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Deep Brain Stimulation for Obsessive-Compulsive Disorder: Subthalamic Nucleus Target

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Key words
- Basal ganglia
- Deep brain stimulation
- Obsessive-compulsive disorder
- Psychiatric disorders
- Subthalamic nucleus
- Surgery

Abbreviations and Acronyms
AC-PC: Anterior-posterior commissural
CBT: Cognitive-behavior therapy
DBS: Deep brain stimulation
EEG: Electroencephalogram
GAF: Global assessment of functioning
HFS: High-frequency stimulation
MRI: Magnetic resonance imaging
noM-STN: Nonmotor subthalamic nucleus
OCD: Obsessive-compulsive disorder
PD: Parkinson disease
STN: Subthalamic nucleus
STOC: Stimulation "dans le Trouble Obsessionnel Compulsif"
Y-BOCS: Yale-Brown obsession compulsion scale

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Because of its reversibility and adaptability, deep brain stimulation (DBS) has recently gained interest in psychiatric disorders, such as obsessive-compulsive disorders (OCD) and depression. In OCD, DBS is now an alternative procedure to lesions of fascicles such as the anterior capsule, which links the orbitofrontal cortex, the cingulum, and the thalamus, and has been applied to new target such as the nucleus accumbens, with promising results. However, a recent interest has been developed toward the subthalamic nucleus (STN), a key structure of the basal ganglia that connects the motor, limbic, and associative systems. It is known from patients with Parkinson disease that STN-DBS can have significant effects on mood and cognition. Those transient effects are usually seen as "side effects" in Parkinson disease, but are clues to the underappreciated role that STN plays in the limbic circuitry, a role whose precise details are as yet unknown and under active investigation. We present the rationale supporting the use of nonmotor STN as a therapeutic target to treat OCD. In particular, we discuss the recent experience and preliminary results of our group after 6 months of nonmotor STN-DBS in patients with severe OCD.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a major cause of disability and can be responsible for severe impairment in quality of life. It is one of the most frequent and disabling psychiatric problems after phobia, mood disorders, and substance abuse (13). It affects 2%–3% of the population. OCD is characterized by recurrent unwanted ideas, images, or impulses (obsessions), and repetitive, stereotyped behaviors or mental acts (compulsions), often intended to neutralize the anxiety induced by the obsessions. The variability of symptoms mirrors their heterogeneity in response to conventional treatments. OCD usually tends to be chronic and might require long-term medication and cognitive-behavior therapy (CBT). First-line treatments for OCD are well established and consist in CBT, including exposure and ritual prevention, associated with medications, particularly selective serotonin reuptake inhibitors (12). Such conventional treatments can lead to satisfactory responses but improvement after medication and CBT is usually partial. After conventional treatments, 20%–40% of patients with OCD remain severely disabled. Surgery is an option for treatment-refractory patients who are usually those most severely affected.

Surgical Treatment for OCD: From Lesions to Deep Brain Stimulation

For decades, surgery has consisted in thermolesion of different key structures supposedly involved in the control of OCD. OCD was one of the rare indications responding successfully to lobotomy (24), but at the price of a severe frontal syndrome. The patient is apathetic and disinhibited. This leaves the patient suffering from major changes in personality and behavior (35). Stereotactic surgery was first developed in 1947 by Spiegel et al. (31) with the aim of performing small selective thalamic lesions aiming at interrupting cortico-thalamo-cortical loops (30) to avoid or reduce the side effects of lobotomy. Since then different targets have been explored including thermolesion in the cingulate cortex, the anterior limb of the internal capsule, or the subcaudate region. Leukotomies combined cingulotomy and subcaudate tractotomy. Different centers worldwide have established the efficacy of such surgical treatments, which are still proposed in cases of intractable OCD (7, 8, 11, 20, 29). In the past decade, the use of deep brain stimulation (DBS) has progressively replaced lesions and Bart Nuttin and his team (25) were the first to apply the concept of high frequency stimulation of a deep target, the anterior limb of the internal capsule, to treat patients suffering from severe OCD. Since this original report in 1999, there has been a growing interest in the neurosurgical field to define new brain structures that could be

targeted by DBS, which has the advantage (versus ablative surgery) of reversibility and adaptability. The surgical experience accumulated in the field of movement disorders surgery, the development of functional imaging leading to better comprehension of neuronal networks involved in OCD and depression, the observation of nonmotor (side) effects of DBS in Parkinson disease (PD), as well as the serendipitous observation of OCD symptoms being improved in some patients with PD on subthalamic stimulation, These experiences have helped to bring electrical stimulation as a therapeutic tool into psychiatric disorders.

Rationale for the Use of Subthalamic Nucleus as a Potential Therapeutic Target

Nonmotor Side Effect Observed After Subthalamic Nucleus-DBS. Behavioral side effects induced by acute changes in stimulation parameters in patients with PD treated with subthalamic nucleus (STN)-DBS include mirthful laughter (19), acute depression (4), aggressiveness (5), and hypomania or full blown mania (19, 23, 33). These clinical observations have been carefully reported and have led to the concept that deep nuclei, such as the STN, a target commonly used to treat patients with PD, could induce limbic side effects systematically reproduced when the stimulator was switched ON. These observations paved the way for new exploratory applications of electrical stimulation targeting limbic/cognitive regions to treat nonmotor symptoms that are encountered in psychiatric disorders such as OCD, depression, Gilles de la Tourette syndrome, or addiction (18). This regain of interest in surgery for mood and cognitive disorders brought together anatomic and physiologic knowledge of the neuronal circuitry involved in these psychiatric disorders. This is an attempt to better understand the close relationships between limbic, cognitive, and motor neuronal networks in the basal ganglia.

Nonmotor Circuitry in the Basal Ganglia. If the dorsolateral motor portion of the STN is known to be a major entry of the motor cortical information into the basal ganglia circuitry, the anteroventral STN also receives information from the dorsolateral and orbitobasal frontal cortex, from the cingulate cortex, and from the lateral temporal neocortex (26, 27, 32). In monkeys, anatomic studies using retrograde tracers have demonstrated the somatotopic organization between associative, motor, and limbic cortex on one hand, and subterritories of the basal ganglia on the other hand. For example, nonmotor territories of the external globus pallidus send massive projections to the nonmotor STN (noM-STN) through the indirect pathway (15). The noM-STN appears to be a key node between the associative/limbic cortex, the nonmotor subterritories of basal ganglia, and the thalamus. Review of the surgical literature in the field of psychiatry (18) has highlighted that all targets shown to improve symptoms of OCD, depression, Gilles de la Tourette syndrome, or addiction involve the nonmotor (limbic and/or associative) corticobasal ganglia–thalamo-cortical loops described in the Alexander model of basal ganglia circuitry (1) (see Temel et al. [32] for review).

Animal Data

Recent experimental data have shed light on the role of the STN in compulsive behavior. It has been shown that in the quinpirole rat model of OCD and in a behavior model of OCD (attenuation rat model of OCD) (16, 38), high-frequency stimulation (HFS) as well as pharmacologic inactivation of the STN alleviated compulsive checking (39). These works are in line with the published literature that has already demonstrated the role of STN in decision process, reward (2), and control of impulsivity and choices. Usually lesions of STN lead to modulation of impulsive choice and action (34, 37). Increase of impulsivity has recently been proposed (18) as one of the mechanism of action of STN-DBS in OCD (discussed later).

In monkeys, stereotypies can be obtained after microinjection of bicuculline into the limbic part of STN (14). In this animal model, it has been reported that acute HFS of the anterior-medial part (limbic) of the STN could dramatically reverse these stereotypies (3). Even if OCD cannot be summarized by successive stereotypies, these data acquired in subhuman monkeys demonstrated the potential powerful effect of electrical inhibition of the noM-STN to treat "compulsive" behavior. Interestingly, the authors did not report any attention or task execution impairment during the experiments.

Serendipity Usually Precedes Innovation

This maxim can be illustrated with the discovery of the potential effect of STN-DBS to treat OCD. Three patients who had a history of severe PD and also intractable OCD symptoms were treated with STN-DBS and had great improvement of PD symptoms and surprisingly also of OCD symptoms.

Mallet et al. (21) first reported the case of two patients who underwent presurgical evaluation for severe PD and who presented OCD as a comorbidity. The patients received bilateral STN implantation to treat PD symptoms. The first patient had a 5-year history of PD and presented with severe OCD (cleaning, arranging, "fear of being dead in a dirty house") that lasted for 33 years. Two weeks after surgery, she spontaneously described a dramatic improvement of OCD symptoms and the Yale-Brown obsessive-compulsive scale (YBOCS) was reduced by 81% (preoperative, 26; postoperative, 5). The second patient had a 16-year history of PD with also a 40-year history of OCD (repeated checking of locks). Two weeks after, OCD were also dramatically improved by 83%. In these two patients, the anti-OCD effect of STN-DBS was still present 1 year after surgery. When looking at the precise location of the lead within the STN, it turned out that the electrodes were slightly anterior and medial and that the current could have potentially diffused to the nonmotor part of the STN.

In 2004, Fontaine et al. (9) confirmed previous findings with the report of the case of a man, aged 49 years, presenting with severe PD and who also suffered from refractory OCD (accumulating, rubbing, gathering) for 16 years. He was operated on for PD with bilateral STN implantation. At 1-year follow-up, PD was improved as expected but at the same time, OCD symptoms disappeared (preoperative YBOCS, 32; postoperative YBOCS, 1).

These three intriguing observations were the basis of a larger pilot study that involved several centers in France and that aimed at evaluating the presumed effect of STN-DBS on OCD.

Results in Humans

In 2002, the French "comité national d'éthique" was asked by one of the senior author (ALB) to answer whether DBS, a surgical methodology developed for movement disorders, could potentially be applied in psychiatric disorders including

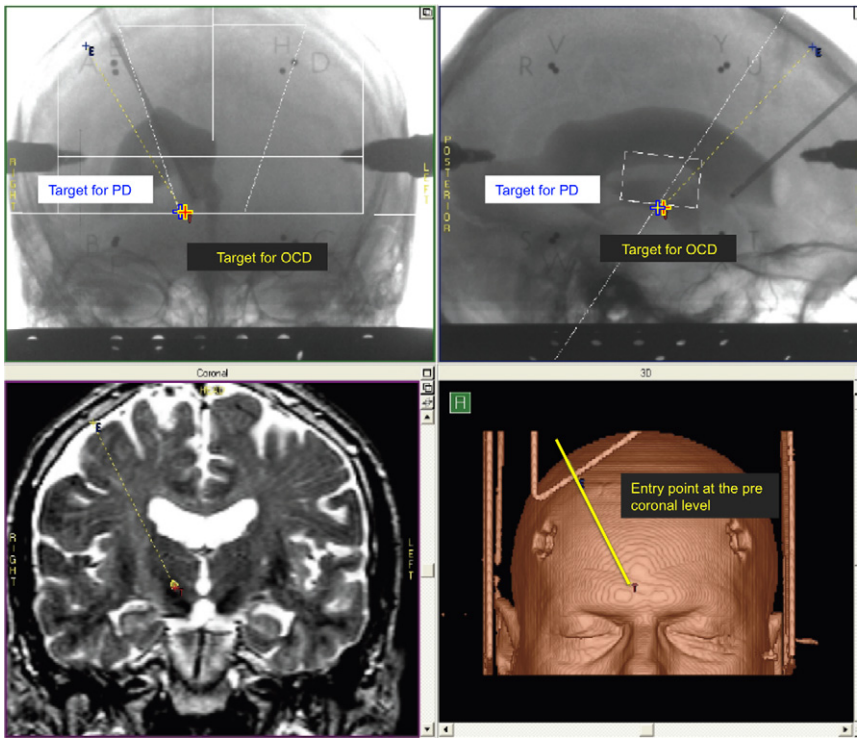

Figure 1. Example of a surgical planning. Targeting of the nonmotor subthalamic nucleus in patients with obsessive-compulsive disorder (OCD) is 2 mm more anterior and 1 mm more medial compared with the motor subthalamic nucleus target usually used for Parkinson disease (PD). Trajectory and entry points vary in relation to sulcal anatomy, ventricle horn dimension, and vessels. Anatomy of each individual is similar to that used in patients with PD.

OCD. This committee stated that OCD patients could be involved in therapeutic trials with the following restriction: 1) the first purpose of the trial must be to treat the patient and research must not be the primary goal, 2) the patient must be able to give inform consent, 3) the trial must be validated by an external adviser, and 4) the presumed reversibility of DBS technique must be continually assessed in its reality.

STOC Study

In 2005, the French Stimulation ≪dans le Trouble Obsessionnel Compulsif≫ (STOC) Study, headed by L. Mallet, started in France, and involved 10 academic centers. This protocol was approved by the local ethical committee of Pitié-Salpetrière. It consisted in a double-blind, crossover study, assessing the efficacy and safety of STN-DBS in 16 patients. The primary outcome measure was the severity of OCD, as assessed by the YBOCS, at the end of two 3-month periods. Inclusion criteria are described (see Selection of Patients and Ethics section).

The main findings have been reported in detail (22) in the original article. In summary, the YBOCS score was significantly lower (decreased by 31% in average) during stimulation than the score after sham stimulation (mean ±SD, 19 ± 8 vs. 28 ± 7; $P = 0.01$). During ON Stim, the Global Assessment of Functioning (GAF) score was significantly higher (56 ± 14 vs. 43 ± 8, $P = 0.005$). Neuropsychological measures, depression, and anxiety were not modified by stimulation.

These positive results were counterbalanced by a relative high number of "serious adverse events." The most severe was an intracerebral hemorrhage that resulted in a palsy of the contralateral hand. Two patients had hardware infections requiring the removal of the stimulator. During stimulation period, transient adverse events developed, which were controlled after adjustment of stimulation parameters (3 patients developed hypomania, 2 developed anxiety, 1 developed dyskinesia with impulsivity, and 1 patient developed dysphagia, dysarthria, and gait disorders). Of importance, during sham stimulation, three patients developed also anxiety or depressive symptoms.

Grenoble Experience: Preliminary Results

At Grenoble University Hospital, based on the promising results of the STOC study, we prospectively enrolled additional patients in a registry to assess efficacy and safety of STN-DBS for OCD. Several concerns were raised during the STOC study: 1) efficacy was clearly demonstrated during the double-blind phase but reached on average only 32% after a 3-month period of stimulation; 2) although transient for most patients, side effects were still frequent; 3) patients differed in the type of OCD symptoms and personality, two factors that could potentially impact on the efficacy; and 4) in this pioneer multicenter study, surgical technique and targeting could have slightly differed among centers and thus was a potential confound issue.

In the present article we illustrate our preliminary results on four patients suffering from intractable OCD and in whom bilateral STN-DBS was applied with at least 6 months of follow-up. Two of the four patients participated to the STOC study.

Selection of Patients and Ethics. At Grenoble University Hospital, inclusion criteria strictly follow those previously used in the STOC study. All patients must suffer from OCD as defined by Diagnostic and Statistical Manual of Mental Disorders IV, must be ≥18 years old, with a YBOCS of >25, a GAF score of <40, and a clinical global impression score of >4. All patients must have failed three serotonin reuptake inhibitors treatments, including clomipramine, after a minimum of 12 weeks of adequate administration. They also must have failed CBT conducted during at least 1 year with two therapists.

Surgery and Targeting. All patients suffering from OCD and referred to our institution are operated under the same surgical procedure routinely used in our center for the implantation of DBS leads in patients with movement disorders and this is described in detail elsewhere (6) (**Figure 1**). Briefly, 2 days before the surgical implantation, a

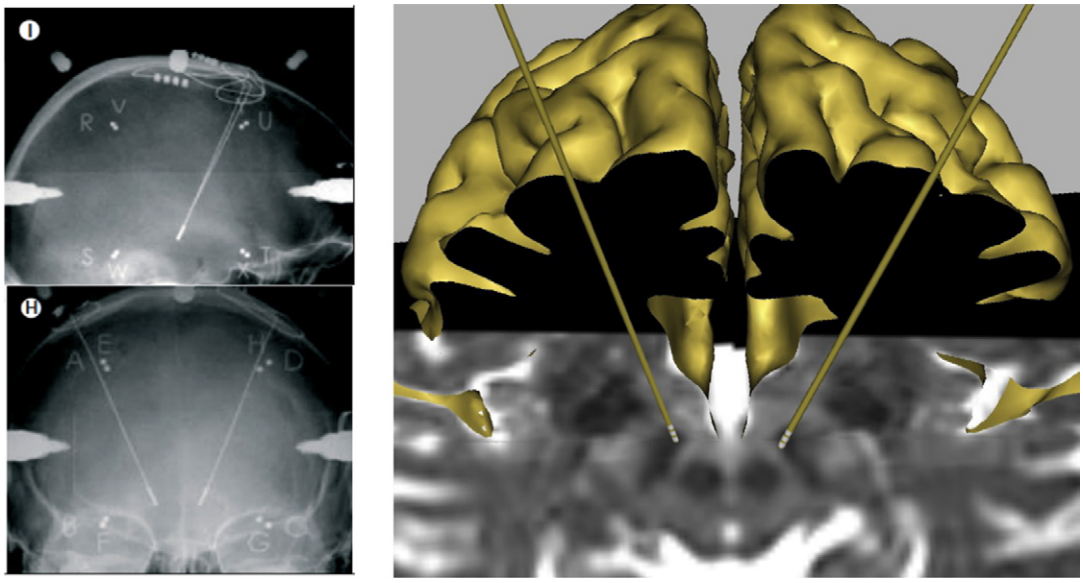

Figure 2. Example of preoperative radiographic control and postoperative magnetic resonance imaging control scans. The patients are typically implanted with a 3389 electrode (Medtronic, Minneapolis, Minnesota, USA) with the upper contact at the level of the anterior-posterior commissural plane. Note that the electrode is inserted medially and anteriorly within the subthalamic nucleus.

stereotactic digital televentriculography (Pixray; BioScan, Geneva, Switzerland) is performed under general anesthesia. Then, for each patient, T_1- and T_2-contrasted three-dimensional cerebral magnetic resonance imaging (MRI) scans are obtained in stereotactic conditions before the surgical implantation of the leads. The targeting of noM-STN is performed on the ventriculographic schema fused with the MRI scans using stereotactic imaging software (Voxim; IVS Solutions, Chemnitz, Germany).

In patients with PD, the following coordinates are frequently used to target the sensorimotor STN: 6/12 of the anterior-posterior commissural (AC-PC) length posterior to the AC, 12 mm lateral to the midline, and 3 mm below the AC-PC line. In patients with OCD, the noM-STN is targeted 2 mm anterior and 1 mm medial to the previous target (**Figure 1**). It is then adjusted during surgical implantation by using multiunit recordings with five microelectrodes. In patients with OCD, the noM-STN is identified by the lack of neuronal responses to passive or active movements and by the lack of sensorimotor side effects such as contralateral paresthesias or motor contractions induced by microstimulations. The final electrode is positioned on the track in which no side effects is obtained during preoperatory microstimulation, and in which no sensorimotor cells have been recorded during microelectrode recordings. Finally, a second electrode is implanted in the contralateral side following the same procedure and both leads are connected to a stimulator (Kinetra; Medtronic, Minneapolis, Minnesota, USA) after MRI control scans are done routinely in our institution (10) (**Figure 2**).

Stimulation Parameters Settings. Postoperatory settings of stimulation parameters follow a pre-established procedure and consist in successive trials of monopolar stimulation, beginning with the most ventral pair of contacts, and followed the by more dorsal contacts. Voltage is increased progressively in 0.5-V steps until side effects are obtained.

All stimulators are set at a frequency of 130 Hz and at a pulse width of 60 μs using a single monopolar, cathodal contact (case being positive). Stimulation of the sensorimotor territory can be limited by stimulation-induced dyskinesia and stimulation of the nonmotor (limbic associative) territories, which can be limited by behavioral side effect with disinhibition of behavior, agitation, anxiety, euphoria, and mania. These behavioral side effects are reversible on reduction of voltage. To avoid such behavioral side effects, the increase in stimulation parameters is performed in an inpatient setting in our institution in the immediate postsurgical period. Side effects related to current diffusion to surrounding structures in the subthalamic area are the same than those described in PD (17). The final contact for chronic stimulation is chosen based on beneficial effects when present and on the threshold for side effects. The contact selection is also greatly helped by postoperative imaging, the contact located in the noM-STN being the first choice (40). Once the contact is chosen, the voltage is then progressively increased during the course of 1–2 weeks in the immediate postoperative period. Stimulation parameters can be adjusted during long-term follow-up, but tend to be rather stable and similar to those used in PD (22).

RESULTS

Electrophysiologic Findings During Microrecordings

We have recently described how STN neurons behave in the noM-STN in patients with OCD (28). Briefly, compared to STN of patients with PD, STN neurons in patients with OCD have a lower frequency rate but, more important, they exhibit a bursting pattern, which we have interpreted as a signa-

Table 1. Clinical Characteristics of Four Patients

Patient (gender)	Age at Surgery (years)	Duration of Disease (years)	Preoperative State			Preoperative Medications	Type of OCD
			Y BOCS (O+C)	CGI	GAF		
1 (M)	39	18	18+19	6	26	Fluvoxamine 200 mg; pimozide 1 mg; clonidine 0.3 mg	Aggressive
2 (F)	43	32	14+18	6	32	Sertraline 100 mg; risperidone 4 mg; alprazolam 0.75 mg	Ordering, checking
3 (F)	35	15	14+15	6	36	Paroxetine 60 mg	Washing
4 (M)	36	17	17+15	5	40	Paroxetine 40 mg	Washing

O, obsessions (from 0–20); C, compulsions (from 0–20); YBOCS, Yale-Brown obsessive-compulsive scale ranges from 0–40 with higher scores indicating worse function; GAF, Global Assessment of Functioning score ranges from 0–90 with higher scores indicating the normal function; CGI, clinical global impression score ranges from 1–7 with higher score indicating the severity of the disease.

ture of dysfunction of the nonmotor basal ganglia network. Interestingly, in patients with OCD, the proportion of neurons with burst activity (70%) is similar to that seen in patients with PD. However, these neurons are significantly more frequent in the left STN, whereas no asymmetry could be noticed in the distribution of bursts in PD. Similar findings have been also reported by Welter et al. (36) based on the STOC study cohort of patients. These investigators found a high proportion of oscillatory activity in STN and interestingly, they correlated the characteristics of bursts of STN neurons with OCD symptom severity and with the clinical response to STN-DBS. In summary, they showed a better improvement after STN-HFS when STN neurons exhibited a lower interburst interval and a higher intraburst frequency. These data suggest that STN neuronal activity characteristics are predictive factors of good therapeutic effect of STN-DBS.

Illustrative Cases

We present three cases to illustrate the potential therapeutic effect of STN-DBS as a surgical treatment for severe, intractable OCD. An additional case is also presented to discuss the factors that can influence the response to STN-DBS. All four patients belong to the Grenoble cohort and the first two patients have been included in the STOC study. **Table 1** illustrates the clinical characteristics of the four patients at the time of surgery. **Table 2** summarizes the stimulation parameters used for chronic stimulation, and the effect on YBOCS after 3 and 6 months of stimulation and, clinical global impression and GAF after 6 months of stimulation.

Case 1. This 39-year-old married patient was suffering from OCD for 18 years and was unemployed in the past 5 years due to severity of his condition. Main obsessions were related to aggressiveness and centered on the potential threat, unbearable loss (mainly due to accidents) of a close person, especially his family members. The associated compulsions consisted in repetitive neutralizing mental operations (matching "positive" images with the names of the concerned persons) and repetitive touching

Table 2. Summary of Stimulation Parameters and Effects of DBS After Three and Six Months of Stimulation

Patient	Contacts Plots (voltage)	Side Effects		Postoperative State					
		Transient	Chronic	YBOCS at 3 Months (O+C)	Y BOCS at 6 Months (O+C)	CGI at 6 Months	GAF at 6 Months	Postoperative Medications	Improvement at 6 Months
1 (M)	−1/-5 (1,2)	Mania Anxiety	Weight gain (9 kg)	0+9	0+9	2	80	Fluvoxamine 200 mg Alprazolam 0.5 mg	75%
2 (F)	−2/-6 (4)	Enuresis Anxiety	No	0+9	2+5	3	68	Sertraline 50 mg; risperidone 2 mg	71%
3 (F)	−1/-5 (2/4)	Hemiballism impulsivity- aggressivity	No	9+9	2+6	2	80	Paroxetine 60 mg	78%
4 (M)	−0;−1/−4;−5 (1,2)	Mild hypomania Infection	Motor contraction Weight gain (+15kg)	11+12	11+10	4	60	Paroxetine 60 mg	34%

DBS, deep brain stimulation; O, obsessions (from 0–20); C, compulsions (from 0–20); YBOCS, Yale-Brown obsessive-compulsive scale ranges from 0–40 with higher scores indicating worse function; GAF, Global Assessment of Functioning score ranges from 0–90 with higher scores indicating the normal function; CGI, clinical global impression score ranges from 1–7 with higher score indicating the severity of the disease.

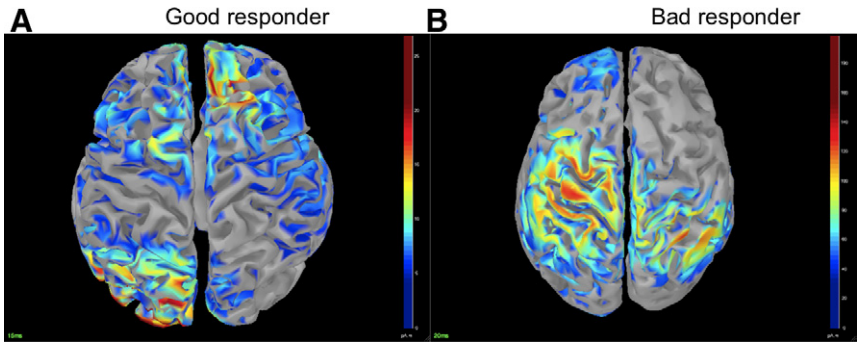

Figure 3. Electroencephalographic source localization of cortical power evoked by subthalamic nucleus-deep brain stimulation (STN-DBS). Example of electroencephalographic source localization evoked by 3 Hz STN-DBS in a patient who responded well to STN-DBS (**A**) and in a patient who did not respond to the stimulation (**B**). Note that in the nonresponder patient, 3-Hz stimulations evoked responses mainly around the central gyrus whereas in the responder patient, 3-Hz stimulations evoked responses more anteriorly in the prefrontal region.

or licking. He also suffered for substance abuse (alcohol consumption used for presume anxiolytic effect according to the patient) that he stopped 1 year before his inclusion in the study. Several medications were tried, all unsuccessful for the past 10 years (fluoxetine, sertraline, paroxetine, venlafaxine, clomipramine, alone or in associations plus risperidone or pimozide at the maximum tolerated doses) as was CBT.

He was implanted with bilateral electrode in the noM-STN. Postoperative MRI confirmed the position of the electrode within the anterior part of the STN. Of interest, during surgery, the patient reported a sensation of well-being correlated with the stimulation that was attributed by the patient as an "antianxiety-like effect" of the stimulation. During the postoperatory period during which parameters of stimulation were assessed, a hypomanic state could be noticed that resumed when the stimulation was reduced in amplitude. A possible subthalamotomy-like effect was noticed after surgery; the patient was still having severe OCD symptoms but with significant reduction of licking compulsion. However, a significant effect alleviation of OCD symptoms appeared quickly after stimulation and after 6 months of stimulation. The clinical severity, assessed by the YBOCS, was improved by 75% (**Table 2**) allowing a professional reintegration perspective and improving his social and family functioning.

Case 2. This 43-year-old woman suffered from OCD since she was 11 years old. OCD symptoms consisted mainly in "just right" obsessions accompanied by magical thinking with repeating, checking, tapping or rubbing, and washing compulsions. Her quality of life was severely impaired and led to an early school interruption. Her daily activities consisted mostly in her rituals, leading to a social withdrawal and blocking any professional reintegration. The patient was unemployed for many years (she had a total of only 4 years of employment in her life). The different medications (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram; clomipramine, amytryptilline, alone or associated with olanzapine, risperidone, cyamemazine, levomepromazine or anticonvulsants such as carbamazepine, different benzodiazepines), electroconvulsive therapy, and several attempts of CBT were unsuccessful. She was implanted with bilateral electrodes within the noM-STN and surgery was uneventful. No anti-OCD effect was noticed during surgery or during the postoperatory period. Despite this, a slight improvement in OCD condition appeared within 1 month after implantation (less "tyrannical" with her OCD against the family circle). She improved significantly during the next 3 months and at 6 months, her condition was dramatically (71%) improved (**Table 2**), which allowed her to gain autonomy.

Case 3. This 35-year-old woman started complaining with OCD at age 20 years with a progressive invalidating evolution, first in the family circle and later in the professional domain. The severity of her OCD leaded to important marital difficulties and to her unemployment 1 year before surgery, despite a clear but insufficient improvement due to different medications (paroxetine, sertraline, clomipramine, and lithium,) and psychotherapy (CBT and psychodynamic therapy). Her main obsessions focused on contamination theme with excessive concern about dirt or germs, but she also described some ordering obsessions that were accompanied by complex washing and cleaning rituals followed scrupulously by herself but also imposed on the whole family. As a consequence, social and professional negative impact increased her subjective suffering, which eventually led her to ask for surgery. Although there was a slight and transitory mood improvement due to electrode implantation, OCD significantly improved (78%) only after the stimulation was started. Clinical improvement was associated with a mild impulsivity that resolved after progressive stimulation intensity adjustment.

Case 4. This 36-year-old patient, with an obsessive personality disorder, was suffering from OCD for 17 years, which led to an important social and family negative impact and interference with his professional life. His OCD mainly consisted in contamination obsessions with excessive concern about dirt or dust, accompanied by complex and time-consuming cleaning rituals. A significant resistance to CBT and different serotoninergic medications (paroxetine, sertraline, clomipramine) has been noticed. The patient developed a serotoninergic syndrome with clomipramine (75 mg/day), although he had already been treated with much higher doses in the past (450 mg/day). After surgery, a transient and mild improvement of OCD that lasted less than 1 week (subthalamotomy-like effect) was noticed. During the postoperatory period, a subcutaneous infection at the frontal level required surgical cleaning and antibiotics for 3 months, which avoided the removal of the leads. Stimulation was limited by right inferior limb motor contraction, which required optimization of parameter settings, mainly bipolar stimulation. In the right lead, one of the contacts located in the STN was not usable due to very high impedance. Despite different stimulation adjustment, only limited clinical improvement was achieved at 6 months, with no improvement in his GAF. Electroencephalographic (EEG) source localization of DBS responses performed in this patient suggested that at least one of the lead activated the central motor area (**Figure 3**).

DISCUSSION

Responder versus Nonresponder

In our cohort, one patient (case 4) responded partially (improvement of about 34%) to chronic stimulation despite optimal anatomic placement of the lead within the anterior part of STN, and despite multiple stimulation parameter settings (monopolar, bipolar, stimulation of multiple contacts). In this patient, neither the semiology of OCD symptoms, nor his past history and medication, differed from other patients who did respond to the stimulation. However, several issues were raised during chronic stimulation: 1) due to hardware problem, one of the contacts (contact 1, located in the STN) could not be chronically stimulated on the right side; 2) left chronic monopolar stimulation on contact 4 resulted in a contralateral motor side effect, defined by the patient as a feeling of mild stiffness, which made this contact unavailable for chronic stimulation. To investigate the possible functional misplacement of the lead, we performed a EEG localizing source study using 96-channel EEG, which we compared to an EEG from a patient with OCD who did respond to chronic STN-DBS. Toward that goal, the stimulator was set at 3 Hz to be able to measure evoked potentials to DBS after averaging on stimulation artifacts. After artifact correction, a standard distributed source analysis of the evoked response was performed using the minimum norm approach and source power averaged during a 100-ms period after DBS pulses was plotted on a mesh of the cortical mantle of the patient.

The main results of this preliminary study were as follows. In the nonresponder patient, only the brain region located around the central sulcus was significantly activated, whereas in the responder patient, the orbitobasal and prefrontal cortex were activated (**Figure 4**). Also, the cortical evoked responses were asymmetric in the responder patient, mainly left sided. These preliminary results must be taken cautiously because of the number of patients (case control series) and of the relative high sensitivity of EEG source localization technique to DBS artifact filtering. However, it gives some insights in the neuronal networks that are actually modulated by DBS that one would be able to obtain during the patient's follow-up. Potentially after correlation with clinical scores the neuronal network that needs to be modulated by DBS to obtain a clinical response. Also, one can imagine that even if the leads were accurately placed in the anterior part of the STN, it remains possible that the distribution of STN motor and nonmotor neurons was different in this patient. This, if confirmed, would potentially lead us to reoperate on the patient and place the electrodes differently.

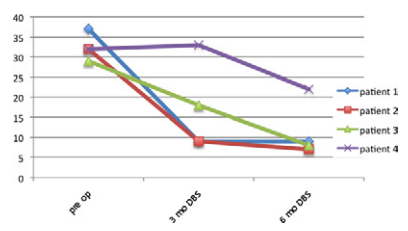

Figure 4. Graph showing the Yale-Brown obsession compulsion scale score of all patients at baseline, and after 3 and 6 months of stimulation. First 3 patients improved by more than 70% after 6 months of stimulation but patient 4 was not considered as responder (<35 % of improvement). DBS, deep brain stimulation.

Place of STN Among Other Targets

Since the past decade DBS has replaced lesions and several targets are potentially effective against severe OCD. STN appears to be a new challenger for several reasons: 1) preliminary results are very encouraging and show up to 78% improvement in the present small series that will have to be confirmed by larger studies with longer follow-up; 2) STN is a well-known structure as surgeons and neurologists have stimulated this target for the past two decades for PD; 3) the anatomic definition of the nonmotor STN can be determined on MRI (directly or indirectly) and the surgical targeting is potentially well known by surgeons who are treating in routine PD by DBS; 4) biomarkers of the nonmotor STN can be obtained during intraoperative MRI scans, which facilitates the targeting; and 5) voltage required for efficacy is lower than that used in anterior capsule or striatum and might be economically efficient.

However, one must be cautious when setting up the voltage to avoid hypomania, which has to be anticipated and managed during the first hours and days of stimulation. Larger studies will have to demonstrate that STN-DBS can be a safe strategy to treat patients with severe OCD.

CONCLUSION

Surgical treatment of psychiatric disorders in general, and for OCD in particular, is entering a new area because options, such as DBS, can be proposed in addition to conventional lesions or gamma knife surgery. Among DBS targets that are currently investigated, the nonmotor subdivision of the STN is promising. Our preliminary results show a benefit of STN-DBS that can reach 50%–75% on the YBOCS. Side effects are voltage-dependant and comprise hypomania and anxiety, which require fine-tuning but are transient in most of the cases, except with weight gain as was observed in two patients. Chronic DBS parameter settings are similar to those routinely used for PD. In particular, the voltage required to observe therapeutic effect is low and permits great longevity of the battery.

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