

## ORIGINAL ARTICLE

# Subthalamic Nucleus Stimulation in Severe Obsessive–Compulsive Disorder

Luc Mallet, M.D., Ph.D., Mircea Polosan, M.D., Nematollah Jaafari, M.D.,  
 Nicolas Baup, M.D., Marie-Laure Welter, M.D., Ph.D.,  
 Denys Fontaine, M.D., Ph.D., Sophie Tezenas du Montcel, M.D., Ph.D.,  
 Jérôme Yelnik, M.D., Isabelle Chéreau, M.D., Christophe Arbus, M.D.,  
 Sylvie Raoul, M.D., Ph.D., Bruno Auouizerate, M.D., Ph.D.,  
 Philippe Damier, M.D., Ph.D., Stephan Chabardès, M.D., Ph.D.,  
 Virginie Czernecki, Ph.D., Claire Ardouin, Ph.D., Marie-Odile Krebs, M.D., Ph.D.,  
 Eric Bardin, Ph.D., Patrick Chaynes, M.D., Ph.D., Pierre Burbaud, M.D., Ph.D.,  
 Philippe Cornu, M.D., Philippe Derost, M.D., Thierry Bougerol, M.D., Ph.D.,  
 Benoit Bataille, M.D., Vianney Mattei, M.D., Didier Dormont, M.D., Ph.D.,  
 Bertrand Devaux, M.D., Marc Vérin, M.D., Ph.D., Jean-Luc Houeto, M.D., Ph.D.,  
 Pierre Pollak, M.D., Ph.D., Alim-Louis Benabid, M.D., Ph.D.,  
 Yves Agid, M.D., Ph.D., Paul Krack, M.D., Ph.D., Bruno Millet, M.D., Ph.D.,  
 and Antoine Pelissolo, M.D., Ph.D., for the STOC Study Group\*

## ABSTRACT

**BACKGROUND**

Severe, refractory obsessive–compulsive disorder (OCD) is a disabling condition. Stimulation of the subthalamic nucleus, a procedure that is already validated for the treatment of movement disorders, has been proposed as a therapeutic option.

**METHODS**

In this 10-month, crossover, double-blind, multicenter study assessing the efficacy and safety of stimulation of the subthalamic nucleus, we randomly assigned eight patients with highly refractory OCD to undergo active stimulation of the subthalamic nucleus followed by sham stimulation and eight to undergo sham stimulation followed by active stimulation. The primary outcome measure was the severity of OCD, as assessed by the Yale–Brown Obsessive Compulsive Scale (Y-BOCS), at the end of two 3-month periods. General psychopathologic findings, functioning, and tolerance were assessed with the use of standardized psychiatric scales, the Global Assessment of Functioning (GAF) scale, and neuropsychological tests.

**RESULTS**

After active stimulation of the subthalamic nucleus, the Y-BOCS score (on a scale from 0 to 40, with lower scores indicating less severe symptoms) was significantly lower than the score after sham stimulation (mean [±SD], 19±8 vs. 28±7;  $P=0.01$ ), and the GAF score (on a scale from 1 to 90, with higher scores indicating higher levels of functioning) was significantly higher (56±14 vs. 43±8,  $P=0.005$ ). The ratings of neuropsychological measures, depression, and anxiety were not modified by stimulation. There were 15 serious adverse events overall, including 1 intracerebral hemorrhage and 2 infections; there were also 23 nonserious adverse events.

**CONCLUSIONS**

These preliminary findings suggest that stimulation of the subthalamic nucleus may reduce the symptoms of severe forms of OCD but is associated with a substantial risk of serious adverse events. (ClinicalTrials.gov number, NCT00169377.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Mallet at the INSERM Avenir Team IFR 70 — Behavior, Emotion, and Basal Ganglia, Centre d'Investigation Clinique, CHU Pitié–Salpêtrière, 47 Blvd. de l'Hôpital, 75013 Paris, France, or at luc.mallet@psl.aphp.fr.

\*Members of the French Stimulation dans le Trouble Obsessionnel Compulsif (STOC) Study Group are listed in the Appendix.

This article (10.1056/NEJMoa0708514) was last updated on September 2, 2009, at NEJM.org.

N Engl J Med 2008;359:2121–34.  
 Copyright © 2008 Massachusetts Medical Society.

**S**EVERE OBSESSIVE–COMPULSIVE DISORDER (OCD) is characterized by intrusive, anxious thoughts and repetitive, ritualized behaviors. It is one of the most disabling of the chronic psychiatric disorders and has considerable repercussions on family relationships, social life, and the ability to function at work.<sup>1</sup> The current treatment of OCD consists of a combination of serotonin-reuptake inhibitors and cognitive–behavioral therapy; with this treatment, however, 25 to 40% of patients have persistent symptoms and lasting functional repercussions.<sup>2</sup> In the hope of reducing the disability and debilitation of patients whose OCD is highly refractory, ablative neurosurgical stereotactic treatments have been attempted, but the efficacy of these treatments has been variable.<sup>3</sup> In contrast, deep-brain stimulation, which has been proved effective in the treatment of movement disorders, is a therapeutic alternative that is adaptable and reversible, permitting the modulation of the dysfunctional neural networks<sup>4</sup> that are involved in the pathophysiology of OCD.<sup>3,5</sup> Different parts of the orbito–fronto–striato–thalamo–cortical circuit, including the ventral striatum, internal capsule, and nucleus accumbens, have been targeted for stimulation, as described in several case reports<sup>6–11</sup> and in a report on a prospective open-label study<sup>12</sup>; the long-term results have been variable but promising. Furthermore, studies of stimulation in patients with Parkinson’s disease have highlighted the putative role of the subthalamic nucleus in behavioral integration<sup>13</sup> and the efficacy of subthalamic nucleus stimulation in reducing repetitive behaviors,<sup>14</sup> anxiety,<sup>15</sup> obsessive–compulsive symptoms,<sup>16</sup> and OCD.<sup>17,18</sup> These results, combined with the long-term effects of stimulation of the subthalamic nucleus<sup>19</sup> and the ability to target small, well-defined structures<sup>20</sup> with the use of validated procedures,<sup>21,22</sup> led us to propose the subthalamic nucleus as a target for the treatment of highly resistant OCD. Here we report on a randomized, double-blind, crossover study comparing stimulation of the subthalamic nucleus with sham stimulation. The change in symptoms of OCD was the primary outcome measure.

## METHODS

### PATIENTS

We enrolled patients with refractory OCD in the study. Patients were eligible for inclusion if they

were between 18 and 60 years of age and had received a primary diagnosis of OCD, defined according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), and established with the use of the Diagnostic Interview for Genetic Studies,<sup>23</sup> with a disease duration of more than 5 years, a score on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS)<sup>24</sup> of more than 25 (on a scale from 0 to 40, with lower scores indicating less severe symptoms) or one subscale score of more than 15 (on a scale of 0 to 20); a score on the Global Assessment Functioning (GAF)<sup>25</sup> scale of less than 40 (on a scale from 1 to 90, with higher scores indicating higher levels of functioning); and a score for severity of illness on the Clinical Global Impression (CGI) scale of more than 4 (on a scale of 1 to 7, with higher scores indicating greater severity of the disease).<sup>26</sup>

Additional inclusion criteria were a lack of response to drug therapy after adequate administration (defined as more than 12 weeks at the maximum tolerated dose) of at least three serotonin-reuptake inhibitors, one of which had to be clomipramine, with augmentation over a period of at least 1 month with risperidone or pimozide and one of the following: lithium, clonazepam, buspirone, or pindolol<sup>2</sup>; lack of response to cognitive–behavioral therapy (exposure and response-prevention technique) over the course of 1 year of therapy or after 20 sessions with at least two therapists; normal cognitive status (a score of >130 on the Mattis Dementia Rating Scale, which ranges from 0 to 144, with lower scores indicating more severe dementia)<sup>27</sup>; normal findings on magnetic resonance imaging (MRI) of the brain; and no contraindications to surgery or anesthesia.

Exclusion criteria were schizophrenic disorder; bipolar disorder; substance abuse or dependence (except for dependence on nicotine), as assessed with the use of the Mini-International Neuropsychiatric Interview (MINI 5.0.0)<sup>28</sup>; cluster A or B personality disorder according to DSM-IV criteria, as assessed with the use of the Structured Clinical Interview II<sup>29</sup>; a current severe major depressive episode, determined according to DSM-IV criteria (as assessed with the use of the MINI 5.0.0) and defined by a Montgomery and Åsberg Depression Scale (MADRS)<sup>30</sup> score of more than 20 (on a scale from 0 to 60, with higher scores indicating greater severity of depressive symptoms) (a depressive episode with a MADRS score of <20 or a MADRS score of ≥20 without depressive-episode criteria

was not a criterion for exclusion); and a risk of suicide (a score of  $>2$  on MADRS item 10).

For each patient, unstructured interviews were conducted by three psychiatrists to establish the appropriateness of neurosurgery. The reports on these evaluations and interviews were reviewed by an independent selection committee of three expert psychiatrists, who made the final decisions with respect to eligibility.

#### STUDY DESIGN

The study had a randomized, double-blind, cross-over design with two 3-month phases separated by a 1-month washout period (Fig. 1). The trial was conducted at 10 academic centers in France in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Pitié-Salpêtrière University Hospital. All patients provided written informed consent. Eligible patients were randomly assigned in a 1:1 ratio to one of two groups: one group underwent active stimulation followed by a sham-stimulation period (the on-off group) and the other underwent sham stimulation followed by an active-stimulation period (the off-on group). We used a blocking-scheme and a centralized procedure for randomization, without stratification. A clinical examination was performed at each visit by a psychiatrist and a neurologist who were unaware of the stimulation status. Any new symptom or worsening of a preexisting symptom was classified as an adverse event. An adverse event was classified as serious if the patient required hospitalization, if sequelae were present, or if the clinician considered the event to be serious.

#### SURGERY AND STIMULATION

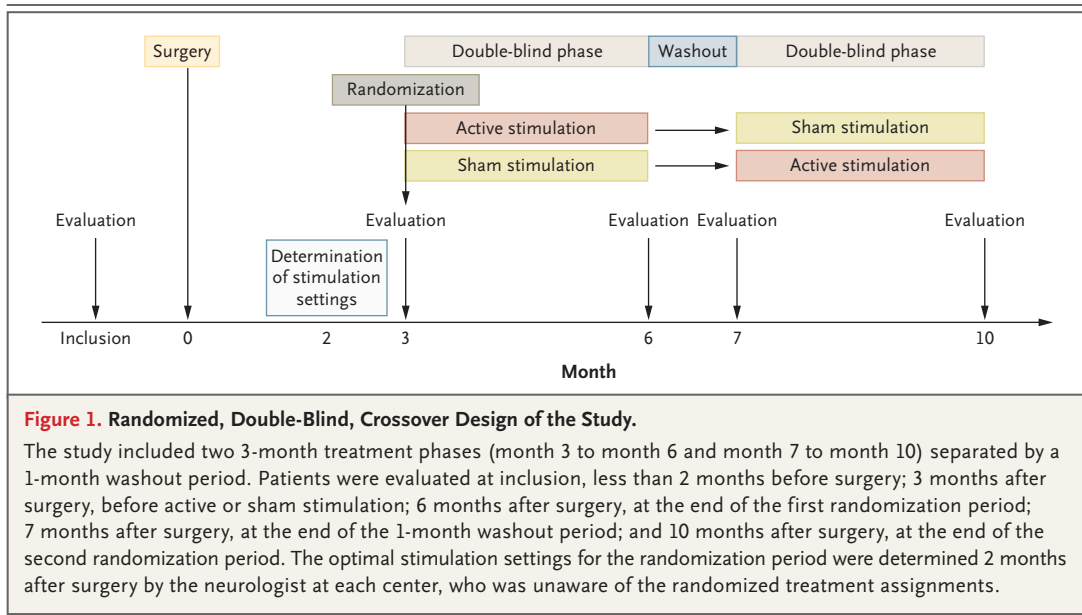
The subthalamic nucleus was preoperatively targeted by means of stereotactic MRI<sup>21</sup> and, depending on the local surgical protocol, by means of ventriculography, with additional targeting performed by the coordinating center<sup>20,31</sup> (Fig. 2). The target in our patients with OCD was 2 mm anterior to and 1 mm medial to the target that is used in patients with Parkinson's disease,<sup>32</sup> at the boundary of the associative and limbic territories of the subthalamic nucleus (Fig. 2).<sup>20,33</sup> Intraoperative microrecordings were performed along three to five trajectories (central, anterior, posterior, medial, and lateral) with the use of standardized procedures<sup>34</sup> by the electrophysiology teams from both the local and the coordinating centers. Intraoperative

macrostimulation was performed along the same trajectories to evaluate the immediate effects.<sup>35</sup> The four-contact definitive electrode (model 3389 DBS, Medtronic) was implanted along the trajectory with the best ratio of beneficial to adverse effects.<sup>35</sup> The position of the electrode was confirmed by atlas-based neuroimaging<sup>13,20,22</sup> before the implantation of the pulse generator (Solettra or Kinetra, Medtronic).

Each contact was tested separately 2 months after surgery (Fig. 1). Stimulation frequency and pulse duration were 130 Hz and 60  $\mu$ sec, respectively, with the voltage adjusted to the individual patient. Side effects were investigated by testing each contact with a progressive voltage increase up to 4 V. The therapeutic contact was selected according to the best immediate clinical effect or, if there was no immediate improvement, according to the intraoperative data and the anatomical localization of each contact as determined postoperatively with the digital atlas.<sup>20</sup> In the absence of side effects, the most ventral contact within the subthalamic nucleus was selected. The voltage for the randomization period was set below the side-effect threshold, and as close as possible to the usual stimulation settings that are used in patients with Parkinson's disease.<sup>19</sup> It was recommended that the patient's medical treatment remain stable. Treatment adjustments necessitated by the patient's psychiatric condition were carefully recorded.

#### STATISTICAL ANALYSIS

The power calculation was based on our estimate that at baseline, the patients' mean Y-BOCS score would be 26, with a standard deviation of 4.65 for the difference between the on-stimulation and off-stimulation periods. The study was designed to have an overall power of 80% to detect a 50% reduction in the primary end point (the Y-BOCS score) during the on-stimulation period (a benefit amounting to a 13-point reduction in the score) and a 10% reduction during the off-stimulation period (a placebo effect amounting to a 2.6-point reduction) as calculated with the use of the Wilcoxon rank-sum test, with six patients per group (two-tailed, type I error rate of 5%). Because of an unexpected increase in the number of eligible patients in most centers and in order to increase the power for secondary end points, the total number of enrolled patients was increased to 18. All analyses included all randomly assigned patients.



The primary outcome was the change in the Y-BOCS score at the end of each period. Analyses of the primary and secondary efficacy outcomes were performed by testing three effects: carryover (some effects, physical or psychological, of the first treatment are still present when the patient enters the second treatment period), period (the effect of stimulation was different in the on-off group than in the off-on group), and treatment effects.<sup>36</sup> All reported P values are two-tailed. A type I error rate of 5% was used except for the analysis of the carryover effect, in which it was fixed at 10%.<sup>36</sup> No interim analysis was performed.

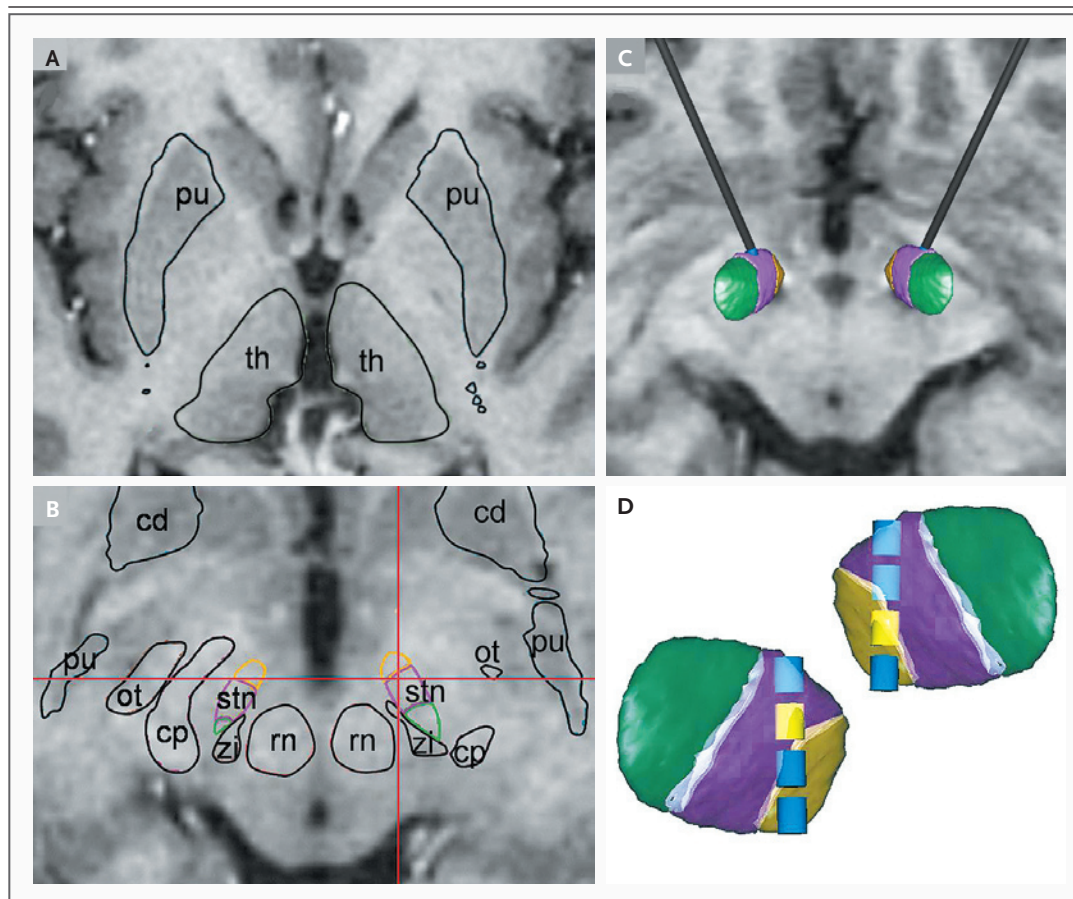
For the treatment effect on secondary outcomes, a Bonferroni correction was applied according to the disciplinary fields, which included two subscores of the Y-BOCS, two measures of global health and functioning (GAF<sup>25</sup> and CGI<sup>26</sup>), a self-reported measure of functional impairment (Sheehan Disability Scale),<sup>37</sup> two measures of major psychiatric symptoms (MADRS<sup>30</sup> and Brief Scale for Anxiety<sup>38</sup>), and seven neuropsychological measures assessing fronto-subcortical functions (attention, executive functions, verbal learning, and decision making).<sup>39-44</sup> The definitions of a response with respect to Y-BOCS and GAF scores — which were not prespecified in the protocol — were a 25% decrease and increase, respectively, at the end of the first phase (6 months after surgery [Fig. 1]).<sup>2</sup> An additional response criterion was defined by a GAF score that was higher than 51, which corresponds to “moderate symptoms

or moderate difficulty in social or occupational functioning.”

## RESULTS

### STUDY POPULATION

A total of 18 patients were enrolled between January 2005 and April 2006. One patient withdrew from the study before the procedure, and stimulators were implanted in the remaining 17 patients. The stimulator and the two electrodes were removed from 1 patient (Patient 9) before randomization because of an infection; thus, 16 patients completed the randomization period (Table 1). At the time of the patients' inclusion in the study, the mean duration of disease was 18 years (range, 6 to 47); two patients fulfilled the criteria for current major depressive disorder but had a MADRS score that was lower than 20 (Table 1). One patient who abused alcohol, which represented a minor deviation from the protocol, was included because the abuse was revealed between the time of inclusion and surgery and was moderate and limited in time. There was no significant difference in baseline (month 3) clinical characteristics between the patients in the two groups (Table 2). Table 1 lists the medications the patients were taking at the time of inclusion. Two patients (Patients 5 and 7) were taking no medication at baseline at their request. Medication was held constant during the 10 months of the protocol except for a transient increase in benzodiazepine therapy in three patients



**Figure 2.** Atlas-Based Targeting on Preoperative MRI and Localization of the Electrodes and Contacts on Postoperative MRI in Patient 1.

Panel A shows the preoperative atlas-based MRI alignment, performed with the use of a three-dimensional histologic atlas of the basal ganglia, adapted to fit the patient's brain geometry. The tracings of the putamen (pu) and thalamus (th) are well aligned with the corresponding structures in the axial plane. Panel B shows localization of the target in the anteromedial subthalamic nucleus (stn) near the boundary between the associative (violet) and limbic (yellow) territories. The exact target is at the intersection of the two red lines. The sensorimotor territory is green. The other atlas structures include the caudate nucleus (cd), cerebral peduncle (cp), optic tract (ot), red nucleus (rn), putamen (pu), and zona incerta (zi). Panel C shows a three-dimensional, superior view of the subthalamic nucleus after fusion with the three-dimensional MRI acquisition, an axial plane of which is shown. The two electrodes enter the associative territory of the nucleus (violet). The sensorimotor territory is green. The limbic territory (yellow), which occupies a small portion of the most anterior part of the nucleus, is small in this superior view. Panel D shows oblique views of each subthalamic nucleus, presented along the long axis of each electrode with transparent rendering of the three territories (associative, violet; sensorimotor, green; and limbic, yellow). The active contacts (yellow) are in the anteromedial (probable associative–limbic) part of the subthalamic nucleus. The nonactive contacts are in blue.

(two during the on-stimulation period and one during the off-stimulation period) and augmentation of neuroleptic treatment in one patient (off-stimulation period) owing to exacerbated anxiety. All 16 patients completed both periods of the study.

#### EFFICACY OF THE STIMULATION

The Y-BOCS score was significantly lower at the end of the active stimulation (on-stimulation period) than at the end of the sham stimulation (off-

stimulation period) (mean score,  $19 \pm 8$  vs.  $28 \pm 7$ ;  $P=0.01$ ), independently of the group and the period. We did not detect any significant carryover effect in Y-BOCS scores ( $P=0.71$ ), indicating that the effects of the first treatment period did not persist after the washout period. Patients who were assigned to have active stimulation first and sham stimulation second (the on–off group) tended to have a larger treatment effect as measured by the Y-BOCS score than those who had sham stimula-

**Table 1.** Clinical Characteristics of the 17 Patients with OCD at Inclusion.\*

Patient No.	Center No.	Group	Sex	Age	Age at Onset	Score on Y-BOCS Obsession Subscale	Score on Y-BOCS Compulsion Subscale	Major Depressive Disorder†	Score on GAF	Score on CGI	Score on MADRS	Score on BAS	Current Medications‡
1	1	On-Off	M	36	7	31	18	Previous	35	7	14	14	SNRI, neuroleptic, benzodiazepine
2	1	Off-On	F	37	8	34	18	Previous	35	7	14	12	Clomipramine, lithium, thyroid hormone
3	1	On-Off	M	56	10	31	16	Previous	35	6	25	16	SNRI, tetracyclic, atypical neuroleptic, neuroleptic, lithium
4	2	On-Off	F	39	12	34	16		31	7	19	19	SNRI, clomipramine, beta-blocker, benzodiazepine
5	2	Off-On	F	49	20	29	14		31	6	6	16	
6	5	On-Off	M	50	27	27	13		30	5	12	9	Clomipramine, beta-blocker, valproate, neuroleptic, benzodiazepine
7	6	Off-On	M	34	8	35	18	Previous, current	25	7	8	18	
8	7	Off-On	M	29	10	27	14		37	6	11	3	SRI, atypical neuroleptic, valproate, clonazepam
9	7		M	32	15	36	17		30	7	16	8	SRI, clomipramine, lithium
10	8	On-Off	M	53	11	35	18		21	6	6	12	SRI, atypical neuroleptic, benzodiazepine
11	9	Off-On	F	45	6	30	12		30	6	4	12	SRI, buspirone, atypical neuroleptic, benzodiazepine
12	9	On-Off	M	50	14	35	20		35	7	7	2	SRI, buspirone, atypical neuroleptic, benzodiazepine
13	9	Off-On	F	47	17	31	13		30	6	5	6	SRI, clomipramine, buspirone, benzodiazepine
14	10	Off-On	M	39	21	37	18		26	6	13	13	SRI, alpha-blocker (clonidine), neuroleptic
15	10	Off-On	M	51	16	35	18	Current	36	6	16	19	SRI, benzodiazepine
16	10	On-Off	F	43	11	32	14		32	6	18	21	SRI, atypical neuroleptic, benzodiazepine
17	10	On-Off	F	42	17	30	15	Previous	36	5	15	26	SRI, SNRI, valproate, neuroleptic, benzodiazepine

\* Scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)<sup>24</sup> range from 0 to 40, with higher scores indicating worse function. The two Y-BOCS subscale scores range from 0 to 20. The presence of a major depressive disorder was assessed with the Mini-International Neuropsychiatric Interview (MINI 5.0.0).<sup>28</sup> Scores on the Global Assessment of Functioning (GAF)<sup>25</sup> range from 1 to 90, with higher scores indicating better global functional status. Scores on the Clinical Global Impression (CGI)<sup>26</sup> range from 1 to 7, with higher scores indicating greater severity of the disease. Scores on the Montgomery and Asberg Depression Scale (MADRS)<sup>30</sup> range from 0 to 60, with higher scores indicating greater severity of depressive symptoms. Scores on the Brief Anxiety Scale (BAS)<sup>38</sup> range from 0 to 60, with higher scores indicating greater severity of symptoms of anxiety. † “Previous” refers to one or more episodes during the patient’s lifetime, and “current” refers to an episode that was ongoing at the time of the patient’s inclusion in the study. A depressive episode was not an exclusion criterion, but a severe current major depressive episode was an exclusion criterion (MINI criteria and MADRS score of ≥20). ‡ Both specific drugs and classes of drugs are listed. SNRI denotes serotonin–norepinephrine reuptake inhibitor, and SRI serotonin-reuptake inhibitor.

tion first and active stimulation second (the off-on group) ( $P=0.06$  for the period effect). The GAF score (in which higher scores indicate higher levels of functioning) was significantly higher after active stimulation than after sham stimulation (mean score at the end of active stimulation,  $56\pm 14$  vs.  $43\pm 8$ ;  $P=0.005$ ). The CGI score (in which lower scores indicate lesser severity of disease) was significantly lower at the end of active stimulation than at the end of sham stimulation ( $P=0.008$ ), with more improvement during active stimulation observed in the on-off group than in the off-on group ( $P=0.03$  for the period effect). Scores on MADRS, the Brief Scale for Anxiety, neuropsychological ratings, and the Sheehan Disability Scale at the end of active stimulation did not differ significantly from the scores at the end of sham stimulation. At the end of the first phase (i.e., 3 months after randomization), six of eight patients (75%) had a response as measured by the Y-BOCS score and eight of eight (100%) had a response as measured by the GAF after active stimulation, as compared with three of eight (38%) as measured by both Y-BOCS and GAF after sham stimulation (Fig. 3B). In addition, five of eight patients (62%) had an increase in the GAF score to 51 after active stimulation as compared with one of eight (12%) after sham stimulation (Fig. 3B).

#### ELECTRODE LOCALIZATION AND STIMULATION SETTINGS

For 27 of 34 implanted electrodes (79%), the electrode trajectory that was chosen was the central one. The anterior trajectory was chosen for 4 electrodes, the posterior for 2, and the internal for 1. Of the 32 electrodes that were implanted in the 16 patients who completed the study, 4 electrodes, in 4 different patients, were not localized within the subthalamic nucleus — 3 were medial to the subthalamic nucleus in zona incerta and field  $H_2$  of Forel, and 1 was lateral to the subthalamic nucleus in the internal capsule. However, each patient had at least one contact within the subthalamic nucleus. Postrandomization anatomical analysis showed that among the 33 contacts selected as therapeutic, stimulation reached the anteromedial part of the subthalamic nucleus in 24 (Fig. 2), the zona incerta in 4, the internal capsule in 4, the substantia nigra in 3, and field  $H_2$  of Forel in 2 (contacts located at the boundary of two regions were counted twice). In two patients, stimulation was applied unilaterally; in one patient

(Patient 8), adverse effects were noted on all contacts from one electrode during the tests 2 months after surgery, and in the other patient (Patient 4), one Soletra stimulator was disconnected owing to infection. Current was delivered through one contact for 27 of 30 electrodes, and two contiguous contacts were used in 3 electrodes (bipolar stimulation). The mean ( $\pm$ SD) voltage was  $2.0\pm 0.8$  V.

#### ADVERSE EVENTS

Fifteen serious adverse events, of which four were related to surgery, were reported in 11 patients (Table 3). The most serious event was a parenchymal brain hemorrhage resulting in a permanent finger palsy in one patient. Seven transient motor and psychiatric symptoms induced by active stimulation occurred in the first month of stimulation and resolved spontaneously or rapidly after adjustment of the setting. Four serious adverse events that were unrelated to either surgery or stimulation were reported in one patient before surgery and in two patients during the washout and sham-stimulation phases. Twenty-three nonserious adverse events were reported in 10 patients (Table 3). During the active-stimulation period, seven behavioral adverse events were reported in five patients.

#### DISCUSSION

In this double-blind, crossover trial, stimulation of the subthalamic nucleus reduced symptoms in patients with severe, highly refractory, primary OCD, with no concomitant neuropsychological deleterious effects. Moreover, the reversibility of the stimulation was demonstrated by the fact that symptoms of OCD tended to return to baseline in patients who underwent stimulation in the first period. There was no significant effect of the stimulation on measures of depression or anxiety, neuropsychological measures, or self-assessment of disability. There were 15 serious adverse events, of which 4 were related to the surgical procedure, including 1 intracerebral hemorrhage and 2 infections requiring removal of the electrode, and 7 were related to the stimulation and were transient. Therefore, the benefits of this surgical treatment for symptoms of OCD should be carefully weighed against the potential occurrence of such serious adverse events.

The improvement in scores observed in the prerandomization postoperative period (months 0 to 3) and the trend toward an effect of the order

**Table 2. Changes in the Severity of OCD, Global Health and Functioning, Anxiety, and Depression.\***

Scale	Active Stimulation Followed by Sham Stimulation (On–Off Group)			
	Baseline (Month 3)	End of On Period (Month 6)	Start of Off Period (Month 7)	End of Off Period (Month 10)
	<i>median (range)</i>			
Y–BOCS				
Overall score	30 (18 to 37)	19 (0 to 28)	28 (24 to 32)	30 (18 to 36)
Obsession subscale	14 (9 to 19)	10 (0 to 13)	16 (12 to 17)	15 (9 to 18)
Compulsion subscale	15 (9 to 19)	8 (0 to 15)	14 (9 to 15)	16 (9 to 18)
GAF	39 (30 to 48)	52 (45 to 90)	40 (35 to 56)	41 (31 to 50)
CGI	6 (5 to 7)	4 (1 to 5)	6 (5 to 6)	6 (5 to 7)
SDS‡				
Work	9 (7 to 10)	4 (0 to 10)	8 (3 to 10)	9 (1 to 10)
Social life and home activities	9 (8 to 10)	4 (0 to 10)	8 (4 to 10)	8 (6 to 10)
Family life and home responsibilities	9 (8 to 10)	7 (1 to 8)	8 (4 to 10)	8 (6 to 10)
MADRS	8 (3 to 26)	8 (0 to 15)	13 (4 to 27)	16 (4 to 27)
BAS	11 (3 to 23)	9 (2 to 15)	12 (5 to 21)	12 (1 to 24)
Hopkins Verbal Learning Test — no. of words	24 (12 to 31)	23 (15 to 29)	24 (18 to 32)	26 (15 to 32)
Trail Making Test				
Test A — sec	48 (30 to 91)	40 (26 to 66)	44 (30 to 81)	32 (22 to 64)
Test B–A — sec§	52 (34 to 114)	81 (38 to 202)	42 (–1 to 93)	58 (27 to 174)
Stroop interference index¶	6 (–8 to 1)	4 (–2 to 16)	7 (–2 to 17)	6 (–10 to 19)
Digit ordering — no. of correct responses	84 (38 to 97)	82 (46 to 97)	82 (38 to 93)	85 (34 to 96)
Digit symbol coding — no. of correct responses	32 (11 to 53)	34 (20 to 57)	40 (17 to 48)	40 (18 to 60)
Lexical fluency — no. of words	50 (38 to 81)	52 (37 to 80)	47 (41 to 75)	50 (36 to 89)

\* Bonferroni correction was applied to the two Y–BOCS subscales, the two global health and functioning measures (GAF, CGI), the two psychiatric measures (MADRS, BAS), the three SDS scores, and the seven neuropsychological tests (Hopkins Verbal Learning Test,<sup>40</sup> Trail Making Test A,<sup>41</sup> Trail Making Test B–A, Interference Stroop score,<sup>42</sup> Digit Ordering,<sup>43</sup> Digit Symbol Coding,<sup>44</sup> and Lexical Fluency). All carryover and period effects were not significant except for the period effect for the CGI scale ( $P=0.03$ ). BAS denotes Brief Scale for Anxiety, CGI Clinical Global Impression, GAF Global Assessment of Functioning, MADRS Montgomery and Åsberg Depression Scale, SDS Sheehan Disabilities Scale, and Y–BOCS Yale–Brown Obsessive Compulsive Scale.

† P values are for the between-group comparison of the difference between active and sham stimulation at the end of each period (month 6 and month 10).

‡ The range for each subscale of the SDS is 1 to 10; higher numbers indicate greater disability.

§ Test B–A refers to the score on Trail Making Test B minus the score on Trail Making Test A.

¶ Higher positive values on the Stroop interference index indicate greater difficulty in blocking interference.

of the study treatments (in favor of the patients who underwent active stimulation during the first period) could reflect nonspecific therapeutic or placebo effects attributable to the positive effect of enrollment and surgery. However, the crossover, double-blind design of the study and the improvement in patients who underwent active stimulation during the second period (the off–on group) do not support this hypothesis. It is unlikely that the decrease in obsessive–compulsive symptoms

reflected an antidepressant effect,<sup>11,12</sup> since no mood changes were reported during the study. Finally, the placement of the electrode in the subthalamic nucleus was meticulously determined and verified with the use of a precise, well-controlled procedure,<sup>13,20</sup> and the intensity of the stimulation was sufficiently limited to confine the current to the targeted part of the structure.<sup>13</sup>

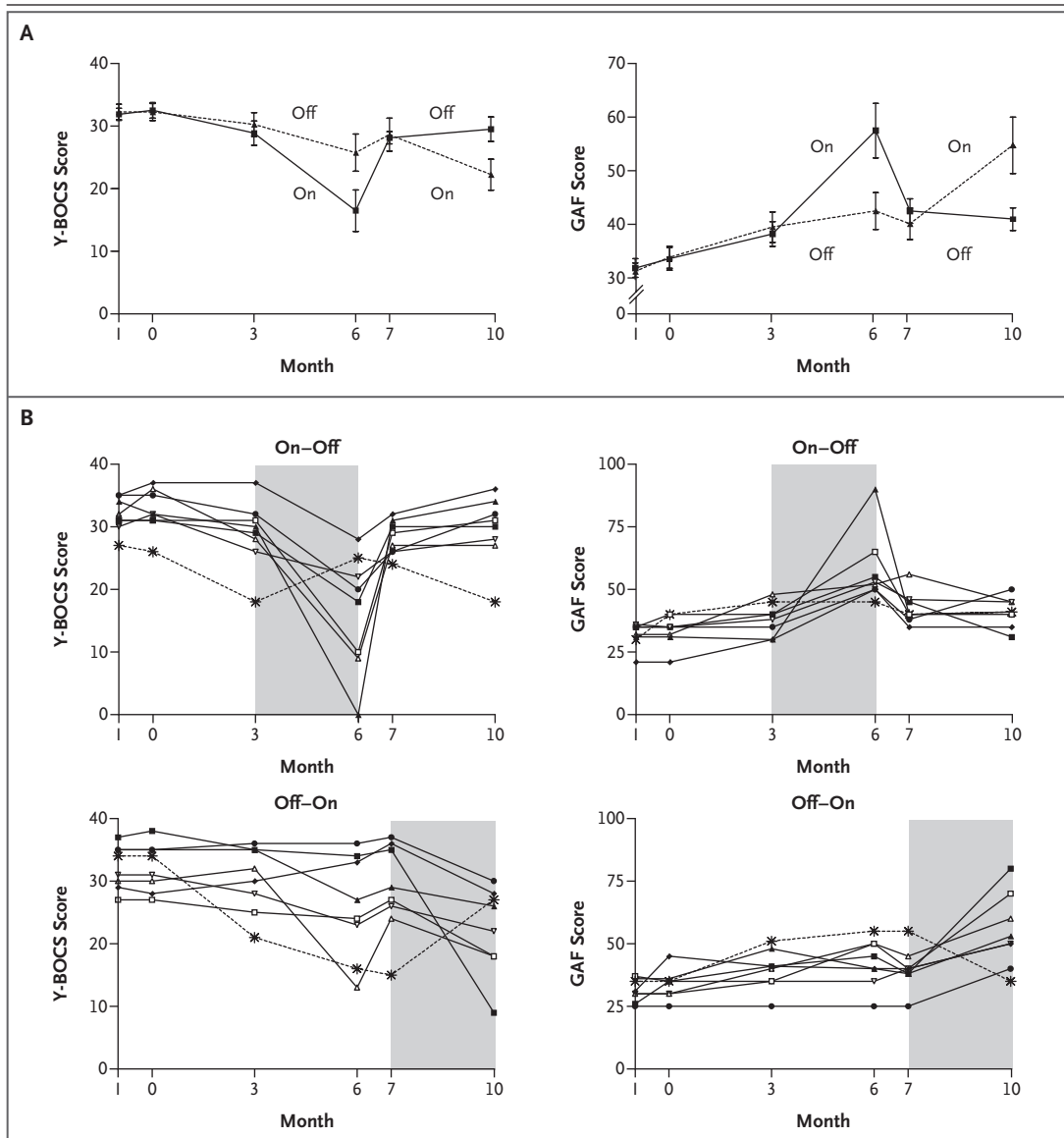
This study confirms our previous finding that obsessive–compulsive symptoms are reduced af-

Sham Stimulation Followed by Active Stimulation (Off-On Group)				Difference between Active and Sham Stimulation in the On-Off Group	Difference between Active and Sham Stimulation in the Off-On Group	P Value for Treatment Effect†
Baseline (Month 3)	End of Off Period (Month 6)	Start of On Period (Month 7)	End of On Period (Month 10)			
<i>median (range)</i>				<i>mean (95% CI)</i>		
31 (21 to 36)	26 (13 to 36)	28 (15 to 37)	24 (9 to 30)	-13 (-23 to -3)	-4 (-12 to 5)	0.01
15 (11 to 19)	12 (7 to 18)	14 (8 to 19)	12 (0 to 15)	-6 (-12 to -0.8)	-21 (-7 to 3)	0.04
16 (10 to 19)	13 (6 to 18)	15 (7 to 18)	12 (9 to 15)	-7 (-12 to -2)	-2 (-5 to 2)	0.03
40 (25 to 51)	42 (25 to 55)	40 (25 to 55)	52 (35 to 80)	16 (3 to 30)	12 (-0.6 to 25)	0.005
6 (5 to 7)	5 (3 to 7)	5 (3 to 7)	5 (2 to 6)	-3 (-4 to -0.8)	-0.3 (-2 to 1)	0.008
9 (1 to 10)	8 (3 to 10)	8 (3 to 10)	8 (2 to 10)	-4 (-7 to -0.5)	-0.6 (-3 to 2)	0.15
8 (5 to 10)	8 (0 to 10)	8 (0 to 10)	8 (1 to 9)	-3 (-6 to 0.5)	0.1 (-3 to 3)	0.66
8 (3 to 10)	7 (0 to 9)	5 (0 to 10)	5 (1 to 10)	-2 (-5 to 0.6)	-0.4 (-4 to 3)	1
6 (2 to 19)	8 (4 to 24)	8 (4 to 20)	12 (3 to 24)	-9 (-19 to 1)	2 (-8 to 11)	0.58
6 (5 to 24)	6 (1 to 27)	6 (2 to 21)	10 (0 to 22)	-3 (-11 to 4)	0.6 (-8 to 7)	1
28 (12 to 32)	28 (18 to 30)	27 (16 to 36)	28 (18 to 33)	-2 (-4 to 0.6)	2 (-1 to 5)	1
32 (24 to 53)	32 (20 to 76)	26 (19 to 48)	26 (21 to 50)	7 (1 to 13)	-6 (-17 to 5)	1
50 (31 to 127)	38 (17 to 77)	36 (24 to 67)	45 (19 to 96)	7 (-32 to 46)	3 (-16 to 22)	1
1 (-7 to 12)	2 (-22 to 12)	0.5 (-3 to 21)	1 (-5 to 9)	0.1 (-6 to 7)	2 (-6 to 9)	1
82 (41 to 98)	86 (29 to 92)	85 (36 to 91)	84 (47 to 96)	1 (-5 to 7)	3 (-3 to 9)	1
36 (24 to 57)	40 (26 to 55)	42 (19 to 62)	43 (27 to 60)	-3 (-8 to 2)	3 (-3 to 9)	1
60 (33 to 79)	58 (37 to 84)	58 (38 to 83)	60 (33 to 79)	1 (-5 to 8)	0.4 (-7 to 8)	1

ter stimulation of the anteromedial subthalamic nucleus,<sup>17</sup> which receives limbic and associative cortical information through an orbitofrontal-striato-pallido-thalamo-cortical circuit.<sup>31</sup> We therefore propose that the decrease in obsessive-compulsive symptoms is due to changes in neuronal activity in the subthalamic nucleus, a theory that is consistent with the concept that the subthalamic nucleus is an integrative center for the motor, cognitive, and emotional components of behavior.<sup>13</sup> Moreover, considering that patients with OCD are engaged in repetitive thoughts that result in the deferral of decision making and action, we propose that stimulation of the subthalamic nucleus may modify the maintenance of a decision-deferring process, as shown in patients with Parkinson's disease,<sup>45</sup> and therefore decrease obsessive-compulsive symptoms.

Previous studies of stimulation in patients with OCD have consisted of uncontrolled, open-label

designs<sup>3</sup>; therefore, a comparison of the findings of those studies with the results of our study is difficult. Two blinded procedures in four patients involved the anterior limb of the internal capsule and produced limited benefit with high voltages.<sup>7,9</sup> In an open collaborative study involving 10 patients whose preoperative clinical characteristics were similar to those of the patients in our study, Y-BOCS scores were reduced by more than 25% in 50% of the patients after 3 months of stimulation of the ventral striatum<sup>12</sup>; in contrast, 75% of the patients in our study had reduced Y-BOCS scores. After 36 months of unblinded stimulation that allowed optimal management of the settings in eight patients, the asymptotic best values for the OCD-severity and global-functioning scores<sup>12</sup> showed less improvement than the scores in our study after 3 months of double-blind stimulation. In all previous studies,<sup>6-12</sup> electrical-stimulation settings were more variable and higher than those



**Figure 3.** Changes in the Severity of OCD and Global Functioning in 16 Patients during the Crossover Study of Stimulation of the Subthalamic Nucleus.

Panel A shows the mean ( $\pm$ SD) scores on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) and the Global Assessment of Functioning (GAF) scale for the on–off group and the off–on group. Data are shown at the time of inclusion in the study (1), at the time of surgery (month 0), before (month 3) and after (month 6) the first period of active or sham stimulation, and before (month 7) and after (month 10) the second period of active or sham stimulation. Panel B shows the individual Y-BOCS and GAF scores for the on–off group and the off–on group. The active-stimulation period is represented in gray. One patient in each group (Patient 6 in the on–off group and Patient 2 in the off–on group) had higher Y-BOCS scores and one patient in the off–on group (Patient 2) had a lower GAF score during active stimulation (dashed lines).

in our study. The rate of serious adverse events related to the surgical procedure in our study was similar to that reported previously for stimulation of the subthalamic nucleus in patients with Parkinson’s disease and for neurostimulation in pa-

tients with OCD (a hematoma rate of 1 to 6% and an infection rate of 1 to 15%).<sup>12,19,46</sup> In our study, hypomania was the main psychiatric serious adverse event. The fact that the symptoms of hypomania resolved after adjustment of the stimulation

**Table 3. Adverse Events.**

Adverse Event	Permanent	Transient
		<i>no. of events</i>
<b>Serious</b>		
Before surgery		
Anxiety	0	1 (Patient 1)
After surgery, before randomization (month 0 to month 3)		
Intracerebral hemorrhage	1 (Patient 6)	0
Clumsiness and diplopia with perielectrode edema	0	1 (Patient 13)
Infection leading to removal of pulse generator	2 (Patients 4 and 9)*	0
After randomization (month 3 to month 10)		
Active-stimulation period		
Hypomanic status	0	3 (Patients 3, 4, and 10)
Anxiety	0	2 (Patients 1 and 14)
Disabling dyskinesias with impulsivity	0	1 (Patient 12)
Facial asymmetry, dysarthria, dysphagia, and walking difficulties	0	1 (Patient 5)
Sham-stimulation period		
Anxiety	0	1 (Patient 12)
Depressive symptoms with suicidal ideas	0	2 (Patient 17)
<b>Nonserious</b>		
After surgery, before randomization (month 0 to month 3)		
Urinary infection	0	1 (Patient 10)
Nocturnal enuresis	0	1 (Patient 16)
Headaches	0	1 (Patient 11)
Pain associated with the neurostimulator	0	1 (Patient 9)
Bronchitis	0	1 (Patient 15)
Anxiety	0	1 (Patient 14)
Obsessions	0	1 (Patient 11)
Lumbosciatic syndrome	0	1 (Patient 17)
Dyspnea	0	1 (Patient 12)
Hypomanic symptoms while stimulation settings were being determined	0	1 (Patient 1)
After randomization (month 3 to month 10)		
Active-stimulation period		
Dyskinesia	0	1 (Patient 13)
Hypomanic status with irritability and impulsivity	0	2 (Patient 12)
Manic symptoms with euphoria	0	1 (Patient 14)
Depressive symptoms	0	1 (Patient 11)
Anxiety	0	1 (Patient 14)
Obsessions	0	1 (Patient 13)
Peripheral vertigo	0	1 (Patient 12)
Achilles tendinitis	0	1 (Patient 1)
Diagnosis of diabetes mellitus	1 (Patient 15)	0
Sham-stimulation period		
Obsessions	0	1 (Patient 12)
Influenza-like syndrome	0	1 (Patient 16)
Hemorrhoidectomy	0	1 (Patient 15)

\* In Patient 9, the two electrodes and the pulse generator were removed, and the patient did not complete the randomization period. In Patient 4, one of the two pulse generators (Soletra) was removed.

settings suggests that they were induced by stimulation of the subthalamic nucleus and highlights the necessity of multidisciplinary expertise in the medical care of patients undergoing stimulation of the subthalamic nucleus. The study did not show an effect on functional impairment at work as measured by the Sheehan Disability Scale. Fifteen of 16 patients had not worked for many years, and given the short (3-month) crossover trial period, we did not expect patients to return to work at the end of the protocol. Finally, interesting short-term and long-term therapeutic results have been shown in studies of the use of cingulotomy or capsulotomy in patients with refractory OCD,<sup>3,47</sup> with variable surgical risks and adverse events; however, given the methodologic heterogeneity of all these procedures, a direct comparison would be necessary to assess precisely the advantages and limitations of each strategy.

The multicenter design of this study has potential limitations. Variation in the targeting of the stimulation was minimized by anatomical and electrophysiological identification performed simultaneously by local and coordinating teams. In addition, patients who had unexpected responses were examined thoroughly at the detailed clinical follow-up examination that was required by the study protocol. For example, two patients had a higher Y-BOCS score after active stimulation (Fig. 3). In one of these patients (Patient 6), the level of anxiety increased when a palsy of his right hand, the hand with which he had engaged in compulsive activities preoperatively, developed as a result of a parenchymal brain hemorrhage after surgery. In the other patient (Patient 2), because low-intensity stimulation of the subthalamic nucleus induced side effects, the intensity chosen for the active-stimulation period (month 7) may have been too low to reduce the symptoms of OCD. Moreover, adjustment of the settings was purposely limited in this study to be under the threshold for the induction of side effects in order to preserve the blinded nature of the protocol. Thus, the

stimulation settings are a further possible limitation of the study. Continued follow-up of patients undergoing stimulation of the subthalamic nucleus is needed to assess any long-term effects of stimulation that have not yet been identified.

In conclusion, findings from this 3-month crossover study suggest that stimulation of the subthalamic nucleus may lessen the severity of obsessive-compulsive symptoms and improve global functioning in patients with refractory, severe OCD. Serious adverse events occurred in 11 of the 17 patients in whom stimulators were implanted. The occurrence of severe adverse events, the small number of patients, and the short duration of the study highlight the risks of stimulation of the subthalamic nucleus and the need for larger studies with longer follow-up. In addition to assessment in a larger number of patients, a comparison with other stimulation targets and surgical procedures would be desirable, as would an evaluation of the long-term benefits of stimulation of the subthalamic nucleus in patients with OCD, notably with respect to their quality of life and their ability to function in social and work environments.

Supported by grants from the Programme Hospitalier de la Recherche Clinique Assistance Publique-Hôpitaux de Paris (AOM 03141) and the Agence Nationale de la Recherche Program for Young Researchers (R05121DS). The stimulators were purchased from Medtronic, which had no role in the study. Medtronic provided funds for the meetings of the investigators of the study.

Dr. Cornu reports receiving consulting fees from Medtronic; Dr. Houeto, lecture fees from Medtronic; Dr. Benadié, lecture fees and grant support from Medtronic; Dr. Agid, consulting fees from Medtronic; Dr. Krack, consulting and lecture fees from Medtronic; and Dr. Millet, grant support from Medtronic. No other potential conflict of interest relevant to this article was reported.

We thank Drs J. Adès, J. Cottraux, M. Goudemand, J.C. Aussiloux, S. Blond, J. Feingold, and D. Sicard for their independent contributions to the study with respect to ethical and safety issues; staff members of Association Française de Personnes Souffrant de Troubles Obsessionnels et Compulsifs (the French association of patients with OCD) for help in referring patients, and its president, C. Demonfaucon, for his helpful comments on inclusion criteria and ethics in the preparation of the protocol; and Max Westby and Marie Vidailhet for their thoughtful comments on the manuscript.

#### APPENDIX

The authors' affiliations are as follows: INSERM, Avenir Team, Behavior, Emotion, and Basal Ganglia, IFR 70 (L.M., M.-L.W., J.Y., E.B.), Clinical Investigation Center (L.M., M.-L.W., V.C., Y.A.), Pitié-Salpêtrière University Hospital, Assistance Publique-Hôpitaux de Paris, Paris; Departments of Psychiatry (M.P., T.B.), Neurosurgery (S.C., A.-L.B.), and Neurology (C. Ardouin, P.P., P.K.) Grenoble University Hospital, Grenoble; Departments of Psychiatry (N.J.) and Neurosurgery (B.B.), University Hospital, Poitiers; INSERM U796, University of Paris Descartes, University Department of Psychiatry (N.B., M.-O.K.), and Department of Neurosurgery (B.D.), Sainte-Anne Hospital, Paris; Departments of Neurosurgery (D.F.) and Psychiatry (V.M.), University Hospital, Nice; Biostatistics and Medical Informatics Unit and Clinical Research Unit, Pitié-Salpêtrière University Hospital, Université Pierre et Marie Curie-Paris 6, EA 3974, Modeling in Clinical Research, Paris (S.T.D.M.); Neurologie et Thérapeutique Expérimentale, INSERM U679, Université Pierre et Marie Curie-Paris 6, Institut Fédératif de Recherche de Neurosciences Unité Mixte de Recherche S679, Paris (J.Y., Y.A.); Departments of Psychiatry (I.C.) and Neurology (P.D.), University Hospital, Clermont-Ferrand; Departments of Psychiatry (C. Arbus) and Neurosurgery (P.C.), University

Hospital, Toulouse; Departments of Neurosurgery (S.R.) and Neurology (P.D.), University Hospital, Nantes; Department of Psychiatry, Charles Perrens Hospital (B.A.), and Centre National de la Recherche Scientifique (CNRS) UMR5543 (B.A., P.B.), University Bordeaux 2, Bordeaux; INSERM U610 (V.C.), Department of Neurosurgery (P.C.), Department of Radiology (D.D.), Fédération des Maladies du Système Nerveux (M.-L.W, Y.A.), and Department of Psychiatry (A.P.), Pitié-Salpêtrière University Hospital, Paris; Laboratoire de Neurosciences Cognitive et Imagerie Cérébrale, CNRS Unité propre de Recherche 640-LENA, Paris (E.B.); Department of Neurology (M.V.) and Department of Psychiatry (B.M.), University Hospital, Rennes; and Department of Neurology, EA 3808, University of Poitiers, CHU de Poitiers, Poitiers (J.L.H.) — all in France.

Members of the French STOC Study Group are as follows: **Trial Coordination:** L. Mallet. **Steering Committee:** Y. Agid, B. Auouizerate, C. Arbus, T. Bougerol, P. Damier, D. Fontaine, J.L. Houeto, M.O. Krebs, J.J. Lemaire, L. Mallet, B. Millet, P. Pollak. **Logistics and Monitoring:** D. Hourton, S. Aprelon, C. Jourdain. **Coordinating teams: Anatomy** — E. Bardinet, J. Yelnik; **Electrophysiology** — P. Burbaud, M.L. Welter, A.H. Clair; **Neuropsychology** — V. Czernecki, M. Vérin. **Data Management and Statistical Analysis:** S. Tezenas du Montcel, D. Madar. **Writing Committee:** L. Mallet, A. Pelissolo, S. Tezenas du Montcel, M.L. Welter, J. Yelnik. **Centers: Coordinating Center, Paris Pitié-Salpêtrière Hospital** — L. Mallet, A. Pelissolo, Y. Agid, P. Cornu, S. Navarro, M.L. Welter, A. Hartmann, B. Pidoux, D. Grabli, V. Czernecki, D. Dormont, D. Galanaud, J. Yelnik, E. Bardinet, C. Béhar, Y. Worbe, A.H. Clair, B. Moutaud, Centre d'Investigation Clinique staff and nurses; **Bordeaux** — B. Auouizerate, P. Burbaud, E. Cuny, D. Guehl; **Clermont-Ferrand** — P.M. Llorca, I. Chéreau, J.J. Lemaire, F. Durif, P. Derost, J. Coste, J. Gabrillargues, M. Barget, I. de Chazeron; **Grenoble** — T. Bougerol, M. Polosan, A.L. Benabid, S. Chabardès, E. Seigneuret, P. Krack, P. Pollak, P. Arduin, J.F. Le Bas; **Nantes** — P. Damier, Y. Lajat, S. Raoul; **Nice** — V. Mattei, D. Fontaine, M. Borg, P. Paquis, M.N. Magnie-Mauro, P. Robert, E. Michel, F. Papetti; **Paris Sainte-Anne Hospital** — N. Baup, B. Devaux, M.O. Krebs, C. Oppenheimer, J.P. Olié, D. Ranoux, M. Chayet; **Poitiers** — J.L. Houeto, N. Jaafari, B. Bataille, V. Mesnage, R. Gil, V. Audouin, J.L. Senon; **Rennes** — B. Millet, M. Vérin, D. Drapier, P. Sauleau, S. Drapier; **Toulouse** — C. Arbus, Y. Lazorthé, P. Chaynes, N. Fabre, M. Simonetta, L. Schmitt, J.A. Lotterie, C. Camassel. **Direction Régionale de la Recherche Clinique Assistance Publique-Hôpitaux de Paris:** N. Best. **Independent Safety Committee:** J.C. Aussilloux, S. Blond, J. Feingold, D. Sicard. **Independent Selection Committee:** J. Adès, J. Cottraux, M. Goudemand.

## REFERENCES

- Stein DJ. Obsessive-compulsive disorder. *Lancet* 2002;360:397-405.
- Pallanti S, Quercioli L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:400-12.
- Lipsman N, Neimat JS, Lozano AM. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery* 2007;61:1-13.
- Benabid AL, Wallace B, Mitrofanis J, et al. Therapeutic electrical stimulation of the central nervous system. *C R Biol* 2005;328:177-86.
- Aouizerate B, Guehl D, Cuny E, et al. Pathophysiology of obsessive-compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology. *Prog Neurobiol* 2004;72:195-221.
- Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 1999;354:1526.
- Nuttin BJ, Gabriëls LA, Cosyns PR, et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery* 2003;52:1263-74.
- Anderson D, Ahmed A. Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation: case report. *J Neurosurg* 2003;98:1104-8.
- Abelson JL, Curtis GC, Sagher O, et al. Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatry* 2005;57:510-6.
- Sturm V, Lenartz D, Koulousakis A, et al. The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J Chem Neuroanat* 2003;26:293-9.
- Aouizerate B, Cuny E, Martin-Guehl C, et al. Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression: case report. *J Neurosurg* 2004;101:682-6.
- Greenberg BD, Malone DA, Friehs GM, et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* 2006;31:2384-93. [Erratum, *Neuropsychopharmacology* 2006;31:2394.]
- Mallet L, Schüpbach M, N'Diaye K, 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.
- Arduin C, Voon V, Worbe Y, et al. Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. *Mov Disord* 2006;21:1941-6.
- Houeto JL, Mallet L, Mesnage V, et al. Subthalamic stimulation in Parkinson disease: behavior and social adaptation. *Arch Neurol* 2006;63:1090-5.
- Alegret M, Junqué C, Valldeoriola F, et al. Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. *Arch Neurol* 2001;58:1223-7.
- Mallet L, Mesnage V, Houeto JL, et al. Compulsions, Parkinson's disease, and stimulation. *Lancet* 2002;360:1302-4.
- Fontaine D, Mattei V, Borg M, et al. Effect of subthalamic nucleus stimulation on obsessive-compulsive disorder in a patient with Parkinson disease: case report. *J Neurosurg* 2004;100:1084-6.
- Krack P, Batir A, van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003;349:1925-34.
- Yelnik J, Bardinet E, Dormont 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.
- Bejjani BP, Dormont D, Pidoux B, et al. Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. *J Neurosurg* 2000;92:615-25.
- Yelnik J, Damier P, Demeret S, 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.
- Preisig M, Fenton BT, Matthey ML, Berney A, Ferrero F. Diagnostic Interview for Genetic Studies (DIGS): inter-rater and test-retest reliability of the French version. *Eur Arch Psychiatry Clin Neurosci* 1999;249:174-9.
- Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989;46:1006-11.
- Diagnostic and statistical manual of mental disorders, 4th ed. text rev.: DSM-IV-TR. Washington, DC: American Psychiatric Association, 2000.
- Clinical Global Impression. In: Guy W. ECDEU assessment manual for psychopharmacology. Rev. ed. Rockville, MD: National Institute of Mental Health, 1976:218-22.
- Mattis S. Dementia Rating Scale. Odessa, FL: Psychological Assessment Resources, 1988.

28. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59: Suppl 20:22-57.
29. Maffei C, Fossati A, Agostoni I, et al. Interrater reliability and internal consistency of the Structured Clinical Interview for DSM-IV axis II personality disorders (SCID-II), version 2.0. *J Personal Disord* 1997;11:279-84.
30. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
31. Karachi C, Yelnik J, Tandé D, Tremblay L, Hirsch EC, François C. The pallidum-subthalamic projection: an anatomical substrate for nonmotor functions of the subthalamic nucleus in primates. *Mov Disord* 2005;20:172-80.
32. Benabid AL, Koudsie A, Benazzouz A, Le Bas JF, Pollak P. Imaging of subthalamic nucleus and ventralis intermedius of the thalamus. *Mov Disord* 2002;17: Suppl 3: S123-S129.
33. Karachi C, François C, Parain K, et al. Three-dimensional cartography of functional territories in the human striatopallidal complex by using calbindin immunoreactivity. *J Comp Neurol* 2002;450: 122-34.
34. Hutchison WD, Allan RJ, Opitz H, et al. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. *Ann Neurol* 1998;44: 622-8.
35. Pollak P, Krack P, Fraix V, et al. Intraoperative micro- and macrostimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord* 2002;17: Suppl 3: S155-S161.
36. The 2x2 cross-over trial with continuous data. In: Jones B, Kenward MG. Design and analysis of cross-over trials. London: Chapman and Hall, 1989:16-88.
37. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol* 1996;11: Suppl 3: 89-95.
38. Tyrer P, Owen RT, Cicchetti DV. The brief scale for anxiety: a subdivision of the Comprehensive Psychopathological Rating Scale. *J Neurol Neurosurg Psychiatry* 1984;47:970-5.
39. Pillon B, Boller F, Levy R, Dubois B. Cognitive deficit and dementia in Parkinson's disease. In: Boller F, Cappa S, eds. Aging and dementia. Vol. 6 of Handbook of neuropsychology. 2nd ed. Amsterdam: Elsevier, 2001:311-72.
40. Brandt J. The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. *Clin Neuropsychol* 1991;5:125-42.
41. Reitan RM. Trail Making Test results for normal and brain-damaged children. *Percept Mot Skills* 1971;33:575-81.
42. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935;18:643-62.
43. Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain* 1991;114:2095-122.
44. Weschler D. Wechsler Memory Scale. 3rd ed. San Antonio, TX: The Psychological Corporation, 1997.
45. Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science* 2007;318: 1309-12.
46. Rezaei AR, Kopell BH, Gross RE, et al. Deep brain stimulation for Parkinson's disease: surgical issues. *Mov Disord* 2006; 21: Suppl 14: S197-S218.
47. Dougherty DD, Baer L, Cosgrove GR, et al. Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. *Am J Psychiatry* 2002;159:269-75.

Copyright © 2008 Massachusetts Medical Society.

#### CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most clinical trials for publication only if they have been registered (see *N Engl J Med* 2004;351:1250-1). Current information on requirements and appropriate registries is available at [www.icmje.org/faq.pdf](http://www.icmje.org/faq.pdf).