

DEEP BRAIN STIMULATION OF THE ANTERIOR INTERNAL CAPSULE FOR THE TREATMENT OF TOURETTE SYNDROME: TECHNICAL CASE REPORT

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OBJECTIVE AND IMPORTANCE: Medical treatment of Tourette syndrome is often ineffective or is accompanied by debilitating side effects, therefore prompting the need to evaluate surgical therapies.

CLINICAL PRESENTATION: We present the case of a 37-year-old woman with severe Tourette syndrome since the age of 10 years. Her symptoms included frequent vocalizations and severe head and arm jerks that resulted in unilateral blindness. Trials of more than 40 medications and other therapies had failed to relieve the tics.

INTERVENTION: We implanted bilateral electrodes in the anterior limb of the internal capsule, terminating in the vicinity of the nucleus accumbens. At 18-month follow-up, optimal stimulation continued to lower her tic frequency and severity significantly.

CONCLUSION: Our findings suggest that stimulation of the anterior internal capsule may be a safe and effective procedure for the treatment of Tourette syndrome.

KEY WORDS: Deep brain stimulation, Internal capsule, Obsessive-compulsive disorder, Tourette syndrome, Ventral striatum

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Tourette syndrome (TS) is characterized by involuntary motor and vocal tics and is closely associated with the spectrum of obsessive-compulsive disorders (OCDs) (4). The estimated prevalence of TS in the population is 0.5%. Although conventional pharmacological and behavioral therapies can be effective, some patients continue to experience debilitating symptoms. Hence, there is a need for safe alternative treatments that can address both the motor and comorbid psychiatric aspects of the disease. A review of ablative surgeries used to treat TS revealed a diverse set of potential targets, including the frontal lobes, the anterior cingulate gyrus, the thalamus, and the cerebellum, along with the recently reported use of thalamic deep brain stimulation (DBS) in three patients (8, 9). Although ablative surgeries have met with varying degrees of success, they are also associated with a significant incidence of morbidity, including cognitive impairment, hemiplegia, dysarthria, akinesia, and worsened tics (8, 9). Furthermore, lesions are by nature permanent and cannot be adjusted after being created. DBS, in comparison, is adjustable, reversible, and hence offers a significant advantage (9).

The anterior limb of the internal capsule (AIC) subserves limbic system circuitry and contains reciprocal frontothalamic and frontostriatal connections important in motor, cognitive, and emotional function (*Fig. 1*) (3). The AIC has been targeted successfully in the surgical treatment of OCD (6), and thus provides a potentially useful target for TS. Subcaudate tractotomy, an ablative procedure that includes a portion of the ventral striatum, also has been an effective target for the treatment of TS (8). Hence, a reasonable approach was to use a DBS electrode in an effort to target the inferior portion of the AIC and the ventral striatum. Moreover, use of a DBS electrode in this fashion allowed for systematic assessment of the effects of stimulation in both areas (*Fig. 1*).

CASE REPORT

Patient History

We present the results of bilateral electrode implantation in the AIC of a 37-year-old right-handed woman with medically intractable TS. She was diagnosed at age 10 years. Her symptoms at presentation consisted primarily of

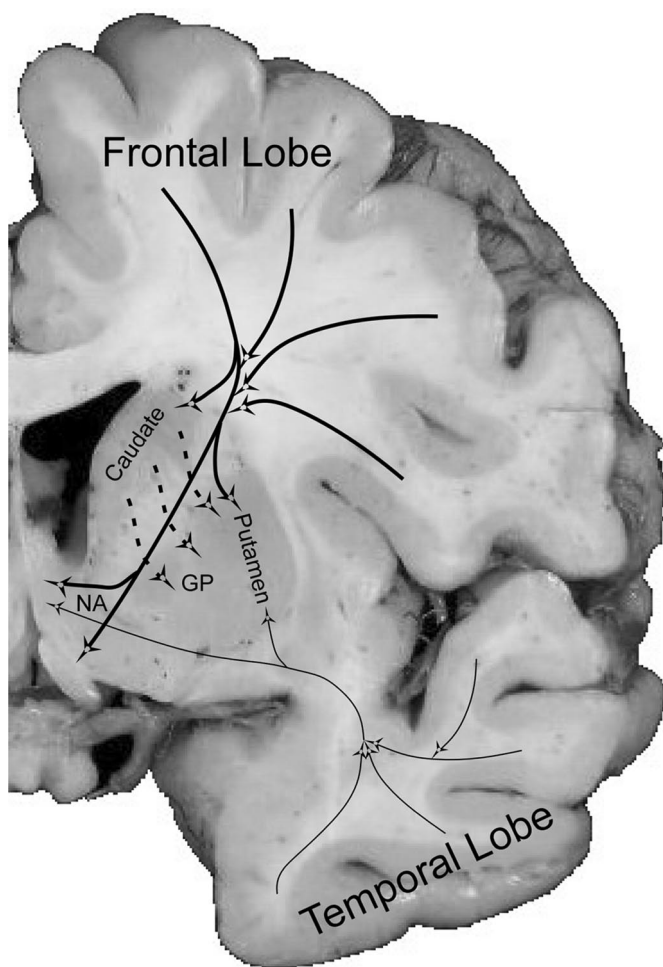


FIGURE 1. Coronal section of an MRI scan of the anterior internal capsule. Frontal projections (to the thalamus, striatum, anterior commissure, and cerebral peduncle) are shown as thick solid lines. Temporal projections (to the striatum and the contralateral limbic system) are shown as thin solid lines. Projections of the caudate (to the lenticular nuclei) are shown as thick dashed lines. GP, globus pallidus; NA, nucleus accumbens.

violent retrocollic head jerks and arm movements. She also experienced frequent vocalizations such as grunts, chirps, and swears. She had sustained limb fractures and repeated retinal detachments resulting from her head movements that ultimately rendered her blind in one eye. Trials of more than 40 medications, from pimozide to tetrabenazine and dronabinol, had been either ineffective or caused significant physical or cognitive impairment. She also tried biofeedback, relaxation techniques, habit reversal therapy, and botulinum toxin injections without significant improvement. The patient had never had symptoms of OCD, depression, or attention deficit hyperactivity disorder. Formal psychiatric evaluation, neuropsychological testing, and personality testing showed only a mild impulsiveness and a mild distractibility.

The patient had no remarkable past medical or family history. Physical examination revealed no sign of neurological diseases other than TS. Facial sensation and strength were normal, and hearing was intact bilaterally. Movement of the jaw, tongue, and palate was normal. Motor examination demonstrated normal tone, strength, bulk, deep tendon reflexes, coordination, stance, and gain. She also had equal sensation to light touch, vibratory sense, and cold. Magnetic resonance imaging (MRI) and positron emission tomography results were unremarkable.

Before surgery, her case was reviewed and approved by the Psychiatric Neurosurgery Committee at Massachusetts General Hospital, which is composed of psychiatrists, neurologists, neurosurgeons, an ethicist, and experienced lay people. The patient was advised of the experimental nature of the procedure and signed an informed consent.

Surgical Technique

The ventral aspect of AIC was targeted using stereotactic MRI and computed tomography. Target coordinates were at the midpoint of the anterior limb of the internal capsule, 12 mm lateral from midline and 7 mm below the anterior commissure. These coordinates are based on the capsulotomy (5, 7) and AIC stimulation (1) experience for OCD patients. As an aid to localization, recordings were made with three tungsten microelectrodes placed in a coronal orientation. Burr holes were placed 3.5 cm lateral to the midline. The electrodes were advanced through three cannulas using a motorized microdrive (Alpha Omega, Nazareth, Israel). Single-unit activity in the medial and lateral electrodes corresponded to the caudate and putamen, respectively (Fig. 2). On several occasions, intraoperative tics seemed to be followed by brief high-frequency neuronal discharges. However, it was difficult to obtain precise timing of tic onset to confirm this observation. As soon as the recordings were completed and the targets were identified, the recording electrodes were removed and two electrodes (Model 3387; Medtronic, Inc., Minneapolis, MN) were placed and secured in position. The 3387 electrodes were selected to stimulate both the AIC and the ventral striatum. The electrodes then were connected to a portable stimulator, and the different lead combinations were tested. There was a significant reduction in the frequency of the patients' tics when stimulating the middle two contacts in either electrode. Postoperative MRI demonstrated both electrodes passing through the AIC and terminating in the ventral striatum (Fig. 3). One week after the initial procedure, two infraclavicular pulse generators were placed (Solettra; Medtronic, Inc.).

Postoperative Course

Bilateral initial settings of 5 V, 180 microseconds, 130 Hz, and contacts 3+, 0- (0 is deepest in the brain, 3 most dorsal) produced a 10 to 15% decrease in tic frequency, without change in tic characteristics or amplitude. After 18 months of follow-up and adjustments, symptoms as measured by the Yale Global Tic Severity Scale had decreased 25% in overall

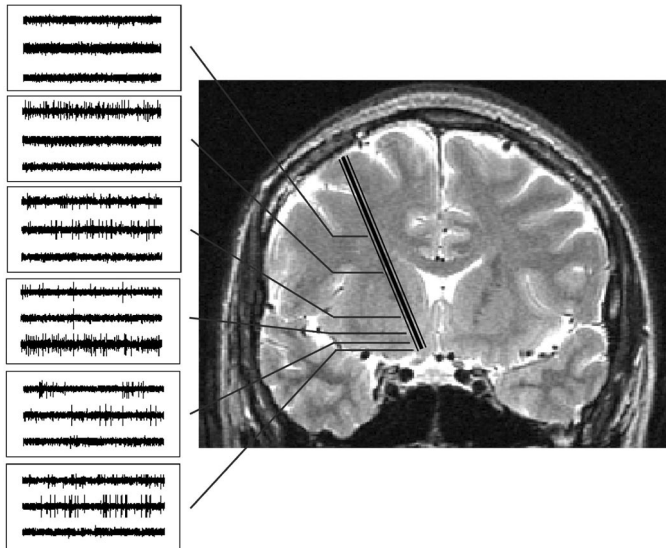


FIGURE 2. Reconstructed electrode trajectory superimposed on preoperative coronal MRI scan. Activity in the medial and lateral electrodes corresponds to the caudate and putamen, respectively. Tracings on the top of each inset correspond to neuronal activity recorded from the medial electrode, whereas tracings on the bottom of each inset correspond to activity recorded from the lateral electrode.

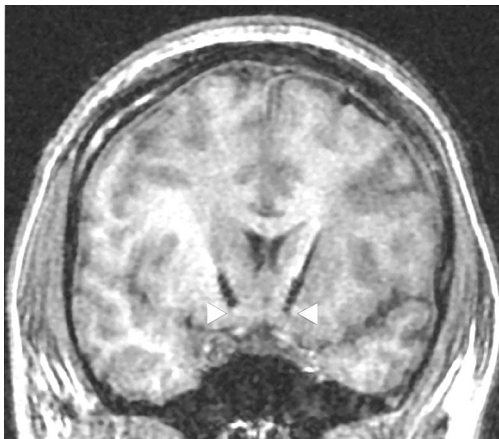


FIGURE 3. Coronal T1-weighted postoperative MRI scan illustrating placement of bilateral deep brain stimulating electrodes. The electrodes traverse the anterior limb of the internal capsule and terminate in the vicinity of the nucleus accumbens (arrowheads).

impairment, 17% in total tic score, and 20% in global severity. According to the patient's logs, the tic frequency and severity decreased by 45%, and the patient's ability to suppress her tics increased. Her eyesight stabilized after the surgery and she has had no significant limb injuries. Nearly all the clinical effects of stimulation were apparent within a few days after each stimulator adjustment. Several settings produced subjective dysarthria, and one setting, with all contacts negative and the case positive, produced mild rhythmic jaw clenching. The greatest improvement in symptoms was noted using settings

of 4.1 V, 210 microseconds, 185 Hz, and contacts 3+ and 1– bilaterally.

In addition to the effect on tics, different electrode settings altered her mood profoundly over hours to days. High-voltage stimulation of the ventral-most contacts, in the vicinity of the nucleus accumbens, produced mild apathy and depression, whereas high-voltage stimulation at the dorsal-most contacts, in the body of the capsule, produced hypomania. These effects took hours to days to be apparent. Middle contact stimulation, which helped tics the most, generated a stable euthymic state. Our stimulation adjustments were aimed to attain the optimal tic reduction while maintaining a euthymic state. Because both agitated hypomania and depression were uncomfortable for the patient, and because they posed a theoretical risk of self-injurious behavior, she was not left at such settings for any length of time. Hence, the patient only spent several days at each of the altered mood states. Stimulation never induced suicidal thoughts or significant disruption of work or home life. On turning the stimulator off, these effects disappeared over minutes to hours.

Several postoperative episodes are instructive because the patient's stimulators malfunctioned without the knowledge of the physician or the patient. In several instances, the pulse generator accidentally was turned off. In another instance, the patient experienced a broken connecting wire because of the tics, which was subsequently replaced. In both episodes, the patient noted that her symptoms worsened considerably and requested an assessment of the stimulators. On resolution of the problem, the patient's symptoms once again improved.

DISCUSSION

To our knowledge, this is the first published report of DBS placement in the AIC for the treatment of TS. Several studies have suggested that symptoms of TS stem from dysregulation of limbic-striatal circuits and circuits connecting the orbito-frontal cortex to the medial thalamic nuclei (3, 4, 8). Both of these pathways pass through the AIC and are thought to underlie the effect of AIC ablation in the spectrum of OCDs. Similarly, stimulation of the AIC has been used with some success for the treatment of refractory OCD. High-frequency stimulation of these AIC tracts may produce an effect similar to ablative lesions (6). Unlike ablation, however, DBS carries the benefit of being adjustable and is less likely to produce the cognitive impairment previously reported with permanent lesions in this area (8, 9). Recent reports suggest that DBS of the medial thalamus also may be useful in treating TS (9, 10). Given that extensive frontothalamic projections pass through the AIC, DBS in this area indeed may provide a beneficial effect by influencing a similar circuitry. Although our clinical outcomes are more modest than those reported for thalamic DBS, AIC stimulation may prove more beneficial in patients in whom OCD is a more prominent component (1, 5, 7). Hence, considerably more study is warranted to determine the best site for stimulation in the surgical therapy of TS.

In addition to its effect on motor tics, another interesting observation in the current study is that the patient experienced reproducible and sustained mood changes from stimulation at specific electrode leads. Stimulation of the upper leads located in the AIC may have a direct impact on limbic projections involved in mood and anxiety, whereas stimulation of lower leads situated in the vicinity of the nucleus accumbens may disrupt signals known to be involved in pleasure and goal-oriented behavior. These findings suggest that similar DBS placements may allow for the rapid alteration of mood in patients with unipolar or bipolar affective disorder. Because treatment for the latter usually requires medications with more disabling side effects, and because bipolar mood states can switch rapidly, alternatives to current therapies are needed (2). Bipolar mood disorder may be especially suited to treatment with DBS electrodes, which can be adjusted rapidly as moods change. Thus, our findings suggest that the AIC may be a target for DBS in both unipolar and bipolar mood disorders.

CONCLUSION

The current case study demonstrates that use of DBS in the AIC provides a safe and potentially useful target for the treatment of medically refractory TS. The patient experienced a moderate and sustained improvement in her symptoms that provided significant benefit over prior medical therapies. The opportunity to influence different regions systematically also provided a unique insight into the functioning of the AIC and ventral striatum and their possible usefulness in the treatment of affective disorders.

DISCLOSURE

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COMMENTS

Flaherty et al. report on a patient with Tourette syndrome treated with deep brain stimulation (DBS) in the anterior internal capsule. This target has been used for patients with obsessive-compulsive disorder (OCD). At 18 months, the frequency and severity of tics were reduced to some extent, reappearing when the stimulators were accidentally turned off and when one of the cables broke. The authors have also reported that stimulation through the bottom and upper contacts induced hypomania and depression, respectively, both improving when the electrode contacts were changed.

Various targets have been proposed to treat Tourette syndrome (1). To date, DBS has been used successfully in the medial part of the thalamus with excellent results. Anecdotal reports in meetings have also shown that the globus pallidus internus and externus may be effective targets to treat the tics that characterize the disease. A study to evaluate these targets in the treatment of Tourette syndrome is needed.

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- Visser-Vandewalle V, Temel Y, Boon P, Vreeling F, Colle H, Hoogland G, Groenewegen HJ, van der Linden C: Chronic bilateral thalamic stimulation: A new therapeutic approach in intractable Tourette syndrome—Report of three cases. *J Neurosurg* 99:1094–1100, 2003.

DBS surgery is being increasingly applied for indications beyond intractable movement disorders. These emerging applications include DBS for the treatment of intractable epilepsy, cluster headaches, neuropathic pain, OCD, major depression, and Tourette syndrome.

The authors report an interesting case of a Tourette syndrome patient who received implants of DBS electrodes in the ventral anterior internal capsule bilaterally. They report two consistent effects from their chronic stimulation: a modest reduction in the motor tic frequency and severity, and alteration of mood. The reduction in tic frequency and severity observed is less than that reported by previous studies using the thalamic target for Tourette syndrome (2). More patients need to be studied and long-term safety and efficacy studies need to be performed to determine whether the internal capsule is a viable target for the tics associated with Tourette syndrome.

In addition to the effects on motor tics, the internal capsule target seems to have a consistent and lasting effect on mood and OCD. The author's target point is more lateral and anterior than recent reports of DBS for OCD, which targeted the anterior capsule for OCD and depression (1). In the past several years, the emergence of DBS technology has resulted in renewed interest in the surgical treatment of refractory psychiatric and parapsychiatric disorders. With the exception of the midline thalamus, most recent studies of DBS for psychiatric disorders have concentrated on the anterior internal capsule as modeled by the stereotactic anterior capsulotomy. In particular, the

ventral aspect of the anterior internal capsule and the nucleus accumbens region has been the focus of much of this renewed interest. Given the proximity of the nucleus accumbens to the ventral aspect of the internal capsule and the fairly high stimulation currents used for OCD DBS, this raises the question as to whether the nucleus accumbens itself may be a functional target of “capsular” stimulation. As the authors point out, the nucleus accumbens lies at the nexus between the frontothalamic and limbic projections. Modulation of activity in this region could very well have significant effects on mood and anxiety, which in turn could be of benefit in many refractory psychiatric diseases.

Overall, this report provides additional insight into the region of the internal capsule and nucleus accumbens as a potential target for anxiety, mood, and potentially Tourette syndrome tics.

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The authors have published a case report that is interesting in several aspects. It is, as far as I know, the first published case demonstrating treatment of Tourette syndrome with electrical stimu-

lation of the anterior limbs of the internal capsule. They have described moderate effects of anterior capsular stimulation in a patient with this disorder. It is evident that further study beyond this one case report is necessary before anterior capsular stimulation can be used as a routine treatment for Tourette patients. Using microelectrodes, they have also screened an area in which the neuronal activity is still not well known. Moreover, they have observed stimulation-induced changes in mood.

Such mood changes have also been observed on stimulation of the same area in a different but associated pathological condition, severe OCD (1), in which the Beck Depression Inventory, measured under blinded and randomly administered stimulation on/off conditions, decreased significantly during stimulation. The currently ongoing trials with anterior capsular stimulation for major depression, which are based in part on that trial, seem to point in the same direction. And last but not least, Mayberg et al. (2) confirm in their recent publication that DBS may induce important mood changes in severely depressed patients.

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