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

Stephan Chabardes,1,2,3 Paul Krack,4,5 Brigitte Piallat,3 Thierry Bougerol,6 Eric Seigneuriet,2 Jerome Yelnik,7 Sara Fernandez Vidal,7 Olivier David,3 Luc Mallet,7,8,9 Alim-Louis Benabid,1 Mircea Polosan3,6

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±3.5 to 15.8±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±3.9 to 66.4±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 worldwide1 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 defined2 3 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 networks4 5 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.6 7

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.7

Multimodal functional imaging studies have led to a better definition of key brain structures involved during the expression of OCD symptoms.8 10 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 al11 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.12

One of the key nodes of this neuronal circuitry is the subthalamic nucleus (STN), which receive not
only hyperdirect connections from the motor and non-motor cortex, but also indirect inhibitory connections from the striatum through the Globus Pallidus externus. From a clinical standpoint, 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. 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. 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 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 OH 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. 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. Most of them were referred 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 except that the OCD target was slightly more anterior and medial. 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) that occurred 2 days after lead implantation. Surgery was allowed intraoperative checking for side effects and for possible acute therapeutic 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 had postoperative CT scan before the implantation of the battery (Kineta 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 therapeutic effects.

Table 1 : Main inclusions and exclusions criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| OCD defined by DSM-IV | Yes |
| Cluster A/B personality disorders | NA |
| Recent severe depression | NA |
| CGI >4 | NA |
| Medications Failure of three serotonin reuptake inhibitors including clomipramine | NA |
| Psychotherapy Failure of cognitive behavioural therapy conducted during at least 1 year with two therapists | NA |
| Risk of suicide (MADRS item-10 score >2) | |

CGI, Clinical Global Impression; DSM-IV, Diagnostic And Statistical Manual Of Mental Disorders- 4th 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.


**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±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. 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 µs 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±3.6 to 18.2±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±3.6 to 17.3±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-responders subgroup 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±3.5 to 15.8±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±3.9 to 66.4±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 3).

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 Kinetta 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...
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 ON, the case being positive in all cases. One patient was stimulated and eight had two cathodes turned on or increasing stimulation amplitude is used as a positive predictor of localisation in noM-DBS (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 PD21 22 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 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.

### Table 2 Clinical features of the patients

| Patient (gender/age) | Age at onset (years) | Duration disease (years) | Pre-op meds (mg/D) | NCD type | Comorbidity | Pre-op YBOCS | O+C |
|----------------------|----------------------|--------------------------|--------------------|----------|-------------|--------------|-----|
| 1 (M/39)             | 21                   | 18                       | Fluoxetine 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      | KLEPTOMANIA (ICD); depression; past suicide attempts | 15+15=30     |     |
| 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        | Anarkasticity | 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      | Hypothyroidism; ICD (dermatillomania) | 14+18=32     |     |
| 8 (F/52)             | 27                   | 25                       | Clomipramine 50 mg; citalopram 20 mg; hydroxyzine 200 mg; zopiclone 7.5 mg | W        | Hypothyroidism; ICD (dermatillomania) | 20+20=40     |     |
| 9 (F/38)             | 27                   | 11                       | Sertraline 100 mg; clonazepam 2 mg; zolpidem 10 mg; piribedil 150 mg | W        | Hypothyroidism; ICD (dermatillomania) | 18+18=36     |     |
| 10 (M/36)            | 19                   | 17                       | Paroxetine 50 mg | W        | Antipsychotic | 17+15=32     |     |
| 11 (F/40)            | 25                   | 15                       | Fluoxetine 200 mg; clomipramine 75 mg; oxcarbazepine 600 mg; clonazepam 2 mg; zolpidem 10 mg | W        | Hypothyroidism; ICD (dermatillomania) | 19+17=36     |     |
| 12 (F/54)            | 32                   | 22                       | Paroxetine 50 mg; lorazepam 3 mg; zopiclone 7.5 mg | C        | Hypothyroidism; ICD (dermatillomania) | 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                       | Busiprone 30 mg; cyamemazine 150 mg; clomipramine 187.5 mg | C-R      | Hypersomnia | 16+16=32     |     |
| 15 (F/31)            | 7                    | 24                       | Venlafaxine 75; levotheroxine 125 mg/j | C        | Hypothyroidism; 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.

### 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 rampan up of parameters settings that resumed just after simulation 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...
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.23

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 al24). 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.25 26

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 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 (38)                   | 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)                    | 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    | 33.31 (3.54)         | 34.52 (3.89)| 18.63 (9.42)              | 17.38 (10.71)             | 15.83 (9.61)              | 66.47 (27.48)           |

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

| Table 4 Statistical analysis of YBOCS and GAF at the group level |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Baseline Mean (SD) | 95% CI | 6 months Mean (SD) | 95% CI | % | P value | 12 months Mean (SD) | 95% CI | % | P value | 24 months 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 | NA | ** | 66.4 (18.8) | 58–74.9 | NA | ** |

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

GAF, Global Assessment Functioning; YBOCS, Yale and Brown Obsessive–Compulsive Scale.
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%.23

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-DBS27 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 al28 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 group29 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.30 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 5 | Responders vs non-responders at a 24-month follow-up |
|---------|------------------------------------------------------|
| 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.
Table 7  Adverse events

| Adverse event                          | Transient | Permanent |
|----------------------------------------|-----------|-----------|
| Surgery related                        |           |           |
| Leadwound 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         |           |
| Dyskinesia                             | 4         | 0         |
| Anxiety                                | 3         | 0         |
| Contralateral motor contraction        | 1         | 0         |
| Ipsilateral monocular deviation        | 1         | 0         |
| Hemicballism                           | 1         | 0         |
| Impulsivity                            | 5         | 0         |
| Irritability                           | 4         | 0         |
| Suicidal ideation                      | 2†        | 0         |
| Suicide attempt (voluntary drug intoxication) | 1       |           |
| Behavioural disinhibition              | 4         | 0         |
| Insomnia restless legs syndrome        | 2         |           |
| Not related to DBS                     |           |           |
| Diabetes type 2                        | 0         | 1‡        |
| Osteomuscular pain                     | 2         | 0         |
| TOTAL                                  | 41        | 3         |

*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.

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.39 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.35

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.36 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.37

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.38 39 Those regions are of paramount importance as they are involved in the decision process and conflict resolution that are core of OCD.40 One could hypothesise that the inhibition of the noM-STN, which is hyperactive in patients with OCD34 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 suggested40 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.
Author affiliations

1 CLINITEC, CEA Clinatec-Minatec, Grenoble, France
2 Department of Neurosurgery, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France
3 Grenoble Institute of neurosciences, University Grenoble Alpes-INSERM U1216, 38000 Grenoble, France
4 Division of Neurology, Department of Neurology, Bern University Hospital, Bern, Switzerland, Bern, Switzerland
5 Department of Neurology, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France
6 Department of Psychiatry, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France
7 Institut du Cerveau, ICM, INSERM U 1127, CNRS UMR 7225, Sorbonne Université, F-75013, Paris, France
8 Département Médical-Universitaire de Psychiatrie et d’Addictologie, Univ Paris Est Créteil, DMU IMPACT, Hôpitaux Universitaires Henri Mondor - Albert Chevèner, Assistance Publique-Hôpitaux de Paris, Créteil, France
9 Department of Mental Health and Psychiatry, Global Health Institute, University of Geneva, Geneva, Switzerland

Contributors SC, PK and MP wrote the manuscript, acquired, analysed and interpreted the data, and managed the patients. SC and ALB operated the patients. JY, LM and SFV reviewed the manuscript, and plotted on the atlas the leads coordinates. TB, BP, ES and OD reviewed the manuscript and acquired clinical data. BP also performed the statistical analysis. All approved the final version of the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Comité consultatif National d’éthique. La neurochirurgie fonctionnelle n’affectations psychiatriques sévères (2002).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Stephan Chabardes http://orcid.org/0000-0002-7930-1476

REFERENCES

1. Rasmussen SA, Tsuang MT. Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. Am J Psychiatry 1986;143:317–22.
2. Rasmussen SA, Eisen II. The epidemiology and clinical features of obsessive compulsive disorder. Psychiatr Clin North Am 1992;15:743–58.
3. Anzai T, Buechel C, D’Esposito M, et al. Functional connectivity of the subthalamic nucleus in obsessive-compulsive disorder. Am J Psychiatry 2014;171:1349–56.
4. Thronson A, Haglund P, Rada J, et al. Emotional processing in obsessive-compulsive disorder: a systematic review and meta-analysis. J Psychiatry 2009;169:1706–15.
5. Anticevic A, Putcha V, D’Souza D, et al. Metabolite connectivity in obsessive-compulsive disorder. JAMA Psychiatry 2014;71:657–65.
6. Benzinger TL, Chabardes S, Mitrofanis J, et al. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson’s disease. Lancet Neurol 2009;8:67–81.
7. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–75.
8. Martinez-Fernandez R, Castrioto A, Krack P. Prefrontal—STN projections, the highway for emotion and cognition control. Mov Disord 2014;29:305.
9. Mallet L, Messenge V, Houeto J-L, et al. Compulsions, Parkinson’s disease, and stimulation. Lancet 2002;360:1320–2.
10. 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.
11. Mallet L, Polosan M, Jaafari N, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 2008;359:2121–34.
12. Comité consultatif National d’éthique. The neurochirurgie fonctionnelle n’affectations psychiatriques sévères (2002).
13. Chabardes S, Polosan M, Krack P. Deep brain stimulation for obsessive–compulsive disorder: subthalamic nucleus target. World Neurosurg 2013;80:S31. e51–S31.e8.
14. 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.
15. Castrioto A, Lhommée E, Moro E, et al. Mood and behavioural effects of subthalamic stimulation in Parkinson’s disease. Lancet Neurol 2014;13:287–305.
16. Jahanshahi M, Obeoi I, Baune C, et al. Parkinson’s disease, the subthalamic nucleus, inhibition, and impulsivity. Mov Disord 2015;30:128–40.
17. Mallet L, Du Montjoy T, Clair A-H, et al. Long-term effects of subthalamic stimulation in obsessive-compulsive disorder: follow-up of a randomized controlled trial. Brain Stimul 2019;12:1080–2.
18. Luyten L, Hendriks D, Raymaekers S, et al. Electrical stimulation in the bed nucleus of the stria terminals alleviates severe obsessive-compulsive disorder. Mol Psychiatry 2016;21:1272–80.
19. Pabhu S, Chabardes S, Sheridi A, et al. Effect of subthalamic nucleus stimulation on ponscillin induced focal motor seizures in primates. Brain Stimul 2015;8:177–84.
20. Chabardes S, Kahane P, Minotti L, et al. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 2002;4 Suppl 3:S83–93.
21. Polosan M, Chabardes S, Bougerol T, et al. Long-term improvement in obsessions and compulsions with subthalamic stimulation. Neurology 2016;87:1843–4.
22. Deny D, Mantione M, Figeé M, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2010;67:1061–8.
23. Raymaekers S, Vansteelandt K, Luyten L, et al. Long-term electrical stimulation of bed nucleus of stria terminals for obsessive-compulsive disorder. Mol Psychiatry 2017;22:931–4.
24. Tynagaraj H, Apergis-Schoute AM, Akram H, et al. A randomized trial directly comparing ventral capsule and anteromedial subthalamic nucleus stimulation in obsessive-compulsive disorder: clinical and imaging evidence for dissociable effects. Biol Psychiatry 2019;85:726–34.
25. de Haan S, Rietveld E, Stokhof M, et al. Effects of deep brain stimulation on the lived experience of obsessive-compulsive disorder patients: in-depth interviews with 18 patients. PloS One 2015;10:e0135524.
26. Alorato F, Cuadras D, Gabrièlis L, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. PloS One 2015;10:e0133591.
27. Giannini G, Francois M, Lhommée E, et al. Suicide and suicide attempts after subthalamic nucleus stimulation in Parkinson disease. Neurology 2019;92:e97–105.
28. Forckke EM, Schuurman PR, Speelman JD. Suicide after deep brain stimulation of the internal globus pallidus for dystonia. Neurology 2006;66:142–3.
29. Weintraub D, Duda J, Carlson K, et al. Suicide ideation and behaviours after STN and GPI DBS surgery for Parkinson’s disease: results from a randomised, controlled trial. J Neurol Neurosurg Psychiatry 2013;84:1113–8.
30. Fernández de la Cruz L, Rydell M, Runeson B, et al. Suicide in obsessive-compulsive disorder: a population-based study of 36 788 Swedish patients. Mol Psychiatry 2017;22:1626–32.
31. Polosan M, Droux F, Kibler A, et al. Affective modulation of the associative-limbic subthalamic nucleus: deep brain stimulation in obsessive-compulsive disorder. Transl Psychiatry 2019;9:73.
32. Mallet L, Schüpbach M, Ni’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.
33. Hayes WA, Haber SN. The organization of prefrontal-subthalamic inputs in primate provides an anatomical substrate for both functional specificity and integration: implications for basal ganglia models and deep brain stimulation. J Neurosci 2013;33:4804–14.
34. Voon V, Droux F, Morris L, et al. Decisional impulsivity and the associative-limbic subthalamic nucleus in obsessive-compulsive disorder: stimulation and connectivity. Brain 2017;140:442–56.
35. Paillat B, Polosan M, Fraix V, et al. Subthalamic neuronal firing in obsessive-compulsive disorder and Parkinson disease. Ann Neurol 2011;69:793–802.