Deep Brain Stimulation for Tourette Syndrome

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KEYWORDS

• Deep brain stimulation • Tourette Syndrome • Tics • Neuromodulation

KEY POINTS

- Deep brain stimulation seems to be efficacious in reducing the frequency and severity of tics in many patients with medically refractory Tourette syndrome.
- The 2 most commonly accepted targets, based on clinical experience and expert opinion, are the centromedian-parafascicular nucleus of the thalamus and the internal globus pallidus.
- Patients with Tourette syndrome seem to be more prone to the infectious complications of deep brain stimulation surgery, including hardware and wound infections.
- Future multicenter clinical trials, and the sharing of the results thereof through the Tourette Syndrome Association online database (http://dbs.tsa-usa.org/), are necessary to determine the efficacy of stimulation at various target sites.

INTRODUCTION

Gilles de la Tourette syndrome (TS) is a movement disorder characterized by repetitive motor and phonic/vocal tics first described in 1885 by George Edouard Albert Brutus Gilles de la Tourette. The onset of the disease is typically during adolescence, with a natural history that consists of the waxing and waning of tics until the second decade of life, when many patients experience almost complete resolution of symptoms.[1] As such, the prevalence of the disease is higher in children, with nearly 1% of the pediatric population being affected, whereas only 0.05% of adults carry the diagnosis.[2] Although the severity and frequency of tics diminishes considerably in adulthood, most patients still have identifiable tics, albeit they are mild and infrequent enough to not require treatment.[3]

In addition to the motor features, TS commonly has multiple neuropsychiatric comorbidities including obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), autistic spectrum disorder, and many others, with almost 90% of patients showing some concomitant disorder.[4] As such, in addition to neuroleptic medications used to control tics, other medications including antidepressants are used to treat these psychiatric comorbidities as well.[5]

Despite advancements in behavioral and pharmacologic therapies, there remains a subset of patients with TS who are resistant to these management modalities.[6,7] As a result, there have been attempts to alter the underlying pathologic neural circuitry to alleviate, if not eliminate, tics by manipulating subcortical circuits. The first report of such methods was in 1970 by Hassler and colleagues,[8] who showed partial relief of tics through the ablative lesioning of thalamic nuclei including the median and rostral intralaminar nuclei and the internal ventral oral nucleus. Subsequent studies reproduced varying degrees of

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symptomatic relief, but at the cost of considerable, and frequent, postoperative morbidity including dysarthria, dystonia, and hemiparesis.[9,10]

In 1999, Vandewalle and colleagues[11] reported on the first deep brain stimulation (DBS) of a patient with medically refractory TS. The stereotactic target was the centromedian-parafascicular (CM-Pf) nucleus and the ventro-oral internus (Voi) of the thalamus based on the work by Hassler and colleagues.[8] The patient experienced a complete resolution of tics and tolerated the procedure well with only minimal neurologic sequelae from stimulation (excessive eye blinking). They and numerous other investigators have subsequently examined the effects of DBS at various targets within the corticostriatothalamocortical (CSTC) network thought to be implicated in the pathophysiology of TS, including the CM-Pf/Voi,[11–32] the globus pallidus internus (GPi),[14,16,17,22,30,33–40] globus pallidus externus (GPe),[41] the anterior limb of the internal capsule (ALIC),[21,22,42,43] the nucleus accumbens (NA),[21,22,44–46] and the subthalamic nucleus (STN).[47]

It is thought that through an aberrancy of the CSTC circuitry, the normal gating mechanisms of the basal ganglia in facilitating and inhibiting competing motor, limbic, and cognitive processes are disturbed, resulting in stereotyped behaviors or tics.[48–50] Although the various hubs within this network allow for a diverse selection of targets for neuromodulation, it has resulted in a collection of nearly 40 studies describing more than 100 patients with varying targets, stimulation parameters, and follow-up time. This article consolidates and summarizes the DBS experience for TS to date.

TARGETS FOR TS NEUROMODULATION

Methods for Literature Review

A PubMed search was conducted with the following terms alone or in combination: deep brain stimulation, DBS, Tourette syndrome, and Tourette's syndrome. Articles describing the implantation of patients with TS with DBS leads were identified, and their references used to acquire other articles not immediately found on initial PubMed query. Thirty-nine articles describing the experience of various groups with DBS for TS were found and included in our analysis. The results of the studies are reported here by target of stimulation.

CM-Pf Nucleus and the Voi Nucleus of the Thalamus

The initial target for DBS for TS was based on thalamic lesioning studies performed by Hassler and colleagues[8] in the late twentieth century. This target, namely the centromedian-parafascicular (CM-Pf) nucleus of the thalamus, along with the Voi, is thought to be situated in a unique position within the action-gating pathways of the basal ganglia.[51] Diffusion tensor imaging (DTI) studies in humans show structural connectivity between the CM-Pf nucleus and the putamen, pallidum, NA, amygdala, and hippocampus.[52] These findings corroborate primate studies that reveal sensorimotor projections from the ventrolateral GPi (motor pallidum) to the CM thalamus, and limbic projections from the ventral striatum/NA to the anteromedial GPi (limbic pallidum), which in turn projects to the rostral Pf thalamus and then back to the ventral striatum/NA region (**Fig. 1**).[53] Through

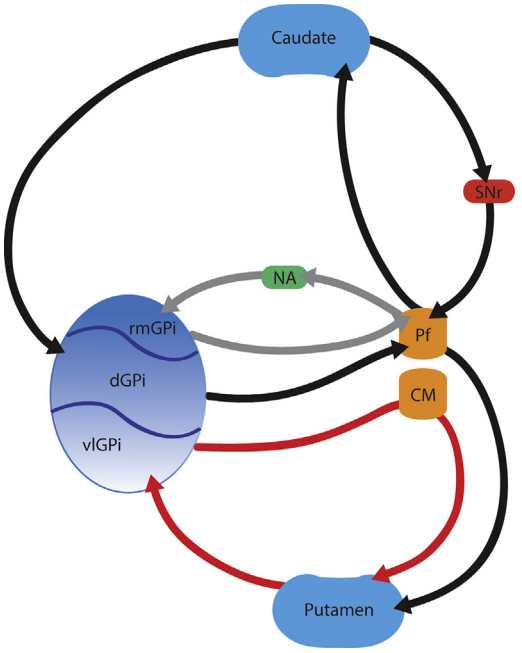

Fig. 1. The putative connectivity of the CSTC circuit in relation to TS DBS targets. The rostromedial (limbic) GPi has limbic projections to the Pf nucleus of the thalamus, which in turn projects to the NA/ventral striatum, which then projects back to the rostromedial GPi (*gray arrows*). The sensorimotor connectivity consists of projections from the ventrolateral (motor) GPi to the CM nucleus of the thalamus, which then projects to the putamen, which then projects back to the ventrolateral GPi (*red arrows*). The cognitive connectivity of the CSTC circuit consists of 2 loops. One consists of projections from the caudate to the dorsal GPi, which in turn projects to the Pf nucleus of the thalamus, which then projects to the putamen (*black arrows*). The other also arises from the caudate, but projects instead to the SNr, and then to the Pf nucleus of the thalamus (*black arrows*). Diagram based on primate studies performed by Sidibe and colleagues[53] (2002). dGPi, dorsal GPi; rmGPi, rostromedial GPi; SNr, substantia nigra pars reticulata; vlGPi, ventrolateral GPi.