. Adverse events

Adverse events	**Serious (n=23)[a]**	**Non-Serious (n=32)**
	No. of events	
Stimulation-related		
Fall with shoulder luxation	1 (P03)	0
Hypomania	3 (P9 and P11)	0
Impulsivity	1 (P11)	4 (P11, 12 and P13)
Dysarthria	0	2 (P12)
Dyskinesia	0	2 (P12)
Disease-related		
Depression	6 (P03, P05, P08, P10 and P11)	0
Increased anxiety	2 (P08 and P11)	3 (P16)
Increased OCD	5 (P10, P12 and P13)	5 (P12 and P16)
Suicide attempt	3 (P10, P13 and P16)	0
Insomnia	0	1 (P09)
Others		
Parkinsonian syndrome	1 (P12)	0
Lumbar-sciatica with motor deficit	1 (P16)	0
Fall while cycling	0	1 (P02)
Urinary incontinence	0	1 (P12)
Finger mycosis	0	1 (P09)
Thoracic pain from unknown cause	0	1 (P10)
Gynecological hemorrhage with uterine polyp resection	0	1 (P10)
Biceps tendinitis	0	1 (P10)
Knee surgery for arthritis	0	1 (P11)
Dyspnea	0	1 (P11)
Asthma	0	2 (P13)
Cephalalgia	0	1 (P13)
Acute alcohol intoxication	0	1 (P13)
Lumbar-sciatica	0	1 (P16)
Colonic polyp resection	0	1 (P10)
Scalp paresthesia	0	1 (P13)

[a] An adverse event was considered as serious if the patient required hospitalization, if sequelae were present, if the event induced vital distress, or if the clinician considered the event to be serious.

Supplementary References

[1] Mallet L, Polosan M, Jaafari N, Baup N, Welter M-LM-LL, Fontaine D, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 2008;359:2121–34. doi:10.1056/NEJMoa0708514.

[2] DSM-IV-TR APA. Diagnostic and statistical manual of mental disorders, text revision. Washington, DC Am Psychiatr Assoc 2000.

[3] Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–11.

[4] Endicott J, RL S, JL F, Cohen J. The global assessment scale: A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–71.

[5] Guy W. Clinical Global Impression BT - ECDEU Assessment Manual for Psychopharmacology. ECDEU Assess. Man. Psychopharmacol., Rockville: revised National Institute of Mental Health; 1976.

[6] Mattis S. Dementia Rating Scale H Geriatric psychiatry. A handbook for psychiatrist and primary care physicians 1976.

[7] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–9.

[8] Kohl S, Schönherr DM, Luigjes J, Denys D, Mueller UJ, Lenartz D, et al. Deep brain stimulation for treatment-refractory obsessive compulsive disorder: a systematic review. BMC Psychiatry 2014;14:214.

[9] Tyrer P, Owen RT, Cicchetti D V. The brief scale for anxiety: a subdivision of the comprehensive psychopathological rating scale. J Neurol Neurosurg Psychiatry 1984;47:970–5.

[10] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

[11] Hodgson RJ, Rachman S. Obsessional-compulsive complaints. Behav Res Ther 1977;15:389–95.

[12] Mundt JC, Marks IM, Shear MK, Greist JM. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002;180:461–4.

[13] Ware JE, Kosinski M, Dewey JE, Gandek B. SF-36 health survey: manual and interpretation guide.

Quality Metric Inc.; 2000.

[14] Sheehan D V, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11 Suppl 3:89–95.

[15] Reitan RM. Validity of the trail making test as an indication of organic brain damage. Percept Mot Ski 1958;8:271–6.

[16] Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992;4:134–9.

[17] Robert P, Onyike CU, Leentjens AFG, Dujardin K, Aalten P, Starkstein S, et al. Proposed diagnostic criteria for apathy in Alzheimer•s disease and other neuropsychiatric disorders. Eur Psychiatry 2009;24:98–104.

[18] Ekman P, Friesen W V. Measuring facial movement. Environ Psychol Nonverbal Behav 1976;1:56–75.

[19] Perris C, Sedvall G, Schalling D, Åsberg M. Comprehensive psychopathological rating scale-CPRS. Scand Soc Psychopharmacol Copenhagen, March 1976.

[20] Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 1976;33:1111–5.

[21] McHorney CA, Ware Jr JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993:247–63.

[22] Yelnik J, Bardinet E, Dormont D, Malandain G, Ourselin S, Tandé D, et al. A three-dimensional, histological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data. Neuroimage 2007;34:618–38.

[23] Yelnik J, Damier P, Demeret S, Gervais D, Bardinet E, Bejjani BP, et al. Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. J Neurosurg 2003;99:89–99.

[24] Miguel EC, Lopes AC, McLaughlin NCR, Norén G, Gentil AF, Hamani C, et al. Evolution of gamma knife capsulotomy for intractable obsessive-compulsive disorder. Mol Psychiatry 2018:1–23. doi:10.1038/s41380-018-0054-0.

[25] Sheth SA. Commentary Stereotactic Radiosurgical Capsulotomy for the Treatment of Refractory Obsessive-Compulsive Disorder. Biol Psychiatry 2018;84:320–1. doi:10.1016/j.biopsych.2018.06.013.

[26] Rasmussen SA, Noren G, Greenberg BD, Marsland R, McLaughlin NC, Malloy PJ, et al. Gamma Ventral Capsulotomy in Intractable Obsessive-Compulsive Disorder. Biol Psychiatry 2018;84:355–64. doi:10.1016/j.biopsych.2017.11.034.

[27] Pugh J, Tan J, Aziz T, Park RJ. The Moral Obligation to Prioritize Research Into Deep Brain Stimulation Over Brain Lesioning Procedures for Severe Enduring Anorexia Nervosa. Front Psychiatry 2018;9:1–4. doi:10.3389/fpsyt.2018.00523.

[28] Deng Z, Pan Y, Zhang C, Zhang J, Qiu X, Zhan S, et al. Subthalamic deep brain stimulation in patients with primary dystonia: A follow-up of more than ten years. Parkinsonism Relat Disord 2018;55:103–10.

[29] Nuttin B, Wu H, Mayberg H, Hariz M, Gabriels L, Galert T, et al. Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. J Neurol Neurosurg Psychiatry 2014:1–7.

[30] Goodman WK, Insel TR. Deep Brain Stimulation in Psychiatry: Concentrating on the Road Ahead. Biol Psychiatry 2009;65:263–6.

[31] Müller S, Riedmüller R, van Oosterhout A. Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness. Front Integr Neurosci 2015;9:27. doi:10.3389/fnint.2015.00027.

[32] Moon W, Kim SN, Park S, Paek SH, Kwon JS. The cost-effectiveness of deep brain stimulation for patients with treatment-resistant obsessive-compulsive disorder. Med (United States) 2017;96:1–8. doi:10.1097/MD.0000000000007397.

[33] Steigerwald F, Müller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device. Mov Disord 2016;31:1240–3. doi:10.1002/mds.26669.

[34] Ghasemi P, Sahraee T, Mohammadi A. Closed- and Open-loop Deep Brain Stimulation: Methods, Challenges, Current and Future Aspects. J Biomed Phys Eng 2018;8:209–16. doi:10.22086/jbpe.v0i0.898.

[35] Fins JJ, Kubu CS, Mayberg HS, Merkel R, Nuttin B, Schlaepfer TE. Being open minded about neuromodulation trials: Finding success in our “failures.” Brain Stimul 2017;10:181–6. doi:10.1016/j.brs.2016.12.012.

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