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Anne E.P. Mulders[1-3], Albert F.G. Leentjens[2], Koen Schruers[2], Annelien Duits[2], Linda Ackermans[1], Yasin Temel[1,3,4]

Key words
- Deep brain stimulation
- Obsessive-compulsive disorder
- Side effects
- Subthalamic nucleus
- Ventral capsule/ventral striatum

Abbreviations and Acronyms
DA: Dopamine
DBS: Deep brain stimulation
MRI: Magnetic resonance imaging
NAc: Nucleus accumbens
OCD: Obsessive-compulsive disorder
PD: Parkinson disease
STN: Subthalamic nucleus
VC/VS: Ventral capsule/ventral striatum
Y-BOCS: Yale-Brown Obsessive Compulsive Scale

From the Departments of [1]Neurosurgery, [2]Psychiatry and Neuropsychology, [3]Neuroscience, Maastricht University Medical Center, Maastricht; and [4]Donders Institute for Brain, Cognition and Behaviour, Department of Neurosurgery, Radboud University Medical Center, Nijmegen, the Netherlands

To whom correspondence should be addressed: Yasin Temel, M.D., Ph.D. [E-mail: y.temel@maastrichtuniversity.nl]

A.E.P.M. collected the clinical data and wrote the first draft of the manuscript. Together with A.D., she applied the Y-BOCS. Y.T. and L.A. performed the DBS surgeries. K.S. was involved in the preoperative screening. A.F.G.L. was the treating physician of the patient and as such involved in preoperative screening, clinical treatment, outpatient follow-up, and DBS programming. All authors were part of the multidisciplinary team involved in the treatment of the patient. All authors gave critical comments on the first and subsequent drafts of the paper and approved the final manuscript.

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BACKGROUND: **Patients with treatment-resistant obsessive-compulsive disorder (OCD) are potential candidates for deep brain stimulation (DBS). The anteromedial subthalamic nucleus (STN) is among the most commonly used targets for DBS in OCD.**

CASE DESCRIPTION: **We present a patient with a 30-year history of treatment-resistant OCD who underwent anteromedial STN-DBS. Despite a clear mood-enhancing effect, stimulation caused motor side effects, including bilateral hyperkinesia, dyskinesias, and sudden large amplitude choreatic movements of arms and legs when stimulating at voltages greater than approximately 1.5 V. DBS at lower amplitudes and at other contact points failed to result in a significant reduction of obsessions and compulsions without inducing motor side effects. Because of this limitation in programming options, we decided to reoperate and target the ventral capsule/ventral striatum (VC/VS), which resulted in a substantial reduction in key obsessive and compulsive symptoms without serious side effects.**

CONCLUSIONS: **Choreatic movements and hemiballismus have previously been linked to STN dysfunction and have been incidentally reported as side effects of DBS of the dorsolateral STN in Parkinson disease (PD). However, in PD, these side effects were usually transient, and they rarely interfered with DBS programming. In our patient, the motor side effects were persistent, and they made optimal DBS programming impossible. To our knowledge, such severe and persistent motor side effects have not been described previously for anteromedial STN-DBS.**

INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by the repeated occurrence of upsetting obsessions or compulsions that are related to substantial dysfunction in multiple domains of life.[1] Despite intensive psychotherapeutic and pharmacologic treatments, a significant proportion of patients fail to respond to therapy.[2] Patients with treatment-resistant OCD are potential candidates for deep brain stimulation (DBS).[3] The ventral capsule/ventral striatum (VC/VS), the nucleus accumbens (NAc), and the anteromedial limbic portion of the subthalamic nucleus (STN) are among the most common DBS targets for OCD.[1] The aim of DBS is to tailor the treatment on a patient-specific basis to deliver optimal therapeutic effects while avoiding stimulation-associated side effects. Minor complications have been reported, of which the majority were time limited and reversed by adjusting the stimulation settings.[1,4,5] We present significant stimulation-associated side effects following DBS of the anteromedial STN that have not been described previously and that required reimplantation to an alternative target—the VC/VS.

CASE DESCRIPTION

A 47-year old woman with refractory OCD was referred to our hospital for DBS. The patient had OCD since the age of 15, and it was characterized clinically by intrusive thoughts about dirt, accompanied with excessive cleaning, washing, and checking compulsions that occupied the entire day. In addition, the patient experienced a lowered mood, anhedonia, and occasional panic attacks, though failing to meet the

Table 1. Patient Characteristics and Stimulation Settings

Medication Used Before Surgery*		
	Clomipramine	Haloperidol
	Sertraline	Oxazepam
	Citalopram	Fluoxetine
	Mirtazapine	Venlafaxine
	Paroxetine	Aripiprazol
Target Coordinates†	**STN**	**VC/VS**
X	10	7
Y	0	12.8(L)/12.7(R)
Z	−4	−3
Stimulator Settings	**Left**	**Right**
Tested STN DBS settings‡	1- C+, 90 μs, 130 Hz	9- C+, 90 μs, 130 Hz
	2- C+, 90 μs, 130 Hz	10- C+, 90 μs, 130 Hz
	3- C+, 90 μs, 130 Hz	11- C+, 90 μs, 130 Hz
	1- 2+, 90 μs, 130 Hz	9- 10+, 90 μs, 130 Hz
	2- C+, 90 μs, 130 Hz	9- C+, 90 μs, 130 Hz
	0- C+, 90 μs, 130 Hz	8- C+ 90 μs, 130 Hz
Final VC/VS DBS settings	1- 2- 3- C+, 3.4 V, 90 μs, 130 Hz	9- 10- 11- C+, 3.4 V, 90 μs, 130 Hz
Y-BOCS		
Preoperative		34
Postoperative VC/VS 1 year FU		29
Postoperative VC/VS 2 year FU		17

STN, subthalamic nucleus; VC/VS = ventral capsule/ventral striatum; DBS, deep brain stimulation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; FU, follow-up.
*Medication used before surgery refers to all the different pharmacologic trials conducted since the patient was first treated until the first surgery. Adequate doses of these drugs were maintained for at least 12 weeks.
†Distance from midanterior/posterior commissure in millimeters.
‡Voltages were slowly increased with every setting. Dyskinesias occurred at voltages between 1.5 and 2.1 V.

criteria for major depressive disorder or any specific anxiety disorder. The patient also showed signs of borderline personality disorder. She had received several psychologic and pharmacologic treatments without any long-lasting relief on symptoms (Table 1). The patient was informed of the risks and benefits of DBS and underwent extensive multidisciplinary evaluation before surgery to ensure her suitability and compatibility for the treatment. The presurgery score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[6] was 34.

In September 2012, when the patient was 49 years old, DBS electrodes (Model 3389 DBS lead; Medtronic, Minnesota, USA) were implanted bilaterally in the anteromedial portion of the STN using a computed tomography–magnetic resonance imaging (MRI) fusion-based stereotactic approach combined with intraoperative micro-electrode recording with 4 electrodes (anterior, medial, central, and lateral). Micro-electrode recording showed approximately 5 mm of typical STN activity along the central trajectory for both left and right sides, which was characterized by increased background activity, high-amplitude discharges, and burst-firing neurons. Postoperative imaging validated appropriate placement of the electrodes (Figure 1). See Table 1 for final target coordinates. Stimulation parameters were as follows: monopolar stimulation (left 1-, right 9-, case+), a pulse width of 90 microseconds, a frequency of 130 Hz, and an amplitude of 1.5 V that had been slowly increased.

After activating the DBS therapy, the patient exhibited an immediate mood-enhancing effect and relief in obsessions and compulsions. However, the patient developed unexpected compulsive behavior toward the operation wounds (scratching and itching), which has likely contributed to the development of a hardware infection. The infection was treated by removing the infected hardware (implanted pulse generator and cables) and antibiotic therapy. Two months later, new hardware was implanted and DBS therapy was reactivated. After this period, the mood-enhancing effect decreased, and the programming was limited by the fact that STN-DBS caused motor side effects upon stimulation greater than approximately 1.5 V. The motor side effects consisted of bilateral hyperkinesia and dyskinesias and sudden large amplitude choreatic movements of the arms and legs.

Following multiple DBS programming sessions (Table 1), including lowering the amplitude and using other contact points, no significant reduction of obsessions and compulsions could be achieved without inducing motor side effects. The patient also experienced mood swings. Despite continuation of pharmacotherapy and additional psychotherapeutic interventions, including intensive day treatment and behavioral therapy, the patient's quality of life remained poor, and the patient required further hospital admissions because of increased suicidal thoughts and an impulsively attempted suicide by autointoxication.

Because of the programming limitations and the fact that any therapeutic benefit was accompanied by intolerable motor side effects, we decided to reoperate and target the VC/VS region. In April 2014, when the patient was 51 years old, she underwent stereotactic reimplantation of the electrodes with the deepest electrode contact point in the area of the NAc (Model 3387 DBS lead;

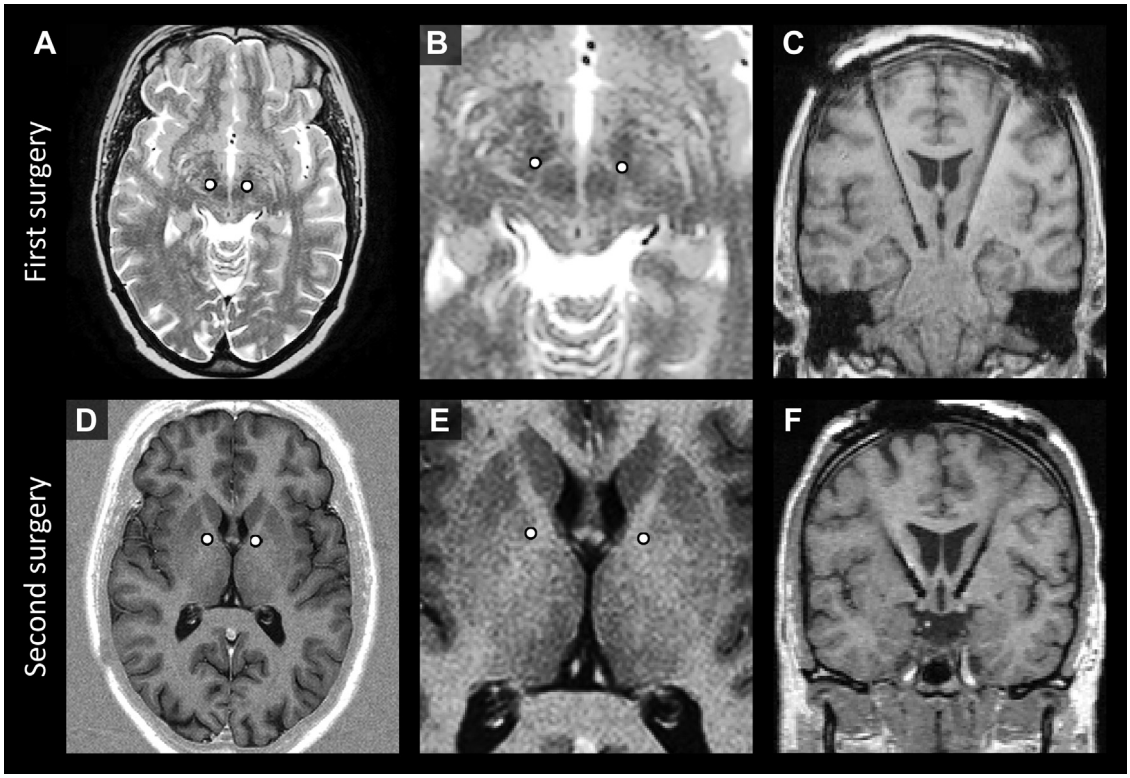

Figure 1. Postoperative location of the electrodes after bilateral anteromedial subthalamic nucleus deep brain stimulation (DBS; **A**–**C**, first surgery) and bilateral ventral capsule/ventral striatum DBS (**D**–**F**, second surgery). (**A**, **D**) Axial preoperative magnetic resonance images and (**B**, **E**) their enlargements. The location of the active contacts in the preoperative images was computed by rigidly registering the postoperative images and their coordinates of the active contacts to the preoperative images with FSL's Linear Image Registration Tool algorithm.[7] (**C**, **F**). Postoperative coronal magnetic resonance images showing the electrodes and contacts.

Medtronic). See Table 1 for final target coordinates. Postoperative imaging showed adequate placement of the electrodes at the planned target (Figure 1). After programming and additional psychotherapeutic therapy, therapeutic effect was achieved without inducing serious side effects. See Table 1 for stimulation parameters. One year postoperatively, the patient's Y-BOCS score was 29; 2 years postoperatively, the score was 17, a reduction of 50% compared with baseline. At present, the patient reports a stabilization of daily life routines and improved quality of life.

DISCUSSION

This case illustrates that DBS of the anteromedial portion of the STN in OCD can cause persistent motor side effects that resemble chorea and ballism. Choreatic movements and (contralateral) hemiballismus have been associated with STN dysfunction[8] and have been reported following STN-DBS in Parkinson disease (PD), in which the dorsolateral sensorimotor portion of the STN is typically stimulated.[9-12] Although these side effects are usually transient in PD,[12] they can make DBS programming difficult.[9,10] Moreover, dyskinetic movements as side effects of STN-DBS in OCD have been reported in 2 patients in the French Stimulation dans le Trouble Obsessionnel Compulsif Study Group in the first month following stimulation. However, these movements resolved spontaneously or promptly after the adjustment of the stimulation settings.[13] To our knowledge, such severe and persistent motor side effects that interfere with DBS programming have not been described previously for anteromedial STN-DBS.

The underlying mechanisms and pathophysiology of DBS-induced motor side effects are not well understood. Several disease-related risk factors have been identified for the emergence of such symptoms following STN-DBS in PD, including severe dyskinesias preoperatively and young onset PD.[9] In addition, STN-DBS has been demonstrated to increase extracellular striatal dopamine (DA) metabolites in animal models of PD.[14] Whereas PD is characterized by a progressive degeneration of nigral DA neurons, one can speculate that STN-DBS can result in an increase in striatal DA release and subsequently in hyperdopaminergic behaviors, such as dyskinesia in a patient with OCD and an intact DA system. This speculation is further supported by the finding that the increase in striatal DA metabolites following STN-DBS in naive rats was accompanied with transitory involuntary movements.[15]

Moreover, dyskinesias following STN-DBS in PD have been associated with contact location within the dorsolateral portion of the STN.[9,11] The idea that choreiform or ballistic movements result from stimulation or lesions of specific subdivisions of the STN is supported by a study in which a gamma-aminobutyric acid receptor agonist was injected into the sensorimotor, associative, and limbic territories of the STN of green monkeys.[16] Other than behavioral changes, no abnormal movements were observed after microinjection in the anteromedial portion of the STN, whereas injection into the dorsolateral and middle portions of the STN resulted in contralateral violent and rhythmic involuntary movements and leg ballismus, respectively.[16]

Despite postoperative imaging showing adequate placement of the electrodes, there are individual differences regarding volume and position of the STN.[17] In addition, a human clinical study using diffusion-weighted tractography indicated a considerable degree of variation across individuals regarding the volume of structural subdivisions of the STN along the limbic, cognitive, and motor domains.[18] In light of the individual differences in structural and functional anatomy of STN subdivisions, it is possible that in the case of the patient discussed, although the anteromedial portion of the STN was targeted, this part did in fact not constitute the nonmotor portion of the STN. Consequently, this may have led to the development of motor side effects, either directly by stimulation of the motor portion of the STN or indirectly by current spreading of contact points in close proximity to the motor portion of the STN. Importantly, while the concept of distinct functional subdivisions within the STN is popular in neuroanatomy research,[19-21] it is still a matter of debate. In addition, others have suggested convergence[22] or large overlap and interactions between these functional subdivisions.[23,24]

Future attempts to manage OCD with STN-DBS should focus in an individualized, patient-specific selection method that can determine the size and location of functional and structural subdivisions of the STN that can be achieved with, for example, preoperative diffusion-weighted imaging and tractography and functional MRI.

CONCLUSION

We have presented a case of persistent bilateral motor side effects in the lower extremities that limited programming possibilities in a patient who had undergone bilateral anteromedial STN-DBS for severe refractory OCD. Reimplantation of electrodes targeting the VC/VS with the deepest electrode contact point in the area of the NAc successfully overcame this limitation and resulted in adequate therapeutic response. Reimplantation to an alternative target should be considered if stimulation-associated side effects interfere with adequate programming of the DBS system, and this cannot be resolved by adjusting stimulation parameters.

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Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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