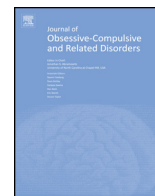




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Deep Brain Stimulation for Tourette syndrome: The Current State of the Field



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ABSTRACT

In 1999, Deep Brain Stimulation (DBS) was introduced as a new therapeutic approach for patients suffering from refractory Tourette syndrome (TS). This initial target was located in the medial part of the thalamus, based on the good results of thalamotomies described by Hassler and Dieckmann (1970). Up until now, more than 100 cases have been published worldwide of Tourette patients receiving DBS. The targets have been diverse and can be divided into four brain areas: the thalamus (medial parts, and ventral parts), the globus pallidus internus (posteroventrolateral part, and anteromedial part), the globus pallidus externus, and the internal capsule/nucleus accumbens. The subthalamic nucleus has also been suggested as a potential target for DBS in TS, based on the good effect of DBS on tics in a patient suffering from Parkinson's disease and TS. In the majority of cases, there was a clear effect on tics. The effect on associated behavioural disorders varies. Although stimulation-induced unwanted effects have been described, severe complications are rare and include two small haematomas at the tip of one electrode.

Serious and lasting side effects or complications are rare. Although stimulation-induced and mainly transient unwanted effects have been described, the positive effect seems clearly to predominate.

The majority of published studies include only a small number of patients. This underlines the importance of all cases being published, and that ideally the same protocol be followed so that results can be compared. A strict selection of patients and a standardized evaluation of the effects on tics, associated behavioural disorders, complications and exact position of the electrodes are therefore of great importance.

The actual published reports suggest that the best effects can be obtained with DBS of the thalamus, and the anteromedial part of the globus pallidus internus.

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1. Introduction

Historically, there have been various attempts to address the symptoms of severe Tourette syndrome (TS) through neurosurgical ablative procedures (Temel & Visser-Vandewalle, 2004). The target sites employed have in general been diverse and have included the frontal lobe (prefrontal lobotomy and bimedial frontal leucotomy), the limbic system (limbic leucotomy and anterior cingulotomy), the thalamus, and also the cerebellum. Additionally there have been

combination approaches such as anterior cingulotomy plus (an) infrathalamic lesion(s). The results, although poorly documented in many cases, often were suboptimal and major side-effects were reported with some ablative approaches and included hemiplegia and dystonia (Temel & Visser-Vandewalle, 2004).

In 1987, Deep Brain Stimulation (DBS) was re-introduced as a treatment for intractable tremor (Benabid, Pollak, Louveau, Henry, & de Rougemont, 1987; Benabid, 2007), following a critical observation that chronic high-frequency stimulation had similar clinical effects to an ablative lesion. Over the last two decades, indications for DBS have evolved beyond tremor, Parkinson's disease and dystonia and the field has moved toward researching neuropsychiatric indications.

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In 1999, DBS was introduced as a chronic therapy for the treatment of intractable TS (Vandewalle, van der Linden, Groenewegen, & Caemaert, 1999). The brain target was chosen based on the previously reported positive results of thalamotomies performed by Hassler and Dieckmann (1970). Since this first report reports that more than 100 patients have been published in the medical literature. Nine different targets have been utilized. These targets can be divided into four brain areas: the thalamus, the globus pallidus internus, the globus pallidus externus, and the internal capsule/nucleus accumbens.

2. Targets

2.1. Thalamus

Following the promising results of TS DBS in the index patient described by Vandewalle et al. (1999), the results were followed up in a second paper authored by the same group. This paper described the general beneficial effects of DBS at 5 years, 1 year and 8 months follow-up in three patients (Visser-Vandewalle et al., 2003). Investigators blinded to the stimulation status recorded tic suppression of 90%, 72% and 83% with stimulation on compared with the stimulation off condition on 10 min long video segments. The authors also observed an improvement but not resolution of associated behavioural disorders. Stimulation induced side-effects included drowsiness, and in a single patient, changes in sexual function (Visser-Vandewalle et al., 2003; Temel et al., 2004). Long-term outcome of the first and second patient was described in a recent report penned by the same authors (Ackermans, Duits, & Temel, 2010). Tic improvement observed at 5 years in patient 1 (90%) was maintained at 10 years (93%). In patient 2, the tic improvement from baseline at 8 months (82%) was similar at 6 years (78%). In a double-blind randomized controlled trial including six patients, performed by the same group, DBS of the medial thalamus showed a significant effect on tics (49% tic reduction after one year) (Ackermans, Duits, & van der Linden, 2011). Reduction of energy levels and subjective changes in ocular movements were described as stimulation-induced side-effects. One patient suffered from transient upward gaze paralysis due to a small haematoma ventral to the tip of one electrode (Ackermans, Temel, Bauer, & Visser-Vandewalle, 2007).

Maciunas et al. (2007) described the effects of DBS in five patients with intractable TS, who underwent close clinical follow-up over a three month period. These authors utilized the same target as previously described by Vandewalle et al. (1999). After the first four post-operative weeks, randomized double-blinded assessments revealed a statistically significant reduction in motor and in vocal tics. At three months, open label assessments revealed that in three out of five patients an average tic reduction of 50% was achieved. Secondary outcome measures of anxiety, depression and obsessive compulsive disorder (OCD) revealed a trend towards improvement. In one patient, a psychotic event was described as stimulation-related.

Bajwa et al. (2007) also reported a reasonable effect of DBS on the medial thalamic target in a single 50 years old patient suffering from TS, OCD, and self-injurious behaviour (SIB). After 24 months of stimulation there was a 66% improvement on the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989), and also a 76% reduction of the Yale–Brown Obsessive Compulsive Scale (YBOCS) (Goodman et al., 1989).

Servello, Porta, Sassi, Brambilla, and Robertson (2008) reported the largest series to date of medial thalamic DBS for TS, with 18 patients being included. Their target was slightly different from that reported by Vandewalle et al. in that the final DBS lead was placed 2 mm more anterior. These authors reported that in a cohort of patients followed for 3–17 months, there was tic

improvement varying between 24% and 79% based on the YGTSS. Fifteen of 18 patients were noted to improve. The authors also described an overall good effect on behavioural disorders; however specific information was not discussed in detail. Temporary disturbances of eye movement were briefly described. Fifteen of these 18 patients were followed for 2 years and in this sub-cohort, 52% had tic improvement (Porta et al., 2009).

A further report documents the response to DBS of the dorsomedial nucleus of the thalamus in a single patient with TS (Vernaleken et al., 2009). Following unsuccessful DBS of the globus pallidus internus (GPi) (anteromedial part), the DBS leads were removed and replaced with thalamic leads. The greatest beneficial effect occurred, when the dorsal contacts (which were located in the dorsomedial nucleus) were activated (36% improvement).

A Chinese group (Lee, Au-Yeung, Hung, & Wong, 2011) published a case report in 2011, describing DBS into the thalamic targets at the centromedian–parafascicular (cm–pf) complex in a male patient suffering from forceful self-injurious motor tics and socially embarrassing vocal tics. At 18 months postoperatively, there was a 58% improvement in the YGTSS. At the same time, Kaido et al. (2011) reported about three Tourette-patients who were targeted at a similar area (cm–pf complex-ventral oral thalamic nuclei). One year after DBS, the scores for the YGTSS decreased between 55% and 70%, but an increase of OCD- and depressive symptoms was described in one patient.

Savica, Stead, Mack, Lee, and Klassen (2012) described three patients with TS who also underwent DBS targeting the bilateral thalamic cm–pf complex. At one-year-follow-up, the mean reduction in the total YGTSS was 70% (range, 60–80%). A slightly different target was used by Huys et al. (2014) by stimulating the ventral anterior and ventrolateral motor part of the thalamus in eight Tourette-patients, two of them with unilateral stimulation (Kuhn et al., 2011). A significant improvement occurred for the YGTSS total score (~58%) after one year. Analysis indicated a strongly significant and beneficial effect of DBS on TS symptomatology, trait anxiety, quality of life and global functioning, while the side effect profile appeared to be rather low. As a special feature also personality dimensions were first tracked structurally, which could reveal any adverse effects of the stimulation.

2.2. Globus pallidus internus

2.2.1. Posteroventrolateral part

Van der Linden et al. (2002) were the first to describe the effects of DBS of the posteroventral (motor) part of the GPi. The patient initially reported received four DBS leads. Two were placed into the medial part of the thalamus, and two into the ventroposterolateral part (vpl) of the GPi. The choice of the pallidal target was based on the reported beneficial effects of GPi-Stimulation for dyskinesia in Parkinson's disease (Guridi, Obeso, Rodriguez-Oroz, Lozano, & Manrique (2008)). The authors performed elective bilateral stimulation of thalamic versus GPi DBS utilizing externalized electrodes later connected to an internal pulse generator. Ultimately, GPi leads were chosen. Six months follow-up of this patient revealed a tic reduction of 95%.

Diederich, Kalteis, Stamenkovic, Pieri, and Alesch (2005) described the beneficial effects of chronic stimulation of motor GPi, utilizing a follow-up period of 14 months (73% tic reduction). There was no reported change in the “very mild compulsive tendencies”. A small haematoma at the tip of the right electrode was described, and this resulted in a deficit of alternating pronation/supination movements of the left hand. Gallagher, Garell, and Montgomery (2006) published a case report about a male Tourette patient who experienced disappearance of vocal tics and marked improvement in neck movements following placement of bilateral

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