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ORIGINAL RESEARCH

# Deep brain stimulation of the subthalamic nucleus in obsessive–compulsive disorders: long-term follow-up of an open, prospective, observational cohort

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## ABSTRACT

**Background** Obsessive–compulsive disorder (OCD) is a major cause of disability in western country and responsible for severe impairment of quality of life. About 10% of patients present with severe OCD symptoms and require innovative treatment such as deep brain stimulation (DBS). Among possible targets, the non-motor subthalamic nucleus (STN) is a key node of the basal ganglia circuitry, strongly connected to limbic cortical areas known to be involved in OCD.

**Method** We analysed, in a prospective, observational, monocentric, open label cohort, the effect of chronic non-motor STN-DBS in 19 patients with treatment-resistant OCD consecutively operated in a single centre. Severity of OCD was evaluated using the Yale and Brown Obsessive–Compulsive Scale (YBOCS). YBOCS scores at 6, 12 and 24 months postoperatively were compared with baseline. Responders were defined by >35% improvement of YBOCS scores. Global Assessment Functioning (GAF) scale was used to evaluate the impact of improvement.

**Results** At a 24-month follow-up, the mean YBOCS score improved by 53.4% from  $33.3 \pm 3.5$  to  $15.8 \pm 9.1$  (95% CI 11.2–20.4;  $p < 0.0001$ ). Fourteen out of 19 patients were considered as responders, 5 out of 19 being improved over 75% and 10 out of 19 over 50%. GAF scale improved by 92% from  $34.1 \pm 3.9$  to  $66.4 \pm 18.8$  (95% CI 56.7–76.1;  $p = 0.0003$ ). The most frequent adverse events consisted of transient DBS-induced hypomania and anxiety.

**Conclusion** Chronic DBS of the non-motor STN is an effective and relatively safe procedure to treat severe OCD resistant to conventional management.

## INTRODUCTION

Obsessive–compulsive disorder (OCD) is a major cause of disability worldwide<sup>1</sup> and responsible for severe impairment of quality of life. It is one of the most frequent psychiatric conditions just after depression and affects 2%–3% of the population. OCD is characterised by recurrent unwanted ideas, images or impulses (obsessions), and repetitive stereotyped behaviours or mental acts (compulsions), often intended to neutralise the anxiety induced by the obsessions. Several obsessions types can be defined<sup>2,3</sup> like contamination, pathological doubt, somatic, need for symmetry,

aggressive, sexual and other that will lead to associated compulsions such as counting, checking, hoarding, washing, symmetry and precision. These symptoms are supported by different neuronal networks<sup>4,5</sup> that may be of therapeutic interest and the variability of symptoms mirror their heterogeneity in response to conventional treatment. About 30%–40% of patients present with severe (Yale and Brown Obsessive Compulsive Scale (YBOCS) 24–31) to very severe (YBOCS 32–40) OCD symptoms.<sup>5,6</sup>

OCD usually tends to be chronic and might require long-term medication and cognitive-behaviour therapy (CBT). Indeed, first-line treatments for OCD consist of CBT, including exposure and ritual prevention associated or not with medications, particularly serotonin reuptake inhibitors.

The above-mentioned conventional treatment can lead to satisfactory responses but improvement after medication and CBT is usually partial and consequently, a 35% reduction in YBOCS severity scores can be seen as a good response to the treatment and represents a typical response criterion in pharmacological trials. Despite conventional treatment, approximately 10% of patients with OCD remain severely disabled.<sup>7</sup>

Multimodal functional imaging studies have led to a better definition of key brain structures involved during the expression of OCD symptoms.<sup>8–10</sup> The orbital frontal region, the dorsolateral prefrontal cortex and the dorsal cingulum have been identified as key areas during the occurrence of OCD. At the subcortical level, bundles going through the anterior capsule have been identified as key neuronal streams that connect the thalamus to the orbitofrontal region. The accumbens nucleus has also been seen as a pivotal node due to its role in the reward system that is supposedly overactivated in OCD.

The better comprehension of the neuronal circuitry that links motor, cognitive and limbic cortex to the thalamus and the basal ganglia has rendered new surgical strategies possible. In 1999, Nuttin *et al*<sup>11</sup> have proposed to replace lesions of the anterior limb of the capsule by deep brain stimulation (DBS), a surgical therapy developed to treat movement disorders.<sup>12</sup>

One of the key nodes of this neuronal circuitry is the subthalamic nucleus (STN), which receive not



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only hyperdirect connections from the motor and non-motor cortex, but also indirect inhibitory connections from the striatum through the Globus Pallidus externus.<sup>13 14</sup> From a clinical stand point, a posteroanterior gradient from motor, cognitive and limbic territories can explain why stimulations of the posterior and dorsal part of the STN in patient with Parkinson's disease (PD) can alleviate motor symptoms, whereas the more anterior and ventral site of stimulation can impact non-motor symptoms of PD.<sup>15</sup>

This was illustrated by the report of three cases of patients with PD, who also suffered from OCD as a comorbidity, and who improved after STN-DBS.<sup>15 16</sup> In those cases reports, the motor STN was the original target but the leads were a little bit more anteriorly placed, at the junction between motor and non-motor STN (noM-STN). Mallet *et al*<sup>17</sup> reported in 2008 the results of the French multicentre, double-blind, cross-over control study (STOC study) assessing the effect of noM-STN-DBS to treat patients with severe OCD. They mainly showed that the YBOCS was significantly improved by 31% on average as compared with Off condition.

Following this study, we prospectively followed, in an open, observational, prospective, monocentric cohort, 19 consecutive patients suffering from severe OCD refractory to conventional management in order to (1) confirm the potential effectiveness of STN-DBS at short-term and long-term follow-ups (24 months) and (2) assess the safety of STN-DBS for OCD.

**MATERIALS AND METHODS**

All patients gave informed consent before their inclusion in the surgery programme. Inclusion and exclusion criteria strictly followed those previously used in the STOC study.<sup>17</sup> One of the senior coauthors asked the French National Ethical Committee to approve such procedure and a multidisciplinary committee selected the cases to be enrolled.<sup>18</sup> Most of them were referred to by independent psychiatrists.

**Inclusion criteria and ethics (see table 1)**

**Surgery**

The surgical technique used replicated that routinely used to treat patients with PD with STN-DBS<sup>12</sup> except that the OCD target was slightly more anterior and medial.<sup>19</sup> In the first 11 patients, the indirect targeting of the motor STN (M-STN) was determined on the ventriculography schema fused with the MRI and corresponded to the following coordinates: 7 of 12 of the anterior-posterior commissural (AC-PC) length posterior to the AC, 11–12 mm lateral to the midline and 3 mm below the AC-PC line. In patients with OCD, the non-motor-STN (noM-STN) was targeted 2 mm anterior and 1 mm medial to the motor target. Final DBS leads (model 3389, Medtronic, Minneapolis, USA) positioning was refined after microelectrode recordings and microstimulation. More precisely, trajectories that showed STN neuronal activities that responded to proprioceptive movements of the wrist or the leg, indicating the sensorimotor subregion of the STN, or those in which intraoperative stimulation induced motor contraction (indicating capsular current diffusion or too lateral implantation) or ipsilateral eye adduction (indicating diffusion to oculomotor fibre tract or too medial implantation), were rejected.

For the last eight patients, direct targeting was performed based on the visualisation of the STN on 3T MRI scans (T2 sequences). To that aim, we first drew a line at the most anterior border of the red nucleus, and this line delineated, when crossing the STN,

**Table 1** : Main inclusions and exclusions criteria

	Inclusion criteria	Exclusion criteria
OCD defined by DSM-IV	Yes	Yes: bipolar disorder, schizophrenic disorder; current substance abuse or dependence (except nicotine)
Cluster A/B personality disorders	NA	Yes
Recent severe depression	NA	Yes ▶ MADRS score >20 ▶ Risk of suicide (MADRS item-10 score >2)
Age	>18	NA
YBOCS	>25	NA
GAF	<45	NA
CGI	>4	NA
Medications	Failure of three serotonin reuptake inhibitors including clomipramine after a minimum of 12 weeks of adequate treatment and two augmentation strategies	NA
Psychotherapy	Failure of cognitive behavioural therapy conducted during at least 1 year with two therapists	NA

CGI, Clinical Global Impression; DSM-IV, Diagnostic And Statistical Manual Of mental Disorders- 4 th edition; GAF, Global Assessment Functioning; MADRS, Montgomery-Asberg Depression Rating Scale; NA, not applicable; OCD, obsessive-compulsive disorder; YBOCS, Yale and Brown Obsessive-Compulsive Scale .

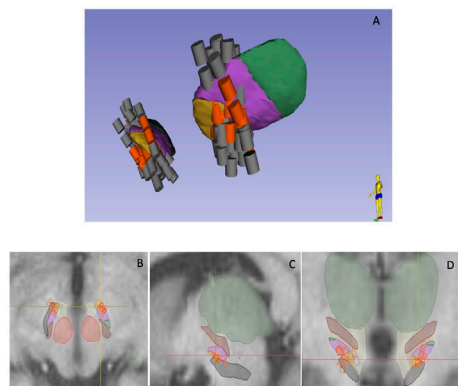
the motor target position. We then marked the point located 2 mm anterior and 1 mm medial to that motor target, in the anteroposterior direction of the main axis of the STN.<sup>17 19</sup> Then, a frameless, robot-assisted surgery was performed using ROSA robotic arm and Rosanna software (Zimmer Biomet, USA) that allowed the fusion of all imaging modalities including preoperative CT scan, T1 and T2 MRI and intraoperative, tele X-ray. All patients had postoperative CT scan before the implantation of the battery (Kinetra then Activa PC, Medtronic, Minneapolis, USA) that occurred 2 days after lead implantation. Surgery was performed in all cases except one under local anaesthesia that allowed intraoperative checking for side effects and for possible acute therapeutical effects.

**Clinical evaluation and outcome measures**

The severity of OCD was evaluated with the YBOCS. Patients were defined as responders if their YBOCS scores decreased by at least 35%. The social and psychological functioning was assessed with the Global Assessment Functioning (GAF) scale.

All patients were prospectively evaluated at 6, 12 and 24 months than once a year. However, patients were also visited when needed to adjust settings parameters. Neither the clinicians nor the patients were blinded during the study. Medications could be adjusted whenever required. However, limited therapeutical adjustments were possible due to the pharmacoresistance of the OCD symptoms already experienced during the preoperative period.

All adverse events (AEs) related to surgery and to stimulation were systematically reported in a database.



**Figure 1** Location of active contacts implanted in the non-motor STN and plotted onto the Yelnik and Bardinet atlas. (A) 3D representation of two STN with functional subdivision (yellow=limbic territory, pink: cognitive territory, green: motor territory). (B–D) Axial, sagittal and coronal 2D views, respectively, STN, subthalamic nucleus.

### Study design and statistics

This was an open, prospective, observational cohort followed at a long-term follow-up focusing mainly on the safety and efficacy of noM-STN-DBS. All patients and clinicians were aware of the stimulation conditions. All values were expressed as mean $\pm$ SD. YBOCS scores were compared at 6, 12 and 24 months with baseline scores using an analysis of variance Friedman test followed by Dunn's multiple tests. GAF scores were compared at 24 months using a Wilcoxon matched pairs signed-rank test. The gender distribution among the responders was studied using a Fisher exact test. Statistical tests were performed using software GraphPad InStat V.3 (GraphPad Software, California, USA). A difference was considered statistically significant for a p value <0.01.

### Leads and contact locations

A postoperative stereotactic 1.5 T MRI or, for the last eight cases, a postoperative CT scan was obtained in all patients. All postoperative images were plotted onto an adaptable atlas developed by Yelnik *et al.*<sup>20</sup> This 3D atlas allowed localising each lead and active contact used during the chronic phase of stimulation within the subregion of the STN (figure 1).

### Parameters settings

Postoperative settings of stimulation parameters followed a pre-established procedure and consisted of successive trials of monopolar stimulation, beginning with the most ventral pair of contacts and followed by the more dorsal contacts. Voltage was increased progressively by 0.5 V steps until side effects were obtained.

All stimulators were set at a frequency of 130 Hz and at a pulse width of 60  $\mu$ s using a single monopolar, cathodal contact (case being positive).

## RESULTS

Between 2005 and 2013, 19 patients (7 male and 12 female individuals) have been operated in our neurosurgery department. The first four were enrolled in the STOC study and two patients were enrolled in a separate multicentric study ('Unibil study' and STOC 2). The clinical features of the patients are summarised in table 2. In this cohort, medications could be modified before and after surgery, but in fact, those medications were not changed to an extent that could in our opinion have changed the evolution

of their disease, mainly because all those medications were used before surgery without success.

### DBS effects on YBOCS and GAF scores

Data are reported in table 3. In patient 2, the stimulation was stopped at 6 months due to personality disorders that were revealed during the follow-up and not detected at the time of the enrolment in the STOC (

Stimulation dans le Trouble Obsessionnel Compulsif)

After 6 months of chronic stimulation, the mean YBOCS score decreased from 33.2 $\pm$ 3.6 to 18.2 $\pm$ 9.5 points (95% CI 13.4–22.9; 44%; p<0.0001). Ten patients out of 18 were considered as responders, defined as a YBOCS score improved by at least 35 %, with a mean decrease of the YBOCS score of 65% (33 vs 11.2, respectively) as compared with 8 patients who did not respond (YBOCS: 25.4%, 30.3 vs 24).

At a 12-month follow-up, the mean YBOCS score decreased from 33.2 $\pm$ 3.6 to 17.3 $\pm$ 10.2 points (95% CI 12.3–22.4; 49.4%; p<0.0001). At the subgroup level, 2 additional patients were considered as responders (patients 8 and 9) with a mean decrease of the YBOCS score of 60.5% (YBOCS: 33 vs 10.2), whereas patient 11 did not respond any more. The non-responder subgroups had a mean decrease in the YBOCS score of 13.2% (YBOCS: 30.3 vs 24.2).

At a 24-month follow-up, the mean YBOCS score decreased from 33.3 $\pm$ 3.5 to 15.8 $\pm$ 9.1 points (95% CI 11.2–20.4; 53.4%; p<0.0001). At the subgroup level, three additional patients were considered as responders (patients 4, 11 and 15) with a mean decrease of the YBOCS score of 58.3% (YBOCS: 33 vs 11.8). The non-responders subgroup had a mean decrease in the YBOCS score of 9.3% (YBOCS: 30.3 vs 22.6).

Importantly, no patient worsened after stimulation between baseline and 24 months follow-up. At 24 months, 14 out of 19 (we included for final analysis, patient #2 even if he was not analysed at 24 months) were considered as responders, with 5, 5 and 4 patients being improved more than 75%, 50% and at least 35%, respectively (figure 2).

The GAF scale was significantly improved from 34.1 $\pm$ 3.9 to 66.4 $\pm$ 18.8 (95% CI 56.7–76.1; improvement of 92%) at a 24-month follow-up (p=0.0003) (figure 3).

### Responders versus non-responders

At a 2-year follow-up, 14 patients had an improvement of at least 35% and were considered as responders. No differences regarding age at onset, at surgery and duration of the disease were noticed. The ratio of female/male was significantly higher in the responder group (p=0.0018) and all female individuals were responding to the therapy (table 5).

Regarding the type of obsessions and compulsions, no statistically significant differences were shown between the two groups of patients.

### Stimulation parameters and active contacts

The Medtronic 3389 lead model was used in all patients, connected to a Kinetra or an Activa PC. Voltage ranged from 1.1 to 3.6 and was adapted if required. Stimulation of the non-motor (limbic-associative) territories could be limited by behavioural side effects like disinhibition of behaviour, agitation, anxiety, euphoria and mania. To avoid them, the increase in stimulation parameters was performed progressively in an inpatient setting in our institution in the immediate postsurgical period. In most of the cases, after the clinical response, the voltage was set and remained stable over time. At the last follow-up, nine patients

Table 2 Clinical features of the patients

Patient (gender/age)	Age at onset (years)	Duration disease (years)	Pre-op meds (mg/D)	OCD type	Comorbidity	Pre-op YBOCS (O+C)
1 (M/39)	21	18	Fluvoxamine 200 mg; clonidine 0.3 mg; pimozide 1 mg	A	Tourette	18+19=37
2 (M/51)	16	35	Fluoxetine 20 mg; prazepam 20 mg	C	Personality disorder; ICD (kleptomania)	18+17=35
3 (F/43)	11	32	Risperidone 4 mg; sertraline 100 mg; alprazolam 0.75 mg	C-R		16+20=36
4 (F/42)	17	25	Fluoxetine 20 mg; venlafaxine 75 mg; valproate 1000 mg; levomepromazine 25 mg; bromazepam 6 mg	W	Kleptomania (ICD); depression; past suicide attempts	15+15=30
5 (F/34)	10	24	Paroxetine 60 mg	W		17+17=34
6 (F/35)	20	15	Clobazam 5 mg; prazepam 10 mg; lamotrigine 75 mg; escitalopram 30 mg; zolpidem 10 mg	C	Left temporal surgery (3 y before DBS) for refractory epilepsy	14+15=29
7 (F/37)	32	5	Venlafaxine 150 mg; bromazepam 9 mg	C-R		14+18=32
8 (F/52)	27	25	Clomipramine 50 mg; citalopram 20 mg; hydroxyzine 200 mg; zopiclone 7.5 mg	W		20+20=40
9 (F/38)	27	11	Sertraline 100 mg; clonazepam 2 mg; zolpidem 10 mg; piribedil 150 mg	W		18+18=36
10 (M/36)	19	17	Paroxetine 50 mg	W	Anankastic personality	17+15=32
11 (F/40)	25	15	Fluvoxamine 200 mg; clomipramine 75 mg; oxcarbazepine 600 mg; clonazepam 2 mg; zolpidem 10 mg if needed	W	History of eating disorder, alcoholism, 1 seizure; pruritus	19+17=36
12 (F/54)	32	22	Paroxetine 50 mg; lorazepam 3 mg; zopiclone 7.5 mg	C	Depression; Minkowski-Chauffard syndrome with splenectomy; osteoporosis	17+16=33
13 (M/27)	17	10	Sertraline 150 mg; amisulpride 300 mg	C-R	Hypersomnia	18+20=38
14 (M/34)	21	13	Buspirone 30 mg; cyamemazine 150 mg; clomipramine 187.5 mg	C-R		16+16=32
15 (F/31)	7	24	Venlafaxine 75; levothyroxine 125 mg/j	C	Hypothyroidia; ICD (dermatillomania)	16+18=34
16 (M/46)	20	26	Paroxetine 40 mg	C-H	Social phobia	15+18=33
17 (M/55)	16	39	Acamprosate 1998 mg	C-R	History of addiction and suicide attempt history of tuberculosis	15+16=31
18 (F/36)	18	18	Escitalopram 30 mg	A	Baby birth at M10	12+13=25
19 (F/33)	12	21	Venlafaxine 225 mg; alprazolam 0.375 mg	C	ICD (dermatillomania)	15+15=30

\*OCD type: C: doubt/checking; W: contamination/washing; A: aggressive; H: hoarding; R: repetitive, just right obsessions.

ICD, Impulsive Compulsive Disorder; OCD, obsessive-compulsive disorder; Pre-op, preoperative; YBOCS, Yale and Brown Obsessive-Compulsive Scale.

had a monopolar stimulation and eight had two cathodes turned ON, the case being positive in all cases. One patient was stimulated using a bipolar mode. Contacts 1 and 5, located at the ventral part of the noM-STN, were the most preferred contacts used in 14 patients (table 6).

Patients with STN-DBS in the noM-STN typically develop euphoria, agitation, hyperactivity, decrease in sleep time and disinhibited behaviours, as also described in PD<sup>21 22</sup> and in our experience, this is indicative of best electrode localisation. Acute psychotropic effects of STN-DBS seen within 24 hours after switching on or increasing stimulation amplitude is used as a positive predictor of localisation in noM-STN and improvement in OCD, similar to dyskinesia that can guide towards motor STN in PD. The main side effects of STN-DBS in anteromedial localisation of STN electrodes are ipsilateral eye adduction as a consequence of current diffusion to the oculomotor fibre tract. In such localisation, the patients can also subjectively complain about double vision, which can be avoided by decreasing stimulation intensity, choosing a more dorsal contact or using bipolar stimulation. Double monopolar stimulation is rarely used in the absence of offside effects if two adjacent contacts both induce beneficial but too small effects without side effect.

### Adverse events

Most of the AEs were related to the simulation and consisted of hypomania in three cases and anxiety reactions in three cases. Impulsivity, irritability and behavioural disinhibition were the most frequent AE encountered during post op period. Four patients experienced contralateral dyskinesia during the ramping up of parameters settings that resumed just after stimulation adjustment. One patient showed contralateral pyramidal contraction at 3 V that also vanished after decreasing the amplitude of stimulation. AEs related to surgery were represented by an extracranial infection at the level of the lead that required a surgical cleaning and antibiotics for 3 months without any removal of the lead. Another patient suffered from a postoperative left thalamic contusion with a dysarthria at a 6-month follow-up, mild but persistent at the last follow-up. No seizures were noticed in any of the patients (table 7).

During the first year of follow-up, two patients had transient suicidal ideation. However, at the time of finalising this report, two patients died from suicide at 3-year and 5-year follow-ups. The first one was a woman who experienced a 90% reduction in the YBOCS at 2 years. She committed suicide in the context of a reactive depression unrelated to her OCD. The second patient



**Table 3** Effects on YBOCS and GAF

Patient	Baseline YBOCS (O+C)	Baseline GAF	YBOCS 6 m (% improvement)	YBOCS 12 m (% improvement)	YBOCS 24 m (% improvement)	GAF 24 m (% improvement)
1	18+19=37	26	12 (67)	21 (43)	18 (51)	67 (61)
2	18+17=35	36	26 (25)	NA	NA	NA
3	16+20=36	32	7 (80)	7 (80)	5 (86)	85 (62)
4	15+15=30	36	20 (33)	20 (33)	18 (40)	68(47)
5	17+17=34	36	8 (76)	10 (70)	8 (76)	85(57)
6	14+15=29	36	10 (65)	6 (79)	12 (58)	56(35)
7	14+18=32	33	7 (78)	3 (90)	4 (87)	87(62)
8	20+20=40	33	28 (30)	16 (60)	14 (65)	58(43)
9	18+18=36	32	30 (16)	6 (83)	6 (83)	87(63)
10	17+15=32	41	21 (34)	28 (12)	28 (12)	48(14)
11	19+17=36	34	20 (44)	30 (16)	18 (50)	60(43)
12	17+16=33	30	2 (94)	2 (94)	2 (94)	87 (65)
13	18+20=38	30	20 (47)	22 (42)	23 (39)	50 (40)
14	16+16=32	35	26 (18)	26 (18)	27 (15)	50 (30)
15	16+18=34	40	31 (8)	30 (11)	22 (35)	MD
16	15+18=33	31	31 (6)	32 (3)	29 (12)	36 (13)
17	15+16=31	38	29 (6)	28 (9)	29 (6)	40 (5)
18	12+13=25	40	11 (56)	12 (52)	7 (72)	98 (59)
19	15+15=30	37	15 (50)	14 (53)	15 (50)	68 (45)
Mean (SD)	33.31 (3.54)	34.52 (3.89)	18.63 (9.42)	17.38 (10.71)	15.83 (9.61)	66.47 (27.48)

Patient two disrupted follow-up in our centre due to personality disorders, the IPG was removed 3.5 years after implantation after request of the STOC Study PI.

GAF, Global Assessment Functioning; IPG, Internal Pulse Generator; STOC, Stimulation dans le Trouble Obsessionnel Compulsif; YBOCS, Yale and Brown Obsessive–Compulsive Scale.

was not improved at a 2-year follow-up and asked for suicide assistance in a different European country without our knowledge, and died. We were not aware of this patient's request and were not informed when the patient passed away (for more details, see the online supplemental material).

## DISCUSSION

To our knowledge, this is the largest report of the long-term follow-up of STN-DBS in a series of patients with severe, refractory OCD with long-lasting obsessions and compulsions. This paper reinforces the previous study of STN-DBS for OCD, which was recently updated at the long-term follow-up.<sup>23</sup>

Despite being the first randomised controlled study in psychosurgery, and despite publication in one of the highest-ranking journals, the STOC study did not have a relevant impact in psychiatry up to now. We were however highly impressed by the outcomes of our first patients, more so than in STN-DBS in PD as patients with OCD are younger, have a more severe impairment in quality of life than PD patients. As they do not have a degenerative progressive disorder, an efficacious symptomatic treatment will have life-long benefit. In this setting, after Prof Benabid had asked the French National Ethical Committee for authorisation

to perform DBS in refractory OCD, the present study was aimed at looking at the long-term follow-up and safety.

Indeed, safety was the first concern in this population suffering from a non-degenerative disorder. Surgery was well tolerated in all patients except one who experienced a left thalamic contusion responsible for mild partially reversible dysarthria and for another one who had a hardware-related complication. AEs related to stimulation were all reversible (see table 7) after decreasing the voltage. The active contacts were located into the anterior part of the STN in all cases, but in one patient, the stimulation induced motor contraction at a low threshold, whereas the lead location was indeed into the anteromedial part of the STN.

No seizures were reported in our series, which contrasts with other studies that reported a high rate of seizures (5/24 reported by Luyten *et al*<sup>24</sup>). The low voltage used in our patient might be one of the explanations for that, associated with the fact that STN stimulation has been reported in animals and in epileptic patients to have a possible antiepileptic effect.<sup>25 26</sup>

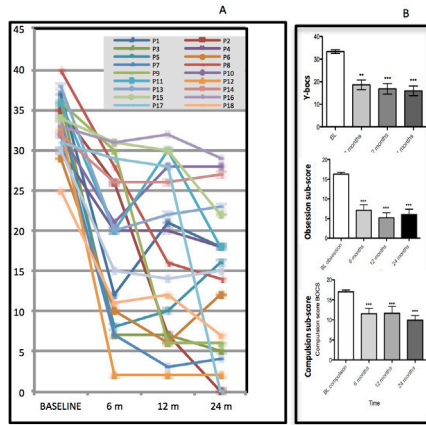
The severity of OCD was significantly improved over time (mean decrease of the YBOCS: 53.4% at 24 months) as did the number of responders (14 out of 19 at 24 months). Our results

**Table 4** Statistical analysis of YBOCS and GAF at the group level

	Baseline		6 months				12 months				24 months			
	Mean(SD)	95% CI	Mean (SD)	95% CI	%	P value	Mean (SD)	95% CI	%	P value	Mean (SD)	95% CI	%	P value
YBOCS total score	33.3 (3.5)	31.7–34.9	18.6 (9.4)	14.4–22.8	44	***	16.8 (10.2)	12.2–21.4	49.4	***	15.5 (9.4)	11.1–19.9	53.4	***
Obsession score	16.3 (1.9)	15.2–17.3	7.1 (6.2)	4.3–9.9	56.5	**	5.2	2.6–7.8	69	**	5.8 (5.5)	2.9–8.6	64	**
Compulsion score	17 (1.9)	15.9–18.1	11.5 (5.9)	8.8–14.2	32.4	**	11.6	8.2–15	32	**	9.7 (4.7)	7.3–12.1	42	**
GAF score	34.5 (3.9)	32.8–36.2	NA				NA				66.4 (18.8)	58–74.9		**

\*\*\*p<0.0001; \*\*p<0.0005.

GAF, Global Assessment Functioning; YBOCS, Yale and Brown Obsessive–Compulsive Scale.

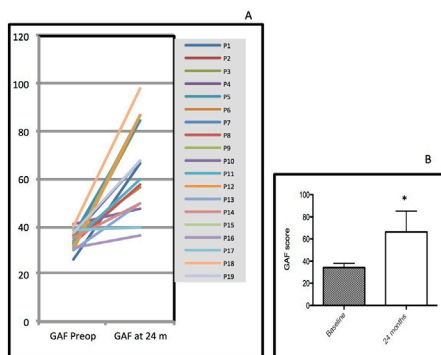


**Figure 2** (A) Individual (all patients) YBOCS scores at baseline, 6, 12 and 24 months postoperatively. (B) Averaged YBOCS scores and subscores for obsessions and compulsions at baseline, 6, 12 and 24 months postoperatively. YBOCS, Yale and Brown Obsessive–Compulsive Scale; \*\*,  $p < 0.0005$ ; \*\*\*,  $p < 0.0001$ .

confirm the favourable long-term outcome reported by Mallet *et al* who showed that 9 out of 14 patients were full responders at the last follow-up, with a median improvement of 50%.<sup>23</sup>

Up to now, only one paper from our group has reported the outcome at a very long-term follow-up of an OCD case as a comorbidity in Gilles de la Tourette syndrome treated by noM-STN-DBS<sup>27</sup> that illustrated the long-term efficacy of this technique applied on a new target, the noM-STN. In the present study, the same target located in the anteromedial STN was used in all patients and parameter settings were similar to those usually used in patients with PD. This could be seen as an advantage of this target as the voltages used during chronic stimulation were quite low saving current drain and increasing battery life and thus decreasing cost and complications.

The results of the present study confirm also the value of DBS as a surgical technique to treat severe OCD with good outcomes at a long-term follow-up. The vast majority of patients worldwide have been implanted in the anterior capsule or in the nucleus accumbens with similar results on the YBOCS. Denys *et al*<sup>28</sup> reported a series of 16 patients who received a bilateral chronic stimulation above the nucleus accumbens, with 9 out of 16 being considered as responders at 84 weeks. During the double-blind phase, a significant difference was found in 14 out of 16 patients between the OFF and ON phase. Nuttin's group<sup>29</sup>



**Figure 3** (A) Individual (all patients) GAF scores at baseline and 24 months postoperatively. (B) Averaged GAF scores at baseline and 24 months postoperatively. GAF, Global Assessment Functioning. \*\*,  $p < 0.0005$ ; \*\*\*,  $p < 0.0001$ .

**Table 5** Responders vs non-responders at a 24-month follow-up

	Responders (n=14/73.7%)	Non-responders (n=5/26.3%)	P value
Gender (M/F)	2–12	5–0	0.0018
Age at onset (years)	10.7±8	18.4±2.3	NS
Age at surgery (years)	38.6±7.4	44.4±9.2	NS
Duration	18.9±7.2	26±11.2	NS
Type of OCD			
C	7	3	NS
W	5	1	NS
A	2	0	NS
H	0	1	NS
R	3	2	NS

OCD type=C: doubt/checking; W: contamination/washing; A: aggressive; H: hoarding; R: repetitive, just right obsessions. A same patient can suffer from different types of OCD symptoms. NS, no statistically significant difference; OCD, obsessive–compulsive disorder.

have also reported their long-term follow-up of DBS of the bed nucleus of the stria terminalis. The responder rate at 3 years was 52% and improved over time to reach 65% at 6 years and was stable (60 %) at 9 years (but data were available only in 10 out of 24 patients). Some AEs were also reported.

Recently, a small series of patients have been implanted both into the anterior capsule and the STN, with four electrodes.<sup>30</sup> The result showed that DBS of the anterior capsule and STN were efficient to improve the severity of the OCD (reduction by 53% and 46%, respectively, of the YBOCS,  $p$ : NS) with a better effect on mood for the anterior capsule and a better effect on cognitive flexibility for the STN, probably due to the modulation of two close but distinct neuronal networks.

Surprisingly, GAF was improved in most cases at 24 months, even in patients who were not considered as responders. This average good improvement is partly explained by the number of good responders. But it is likely that other factors such as the

**Table 6** Active contacts and parameters settings at the last follow-up (2 years)

Patient	Active contacts		Voltage (R/L)
	Right	Left	
1	1	5	1.2
2*	2	6	1
3	2	6	4
4	1	5	1.3/1.5
5	1	5	1.3
6	2	6	1.3
7	2	6	1.5
8	1	5	1.1
9	0–1–	4–5–	1.6
10	1–2–	5–	2.3/1
11	1+2–	5+6–	3.3
12	1	5	1.5
13	1–2–	5–6–	3.6
14	1–2–	5–6–	1.9
15	1–2–	5–6–	2.4
16	0–1–	4–5–	1.6
17	0–1–	4–5–	2.3
18	0–1–	4–5–	2
19	0–1–	4–5–	1.6

\*Data available at 6 months postoperatively only.

**Table 7** Adverse events

Adverse event	Transient	Permanent
Surgery related		
Lead/wound infection	1	0
Headaches	2	0
cerebral contusion	1*	0
Dysarthria	0	1*
Delirium	1	0
Nocturnal enuresis	2	0
Hardware related	0	1
Stimulation related		
Hypomania	3	0
Mania	1	0
Dyskinesia	4	0
Anxiety	3	0
Contralateral motor contraction	1	0
Ipsilateral monocular deviation	1	0
Hemiballism	1	0
Impulsivity	5	0
Irritability	4	0
Suicidal ideation	2†	0
Suicide attempt (voluntary drug intoxication)	1	0
Behavioural disinhibition	4	0
Insomnia restless legs syndrome	2	0
Not related to DBS		
Diabetes type 2	0	1‡
Osteomuscular pain	2	0
<b>TOTAL</b>	<b>41</b>	<b>3</b>

\*Left thalamic contusion responsible for mild dysarthria.

†Occurred at 6 months and 9 months postoperatively.

‡Discovered at a 9-month follow-up.  
DBS, deep brain stimulation.

intense psychological support in this selected population might have played a role. Despite possible confounding factors, the severity of impairment in some functional aspects as revealed by a low mean GAF at baseline was dramatically improved at 24 months, suggesting that STN-DBS was effective not only on the YBOCS score but also on functioning and daily life activities. It has already been shown that patients with OCD who were treated with DBS improved their scores on the WHO Quality of Life Scale in all domains, except for the social domain.<sup>31</sup> A clinical trial dedicated to the study of quality of life after noM-STN-DBS has started and will address this issue (EQUOLOCS study: NCT02844049).

No differences among responders vs non-responders were noticed regarding age at surgery and duration of the disease. However, the female gender was statistically more represented in the responder group as compared with non-responders. This factor was not reported as a predictive factor of good response in a recent meta-analysis,<sup>32</sup> neither was the duration of the disease. However, we did not find any correlation between the late onset of the disease and good response to STN-DBS, in opposition to what has been reported.<sup>32</sup>

Regarding the position of active contacts, they were all located anteriorly, in a subregion of the STN in which cognitive and limbic neurons project. This strong anatomoclinical correlation is a major argument in favour of the use of STN, a well-defined anatomical target.

Two patients committed suicide, despite a very careful clinical evaluation before and after surgery. Suicidality is a complex situation in which several factors interfere. In a large Parkinsonian cohort followed in our institution for 23 years, suicide risk was

<1% over a period of follow-up of 9 years on average.<sup>33</sup> Suicide was more likely to occur during the first 3 years after STN-DBS surgery. The main risk factors were history of preoperative depression and suicidal ideation or attempts and higher depression scores on preoperative evaluation, arguing for selection bias. Surgery not only represents election bias, but can also be seen as a last chance by a patient, which may be dangerous as in these cases depression can be absent immediately before surgery that is creating hope. Deception based on unmet outcomes in this situation can favour reactive depression. It has been postulated that impulsivity triggered by STN-DBS might favour suicides directly via STN-DBS. However, suicides have been reported after surgery in different targets and in different diseases. For example, 2 of 16 patients with GPi (Internal Globus Pallidus)DBS in generalised dystonia without depression on preoperative evaluation committed suicide.<sup>34</sup> In favour of bias as a key factor is also the fact that PD patients randomised into DBS or best medical treatment group did not show statistically significant differences in suicidal outcome and no difference was seen between STN or GPi as targets.<sup>35</sup>

Postoperative suicides remain a major issue. Future studies will have to address this particularly in OCD where depression disorder is the most frequent comorbidity and the rate of suicides is very high. Indeed, patients with OCD have an increased risk of both attempting suicide (OR=5.45) and dying by suicide (OR=9.83), compared with matched controls.<sup>36</sup> A previous suicide attempt is the strongest predictor of death by suicide in an OCD cohort. Having a comorbid personality disorder and a substance use disorder also increases the risk of suicide in this population. As only the most severe and disabled patients are candidates for DBS surgery, one might expect even a higher suicide rate in such a biased population. Teams engaged in this surgery must be cognizant of this risk and must carefully monitor probably for the first 3 years after surgery, mood and suicide ideation.

This study has several limitations including mainly its uncontrolled design, the patient being aware of the condition of stimulation. However, the already published STOC study highlighted via a robust controlled, cross-over, double-blind design the acute effects over a short 3-month period. Another limitation may be the lack of specific assessment of the potential comorbid anxiety disorder or depression. But the main objective of this cohort follow-up was to assess the long-term benefit of STN-DBS on OCD severity as reflected by the YBOCS score. Nevertheless, the YBOCS scale includes the assessment of the anxiety related to obsessions and compulsions, whereas the affective impact of STN-DBS has already been highlighted.<sup>37</sup>

The mechanism of action of the STN target is still not well known, due to the recent use of STN-DBS in OCD. However, the anteromedial subregion of the STN is seen as the cognitive and limbic part of the STN, linked to the orbitofrontal, rostral cingulate and dorsolateral prefrontal cortex.<sup>38 39</sup> Those regions are of paramount importance as they are involved in the decision process and conflict resolution that are the core of OCD.<sup>40</sup> One could hypothesise that the inhibition of the noM-STN, which is hyperactive in patients with OCD<sup>41</sup> using high-frequency stimulation, is likely to modulate this circuitry and would indeed allow to increase decisional impulsivity, and consequently, to decrease the need to accumulate of evidence as already suggested<sup>40</sup> before taking any decision.

## CONCLUSION

This study confirms that a new target, the noM-STN, can be used to treat patients with severe refractory OCD.

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Two patients died in our cohort: one committed suicide and the second one asked for assisted suicide. Suicidality is an important matter, especially when managing patients with psychiatric disorders. In fact, the first patient who committed suicide, did not experience any suicide ideation before she committed suicide. She was by the way, an excellent responder to DBS and she had personal issues related to a divorce when she died as confirmed a posteriori by her general practitioner. However, one cannot be certain what would have happened without STN stimulation but in that case, the relationship between STN-DBS and the cause of the suicide is very unlikely.

More precisely she committed suicide 5 years after surgery, while her OCD was persistently improved (YBOCS score= 6, no medication required, the SSRI agent being discontinued 2 years after surgery). As she lived far from Grenoble center, her routinely medical follow-up was assumed locally. She has had a global psychiatric assessment in our centre 1 year and 4 months before her suicide when we noticed persistent OCD improvement, normal mood (MADRS score <7), and good DBS tolerance with, particularly, no impulsivity. During initial, post surgery, DBS adjustment, she had experienced hyperthymic mood under most ventral contacts stimulation (which have not eventually be chosen for long term stimulation). When we tried to schedule a new clinical assessment in our centre, we learned about her suicide from her general practitioner. Ten months before suicide she had a miscarriage. Before suicide, she was engaged in a separation from her boyfriend and she contacted a new psychiatrist 1 week before. Tragically, we also learned that she was 4 month pregnant when she died.

The second patient has a different story. First, he had a personality disorder history, including anankastic, avoidant and, mainly, dependent traits, as well as addictive behaviours (alcohol, sometimes cannabis) and a major depressive disorder, besides his OCD. His biographical history included some emotional neglect; he was in disability for psychiatric reasons for 27 years before DBS. Related to his depressive disorder, we may notice in his medical history 3 serious suicide attempts (medication, gaz intoxication, mostly fostered by alcohol intake), last one 5 years before including him in the DBS protocol. He has been clinically and biologically monitored on a regular basis for mood stability and alcohol/drug abstinence, as well as some last conventional treatment options for OCD during 2 years previous to his inclusion in the DBS study. Second, OCD was not improved significantly during the 2 years following surgery and this might have been disappointing for the patient, despite pre-op preparation on his expectations. Patient considered DBS as last therapeutical option and preferred getting off the initial protocol 6 months after surgery in order to benefit of freely adjusted DBS and not following the pre-established rules of this protocol. Disappointment regarding the insignificant benefit (less than 20% improvement) may have reinforced his willingness to commit suicide despite a very close clinical monitoring. Potentially, alcohol intake, which has been noticed incidentally during an institutional CBT in a specialized clinic stay 10 months before his death, may have also promoted emotional instability. However, he did not commit suicide himself but asked for euthanasia, which might be interpreted as a clear depressive state but without obvious impulsivity that would have pushed him to commit suicide.