Gilles de la Tourette’s syndrome (TS) is an idiopathic neuropsychiatric disorder with an unknown etiology affecting approximately 1% of the population. Diagnosis is based on the childhood onset of chronic involuntary motor and phonics that are not attributable to drugs or known medical causes and persist for no less than 1 cumulative year. The frequency and severity of tic expression follows a waxing and waning pattern, which is noteworthy when considering therapeutic strategies. Mean onset of symptoms occurs at age 5 to 7 years and peaks at age 10. By late adolescence to early adulthood, symptoms either stabilize or remit in approximately two thirds of the population. The disorder is observed worldwide across a wide range of demographics, occurs approximately 4 times more frequently in children, and of deep brain stimulation (DBS) has since been reported in both men and women. Both motor and phonics may occur. They are sudden, repetitive, and purposeless and can be classified as either simple or complex. Simple tics involve one muscle group and can be tonic, dystonic, and/or clonic. Common examples are the following: (1) tonic—isometric contractions such as tensing of the abdominal muscles; (2) dystonic—shudder rotation and ocular deviation; and (3) clonic—rapid movements such as eye blinking, facial twitches, and head, neck, or limb jerking. Phonically, these are manifest as throat clearing, coughing, or grunting. Complex tics involve the coordination of several muscle groups and often appear purposeful. Examples of these include gesturing, hopping, and body jerking (motoric) and humming, making animal sounds, and coprolalia (phonic).

The ability to suppress tics is observed by age 10, the same age at which patients first report premotoric sensations. These urges are associated with dystonic tics, signal the oncoming behavior, and distinguish TS from similar disorders. Tic suppression typically results in stronger rebound tic expression. The change in symptoms during maturation suggests that TS is a developmental disorder. The disorder is highly heritable but presents with a range of clinical phenotypes, although this is likely due to the substantial rate of comorbidities. High among these comorbidities are attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), each of which may be seen in up to 80% of TS patients. Anxiety disorders, learning disabilities, and affective disorders are also commonly observed.

Although TS is generally self-limiting, a portion of the patient population may experience tic burden that is persistent, severe, and medically refractory. Historically, these patients were treated by neurosurgical lesions at a variety of targets. In 1999 the first reversible neurosurgical procedure was performed in a TS patient using stereotactic high-frequency stimulation. The use of deep brain stimulation (DBS) has since been reported in over 130 patients in approximately 25 centers across 14 countries with good results.

**PATHOPHYSIOLOGY**

Results from electrophysiologic, biologic, and modeling investigations have offered new insights into the underlying pathophysiology of TS, but its true pathogenesis has yet to be elucidated. Evidence suggests that TS is a complex disorder involving both heritable and environmental factors. Although genome-wide association studies did not report any common genetic variants that could be identified as risk factors distinguishable in a substantial portion of the patient population, gene network analysis has identified significant changes in the expression of some genes. Anatomic and physiologic evidence suggests that TS results from dysfunction in the recurrent loops of the cortico–basal ganglia–thalamocortical pathway. Pathologic behavior in this network has also been implicated in ADHD and OCD. This circuit is essential for action gating as well as the conversion of goal-directed behavior to automated behaviors. Importantly, this in the cortico–basal ganglia–thalamocortical network consists of direct and indirect pathways that are topographically organized and can be differentiated histologically. It has been proposed that dopamine and γ-aminobutyric acid are the key neurotransmitters involved in the dysfunction of transmission between the cortex and subcortical structures, although glutamate, histamine, serotonin, acetylcholine, and cyclic adenosine monophosphate have also been suggested to play important modulatory roles. Dopamine dysregulation, as presented in the tonic–phasic model, is the most widely accepted neurobiologic theory of TS, a theory that is supported by the clinical observations that dopamine, receptor antagonists effectively reduce tic severity whereas dopaminergic drugs exacerbate symptoms of TS.

**TREATMENT**

Because there is no cure for TS, treatment is targeted toward relieving tic severity and frequency and the disruptive symptoms presented by comorbidities. Therapeutic strategies should seek to decrease symptoms beginning with puberty. In cases in which tics persist, behavioral, pharmacologic, and/or surgical options are available.

**Comprehensive Behavioral Intervention for Tics and Pharmacologic Treatment**

Behavioral therapy may be recommended as a first-line intervention for children and milder cases of TS. Historically, these patients were treated by neurosurgical lesions at a variety of targets. In 1999 the first reversible neurosurgical procedure was performed in a TS patient using stereotactic high-frequency stimulation. The use of deep brain stimulation (DBS) has since been reported in over 130 patients in approximately 25 centers across 14 countries with good results.

**Comprehensive Behavioral Intervention for Tics**

Because there is no cure for TS, treatment is targeted toward relieving tic severity and frequency and the disruptive symptoms presented by comorbidities. Therapeutic strategies should seek to decrease symptoms beginning with puberty. In cases in which tics persist, behavioral, pharmacologic, and/or surgical options are available.

**Pharmacologic Treatment**

Effective, dopamine blocking agents may induce significant side effects, including extrapyramidal symptoms, sedation, and weight gain. Aripiprazole, a partial agonist and antagonist that is reported to be an effective tic suppressant with a lower incidence of adverse effects, could be considered as an additional treatment option.
of severe side effects, is emerging as the medical treatment of choice for TS.

In patients with significant comorbidities, psychostimulants (e.g., methylphenidate) or selective serotonin reuptake inhibitors may be used for the treatment of ADHD and OCD, respectively. For isolated motor tics, botulinum neurotoxin injections are effective and well tolerated.

**Ablative Surgery**

Surgical intervention may be indicated for patients with TS that is severe and medically refractory. For more than 50 years, several reports described the surgical ablation of many different targets in severe disabling cases of TS. In 1962, Baker published the first paper describing ablation for TS, reporting the results of a bimedial leucotomy in a young male suffering from vocal and motor tics, with concomitant obsessive-compulsive symptoms. Following surgical drainage of a postoperative abscess, a significant reduction of tics and obsessive-compulsive behavior was observed. After this, many other groups attempted diverse neurosurgical ablative approaches that included lesioning of the frontal lobes (bimedial frontal leucotomies and prefrontal lobotomies), the thalamus (medial, intralaminar, and ventrolateral nuclei), the limbic system (anterior cingulotomy and limbic leucotomy), the zona incerta, and the cerebellum, as well as combinations of these targets. Altogether, these reports document more than 70 patients who underwent ablative surgery with varied outcomes and complications that ranged from mild transitory deficits to severe permanent deficits.

**Deep Brain Stimulation**

In 1999 DBS, a safer, reversible alternative to neuroablation, was used for the first time in a TS patient. Benabid and colleagues first described thalamic DBS in 1987 as a treatment for medically refractory tremor; however, the reversibility and dynamic adjustability of DBS offered the possibility of revolutionizing the treatment of multiple functional brain disorders, including TS. Today, DBS is both FDA approved and Conformité Européenne (CE) marked for the treatment of Parkinson’s disease, primary dystonia, essential tremor, and OCD. The treatment of TS is still considered investigatory. Nonetheless, since the first report by Vandewalle and colleagues, the procedure has been performed worldwide in over 130 cases. In these reports, seven different targets have been described; however, the majority of reported cases involve DBS at four brain areas: the medial thalamus, GPi, GPe, and internal capsule/nucleus accumbens (IC/NAcc).

**Thalamus**

Based on the positive results observed with neuroablation of the medial thalamus by Hassler and Dieckmann in 1970, this region was targeted for chronic bilateral stimulation in the first DBS procedure for TS. The specific target was the convergence of the centromedian nucleus, the substantia periventricularis, and the nucleus ventro-oralis internus. The first case was performed in a 42-year-old male whose tics decreased from 38 per minute to zero at 12 months postoperatively. Four years later this group reported long-term follow-up of three TS patients after DBS at this same target, demonstrating the safety and efficacy of this procedure in reducing motor and vocal tics with few side effects. Since then, a total of 70 reported cases in this anatomic region have been performed at various medical centers, with certain targeting variations (Table 99-1). The targets most commonly employed were similar to the original centromedian nucleus–substantia periventricularis–nucleus ventro-oralis internus target employed by Vandewalle. In 2007, Maciunas and colleagues described the first prospective double-blind crossover trial for this target in five patients. The authors documented a mean 67% reduction of tics and a 44% improvement in OCD symptoms, with no severe complications. Four years later Ackermans and colleagues described another prospective double-blind randomized crossover trial in six patients in which a 49% decrease in the Yale Global Tic Severity Scale (YGTSS) was observed after 1 year. There were no improvements in comorbidity measures, and mild adverse effects such as decreased energy levels occurred in all patients, along with one impulse generator infection and one small intracranial hemorrhage resulting in a temporary upward gaze palsy. More recently, Okun and colleagues found an 18% mean improvement in the YGTSS with no major adverse events in a level III clinical trial. These authors reported that tic suppression was achieved most commonly with activation of contacts located ventrally in the centromedian thalamic region.

Besides these reports, only case reports and case series have been published, documenting a wide range of improvements (46% to nearly 100%). In a series of reports, Servello and coworkers documented their results for medial thalamic stimulation, employing a target 2 mm anterior to the original. They reported an average tic reduction of 47% in 31 patients, with significant improvements in associated psychiatric disorders. Lee and colleagues reported that targeting of the centromedian-parafascicular complex (CM–Pfc) resulted in a 62% and 39% improvement of tics at long-term follow-up, respectively. Neither group documented serious adverse events. In another series of papers, Kuhn and coworkers reported on the modulation of the parafascicular nucleus, the dorsomedial nucleus, and the lamella medialis, documenting tic reduction ranging from 30% to 80%. In one of these cases, the patient had previously been treated unsuccessfully with GPi stimulation. In 2011, Kuhn and colleagues reported on unilateral stimulation of the ventro-oralis posterior–ventro-oralis anterior–ventro-oralis internus complex in two TS patients. On this occasion, tic reduction ranged from 70% to 100% as measured with the YGTSS.

**Globus Pallidus Internus**

To date, the results of 38 cases of GPi-DBS in TS patients have been reported. Among these, 18 patients received stimulation in the posteroverentralateral segment of the GPi and 20 patients received stimulation in the anteromedial or limbic segment. In 2002, van der Linden and colleagues described for the first time the effects of bilateral stimulation of the GPi in TS. The authors selected the posteroverentralateral GPi based on the experience that stimulation at this target suppressed hyperkinetic motor symptoms in patients with PD. This first case was performed in a 27-year-old male whose tics decreased by approximately 95% after 6 months of treatment. In reality, this patient

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**Table 99-1** Demographic Table of Patients Undergoing Deep Brain Stimulation for Tourette’s Syndrome

<table>
<thead>
<tr>
<th>Target</th>
<th>Total Number of Patients</th>
<th>Level of Evidence</th>
<th>Maximum Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>70</td>
<td>III and IV</td>
<td>72</td>
</tr>
<tr>
<td>GPi</td>
<td>38 (20 AM + 18 PVL)</td>
<td>IV, IV</td>
<td>72</td>
</tr>
<tr>
<td>GPe</td>
<td>2</td>
<td>IV</td>
<td>24</td>
</tr>
<tr>
<td>IC/NAcc</td>
<td>6</td>
<td>IV</td>
<td>39</td>
</tr>
<tr>
<td>STN</td>
<td>1</td>
<td>IV</td>
<td>12</td>
</tr>
<tr>
<td>Multiple</td>
<td>10</td>
<td>III and IV</td>
<td>60</td>
</tr>
<tr>
<td>AM, anteromedial; GPe, globus pallidus externus; GPi, globus pallidus internus; IC/NAcc, internal capsule/nucleus accumbens; PVL, posteroverentralateral; STN, subthalamic nucleus.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
received four DBS electrodes initially, the two in the GPI and two more placed in the medial thalamus bilaterally, which yielded a tic reduction of 80% when stimulated independently. Three years later Diederich and colleagues reported on the effects of bilateral posteroventrolateral GPI-DBS in another 27-year-old male.92 His tic frequency decreased approximately 73% and the intensity of his vocal tics was significantly reduced after 14 months of therapy; however, the authors reported persistent unilateral bradykinesia caused by a small intraparenchymal hematoma, which partly reversed with cessation of stimulation. Gallagher and colleagues93 and Shahed and associates94 reported similar beneficial effects after posteroventrolateral GPI-DBS. Shahed and associates reported tic reduction of 84%, as well as a 69% mean improvement in associated OCD behavior, in a 16-year-old male patient after 6 months. Of note is that the patient required a body shield to prevent him from compulsively manipulating the generator.95 In a series of reports, Dehning and colleagues reported on the long-term follow-up of six TS patients after bilateral posteroventrolateral GPI-DBS.12 The authors described a decrease in the YGTSS of almost 90% and a significant increase in quality-of-life measures. Nonetheless, in two cases stimulation had to be discontinued because of lack of response. In addition, depression and several mild side effects such as moderate dystrophic speech were reported in the initial postoperative phase. These phenomena were attributed to the patients’ difficulties adjusting to their new situation without tics.106,107 In 2009, Dueck and coworkers reported negative effects of posteroventrolateral GPI stimulation in a 16-year-old male with TS and mental retardation and no associated psychiatric conditions.108 Dong and colleagues in 2012 described the effects of unilateral stimulation of the right posteroventrolateral GPI in two male patients who exhibited a greater than 50% tic reduction with improvements in health-related quality of life and no severe adverse effects after 12 months of stimulation.109 More recently, Motlagh and colleagues described the results of an open-label study in eight TS patients treated with thalamic and globus pallidus DBS, two of whom were implanted in the posteroventrolateral GPI.110 This study showed tic reduction of 20% and 44%, respectively, with no effect on associated psychiatric conditions and mild side effects such as hyperkinesias and restless leg syndrome.111 In 2005, Houeto and associates described the effects of bilateral DBS at the anteromedial GPi.112 They hypothesized that the TS is more a “limbic” than a “motor” disorder and, therefore, targeting the limbic part of the GPi might be more successful than targeting the motor region. In 2011, Martínez-Fernández and colleagues also reported on the beneficial effects of anteromedial GPI stimulation.113 In this study, two patients implanted in the posteroventrolateral GPI were compared to three patients implanted in the anteromedial GPI. All patients experienced improvements in tic severity, but the anteromedial GPi–stimulated patients improved more than the posteroventrolateral GPi–stimulated patients, with tic reductions of 54% and 37%, respectively. Sachdev and colleagues have described the largest series of patients implanted in the anteromedial GPi, reporting a 54% mean tic reduction in 17 patients with follow-up of up to 46 months.114

Globus Pallidus Externus

In 2010, Vilela Filho and coworkers reported on the effects of bilateral GPe stimulation in seven patients.115 The GPe was targeted because of hypothesized hyperactivity in this brain area in TS patients. The results of this prospective double-blind study were a mean 74% reduction of tics with only mild adverse effects such as transient depressive mood in one patient. More recently, Pinede and associates reported on one patient treated with GPe stimulation who experienced a 71% tic reduction after 6 months.116 This patient displayed a significant worsening after 2 years of stimulation as a result of the exhaustion of the generator battery.

Internal Capsule and Nucleus Accumbens

DBS of the anterior limb of the IC/NAcc, as part of the ventral striatum, is an established CE-approved therapy for patients suffering from refractory OCD. The same target has been applied to DBS in TS patients based on the hypothesis that TS and OCD share several clinical characteristics. In 2005, Flaherty and colleagues implanted bilateral electrodes in the IC/NAcc region in a 37-year-old woman with severe TS, observing a 25% tic reduction after 18 months.117 Mild apathy and depression were recorded after high-intensity stimulation of the ventral contacts (NAcc), whereas hypomania was reported when the dorsal contacts (IC) were active. Three years later, the electrodes had to be removed because they were damaged by her residual retrocollicic jerks.118 One year later, the patient underwent bilateral implantation of electrodes in the centromedian nucleus, resulting in significant tic reduction without adrenergic symptoms. In 2007, Kuhn and associates described a case of IC/NAcc DBS in one patient, reporting a tic reduction of 41% and an associated OCD behavior decrease of 64% after 30 months.119 In 2009, Neuner and colleagues reported similar findings of a 44% improvement in the YGTSS score and a 56% reduction in comorbid OCD behavior in a single patient.120 One year later, this patient suffered a severe depressive episode that resulted in a suicide attempt.121 Zabek and coworkers described beneficial effects of unilateral (right) NAcc stimulation in a 31-year-old male patient suffering from TS and self-injurious behavior.122 After 28 months of DBS, the patient exhibited an 80% improvement in tics and a significant reduction in the self-injurious behavior. In 2009, Servello and associates reported on the effects of bilateral IC/NAcc DBS in four TS patients.123 Three of the patients had been previously implanted in the thalamus, so IC/NAcc DBS was performed as a “rescue strategy.” The fourth patient had undergone no prior surgery. The effects in all four were disappointing. Similarly, Burdick and coworkers documented a 20% worsening of symptoms in a 33-year-old man with mild motor and vocal tics who also had severe OCD symptoms.124 After a 30-month follow-up period, the authors also observed no significant improvement of the obsessive-compulsive behavior. Sachdev and colleagues described the case of a 32-year-old woman with severe treatment-refractory OCD and TS, the former being the most disabling condition.125 After 14 months of bilateral NAcc DBS, the patient showed an improvement of 57% in tic severity and a 90% improvement in the OCD measures with no reported adverse events.

Other Targets and Multiple Targets

In 2009, Martínez-Torres and associates described the case of a 38-year-old man with PD who also had a history of tics in whom bilateral subthalamic nucleus DBS improved both PD symptoms and tics.126 The observed tic improvement after a 1-year follow-up period was 97% with no reported adverse events, and unrelated to the improvement of parkinsonian motor symptoms. Based on these findings, the authors proposed the subthalamic nucleus as a potential target for DBS in TS patients. The role of subthalamic nucleus DBS in TS is presently being investigated as part of a study in Europe (personal communication).

In total, 10 reported cases are documented in which multiple electrodes for different targets have been implanted. Of these, most had implanted electrodes in two targets ($n = 9$), in only one case were three brain areas stimulated. This single case refers to a 19-year-old male who displayed no significant improvement in tic reduction or OCD-associated behavior after DBS of the
antermddal GPs, posteroventrolateral GPs, and midline thalamus. In 2005, Houeto and colleagues described the results of DBS in one patient who had received two electrodes in the centromedian nucleus of the thalamus and two in the antermddal GPs. Three years later the same group described results in three TS patients in a double-blind, randomized crossover design who received four electrodes in the two same targets. The first report described that both CM-Pfc and antermddal GPs stimulation had a comparable effect on tics (64% reduction with CM-Pfc and 65% reduction with antermddal GPs) and associated behavioral comorbidity. However, CM-Pfc stimulation improved mood and impulsivity, whereas pallidal stimulation had no effect. The second study reported that antermddal GPs stimulation showed a 65% to 96% tic reduction, whereas CM-Pfc stimulation showed a 65% to 96% tic reduction. Moreover, the combination of both targets showed a tic reduction of only 43% to 76%. As mentioned previously, some of the double targeting cases required additional implantation of electrodes in an attempt to rescue the previous unsuccessful stimulation. This often resulted in unsatisfactory outcomes.

**SELECTION CRITERIA**

The evaluation and selection of TS patients as candidates for DBS is a systematic and strict procedure that should be carried out by an interdisciplinary group of experts. Diagnosis should be based on the official Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria, which require an onset of symptoms before the age of 18 years and the presence of motor and at least one phonie tic for at least 1 year. In principle, DBS should only be considered in severe cases in which the condition is refractory to pharmacologic and behavioral therapies. Since 2006, several groups of experts have defined or suggested guidelines for surgical interventions.

The following selection criteria are based on the latest review manuscript on DBS in TS written under the auspices of the Tourette Syndrome Association, with proposed guidelines based on all DBS in TS cases published to date.

**Inclusion Criteria**

- Diagnosis of TS is made by an expert clinician based on DSM-5 criteria.
- The initial definition of a minimum age of 25 years is not considered to be an absolute criterion anymore. In cases in which the candidate is under 18 years of age, a local ethics committee should be consulted.
- Motor and vocal tics should be chronic, severe, and the main source of disability. The severity of the symptoms should be documented through a videotape assessment together with a standardized rating scale, such as the YGTSS. In this respect, the patient should maintain a tic severity score of 35 out of 50 points or higher for an evaluation period of more than 1 year.
- The condition is refractory to pharmacologic and behavioral therapy. The candidate should have displayed no significant response after treatment with three of the different drug regimens: (1) centrally-acting alpha 2 -adrenergic agonists (e.g., clonidine, guanfacine); (2) at least two dopamine antagonists, one typical (e.g., haloperidol, pimozide) and one atypical (e.g., risperidone); and (3) other drugs (e.g., benzodiazepines, topiramate, sertraline).
- If the patient presents comorbid psychiatric or neurological symptoms, he or she should be under treatment and considered stable over the course of 6 months.
- The candidate must have a stable social environment with adequate support. In addition, the cognitive and psychological profile of the patient must demonstrate a capacity to cope with the demand of the procedure and the requested therapeutic recommendations.

**Exclusion Criteria**

Patients should not be considered as candidates for DBS if the presence of suicidal or homicidal ideation has been documented within 6 months of the planned procedure. Furthermore, recent depressive moods or substance abuse should be under treatment and considered a contraindication if they persist. After rigorous clinical evaluation, there should exist no evidence or suspicion of a factitious disorder or the presence of psychogenic tics. Patients should also be excluded from neuurosurgical treatment if they have a medical or neurological condition that could compromise the success of the procedure or the postoperative care and recovery. Other contraindications for TS DBS are the same as for DBS at other targets and for other diagnoses and include structural brain lesions found on magnetic resonance imaging (MRI), and severe cardiovascular, pulmonary, or hematologic abnormalities.

**SURGICAL PROCEDURE AND PERIOPERATIVE MANAGEMENT**

Symptoms should be assessed with validated clinical rating scales pre- and postoperatively in order to monitor surgical outcomes. Recorded data should include the effects of DBS on motor and vocal tics, associated psychiatric disorders, drug regimens, quality of life, cognitive performance, side effects of stimulation, and adverse events related to surgery or the implanted device. The most common and recommended assessment tools are the YGTSS to evaluate the frequency, intensity, complexity, and interference of the tics, and a blinded video evaluation (Video 99-1) to document the changes before and after stimulation (e.g., Rush Video-Based Tic Rating Scale). Standardized evaluations of these videos should be performed by two independent investigators, who must be blinded to preoperative measurements and postoperative stimulation status (i.e., both “on” and “off” stimulation periods should be recorded).

The DBS implantation procedure is performed similarly to that described for DBS for any other indication. In short, a stereotactic frame is fix to the patient’s skull and imaging is performed according to the surgeon’s preference (e.g., stereotactic MRI or a stereotactic computed tomography scan fused with a preoperative MRI). In contrast to DBS for tremor or Parkinson’s disease, for which the procedure is mostly performed under local anesthesia so that one may perform intraoperative test stimulation, DBS in TS cannot be performed under local anesthesia because of the hyperkinetic nature of the disease. Instead, the stimulating leads are implanted under general anesthesia or conscious sedation. If the patient is considered a good candidate for sedation, this can be carried out with either a combination of lorazepam (or lorazepam) and clonidine or with a propofol infusion. In these cases, intraoperative examination during test stimulation could exhibit a series of undesired stimulation-induced side effects that can only be detected during awake brain surgery. If so, this information is typically used to adjust the electrode position. This might be of particular importance for targets such as the centromedian nucleus of the thalamus, which are not directly visible on standard (1.5-T or 3-T) MRI scans. When performing DBS for movement disorders, microelectrode recordings are often used to characterize single-cell activity and define an “optimal” target for electrode implantation. In TS, intraoperative recordings are more appreciated as a powerful research tool.

The position of the active contacts of stimulation should be verified postoperatively using MRI or computed tomography in order to correlate this information with the best-induced clinical effect. A strict record of stimulation parameters should be kept
CONCLUSION AND FUTURE DIRECTIONS

Although DBS has by and large been an effective therapy for patients suffering from medically refractory TS, definitive rigor in order to optimize future adjustments and avoid stimulation-induced side effects. Rigorous psychiatric and neuropsychological assessments, including standardized rating scales for TS and other comorbid disorders, should be carried out on a regular basis.

CONCLUSION AND FUTURE DIRECTIONS

Although DBS has by and large been an effective therapy for patients suffering from medically refractory TS, definitive rigorous studies are still needed to prove and optimize its efficacy. These studies must also examine important questions about the underlying mechanisms of TS pathophysiology. Although dysfunction in the cortico–basal ganglia–thalamocortical network is readily accepted as the pathophysiologic basis of impairment, there are very few invasive studies in human subjects and only one longitudinal study that directly investigated the pathologic changes believed to underlie the disorder. In this study by Maling and colleagues, data are provided from chronic recordings within the centromedian nucleus of the thalamus over the course of DBS therapy. In a cohort of five patients, therapeutic effects were tracked and correlated with the thalamic network state over the course of 6 months. Local field potential recordings elucidated the temporal effects of DBS on the neuropathophysiologic dynamics of TS. The results of their study showed the first clinical correlation between symptomatology and gamma-synchronized oscillations. A clear correlation was shown between a decrease in tic severity and an increase in the power of gamma-band activity. This correlation was echoed in acute recordings, suggesting these dynamic changes in human thalamic gamma-band activity are relevant to the pathophysiology underlying TS. This was substantiated by the nonresponders in the cohort, who also did not exhibit substantial changes in gamma-band activity. Furthermore, the importance of highly circumscribed implantation location was suggested because the two nonresponders experienced electrode placement that was more anterior or ventral when compared to the rest of the cohort. These results suggest the centromedian nucleus of the thalamus is an important therapeutic focus in the pathologic circuit mediating TS, and offers important insights into tic genesis and expression.

DBS offers the opportunity to take electrophysiologic recordings directly from the purported areas of dysfunction. Potential biomarkers for TS can thereby be revealed by tracking specific neurobiologic changes in dysfunctional circuits. Where aberrant oscillatory behavior has been suggested to subserve various neuropsychiatric disorders, this has now been empirically shown to be true in TS. Although previously suggested to be a disorder of hypersynchrony, results from chronic DBS recordings show it is a disorder of hypsynchronous. Changes in the synchronized rhythms of specific frequency band activity (in this case gamma) are reflected as neurophysiologic fluctuations that could be correlated with alterations in motor and behavioral impairment, such as reported by YGTSS scores. Investigations on causality would provide important information as to the source of these aberrations, and thus allow more effective target selection. The inclusion of modern electrical neuroimaging methods in DBS studies would comprehensively elucidate the mechanisms subserving TS.

Knowledge of these biomarkers and their characteristic involvement in the disease state may allow for real-time improvements in target localization during surgery and promote the development of next-generation technologies such as closed loop stimulation. This in turn would lead to improved patient care and reduced stimulation-induced side effects by providing both objective therapeutic assessment of the efficacy of stimulation parameters and tailored treatment postoperatively.

SUGGESTED READINGS


See a full reference list on ExpertConsult.com