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

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

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

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

INTRODUCTION

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

Surgical Treatment for OCD: From Lesions to Deep Brain Stimulation

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

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

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

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

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

Animal Data

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

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

Serendipity Usually Precedes Innovation

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

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

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

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

Results in Humans

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