Archival Report

Biological Psychiatry

Motor Improvement and Emotional Stabilization in Patients With Tourette Syndrome After Deep Brain Stimulation of the Ventral Anterior and Ventrolateral Motor Part of the Thalamus

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ABSTRACT

BACKGROUND: Since its first application in 1999, the potential benefit of deep brain stimulation (DBS) in reducing symptoms of otherwise treatment-refractory Tourette syndrome (TS) has been documented in several publications. However, uncertainty regarding the ideal neural targets remains, and the eventuality of so far undocumented but possible negative long-term effects on personality fuels the debate about the ethical implications of DBS.

METHODS: In this prospective open-label trial, eight patients (three female, five male) 19–56 years old with severe and medically intractable TS were treated with high-frequency DBS of the ventral anterior and ventrolateral motor part of the thalamus. To assess the course of TS, its clinical comorbidities, personality parameters, and self-perceived quality of life, patients underwent repeated psychiatric assessments at baseline and 6 and 12 months after DBS onset.

RESULTS: Analysis indicated a strongly significant and beneficial effect of DBS on TS symptoms, trait anxiety, quality of life, and global functioning with an apparently low side-effect profile. In addition, presurgical compulsivity, anxiety, emotional dysregulation, and inhibition appeared to be significant predictors of surgery outcome.

CONCLUSIONS: Trading off motor effects and desirable side effects against surgery-related risks and negative implications, stimulation of the ventral anterior and ventrolateral motor part of the thalamus seems to be a valuable option when considering DBS for TS.

Keywords: Deep brain stimulation, Motor tics, Thalamic stimulation, Thalamus, Tic disorder, Tourette, Tourette syndrome, Vocal tics

http://dx.doi.org/10.1016/j.biopsych.2014.05.014

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by the presence of multiple motor and at least one phonic tic persisting for >1 year. In addition, patients with TS frequently have other comorbid psychiatric conditions, such as attention-deficit/hyperactivity disorder, obsessive-compulsive disorder (OCD) and depressive symptoms (1). With regard to the last-mentioned, Eapen *et al.* (2) showed that depressive symptoms correlated significantly with obsessive-compulsive behaviors, aggression, coprophenomena, self-injurious behavior, and TS severity. Higher tic severity and the associated burden of stigmatization and social disability is probably a powerful contributor to the development of depressive symptoms as well (1). However, some studies have shown that depressive symptoms and not tic severity or any other comorbidity was the main predictor of poor quality of life in samples of patients with TS (3,4), underlining the importance of assessing comorbidity.

Based on the assumption that having a socially disabling disorder such as TS would also affect an individual's perception about himself or herself, investigators (5) found that patients with TS differed from healthy controls in terms of personality trait expression. Following the five-factor model of personality, patients with TS and no comorbidities scored lower on both emotional stability, which relates to neuroticism, and extraversion, whereas the whole group of patients with TS, including patients with comorbid conditions—in this case attention-deficit/hyperactivity disorder, OCD, or both—also scored lower on openness and conscientiousness. It was argued that lower scores on emotional stability might indicate a generally increased vulnerability to negative emotions such as anxiety or depression in patients with TS. These subtle differences in emotionality might not be reflected in state measures of negative emotionality, such as the Positive and Negative Affect Schedule and the Beck Depression Inventory, but they increase the likelihood of developing affective disorders at some point in life (5).

A question arising out of these findings is whether comorbid psychopathology ameliorates or personality parameters

SEE COMMENTARY ON PAGE 343

 ISSN: 0006-3223

change if tics decline in response to successful treatment. So far, most investigations have focused on TS and its comorbidity in community or clinical TS populations but not necessarily in treatment-refractory patients. These patients often experience severe TS symptoms and are most likely to display comorbidity (6). Bearing in mind thalamotomies performed in the past and inspired by its positive results in movement disorders such as Parkinson disease, deep brain stimulation (DBS) has also been used to treat TS since 1999 (7). Since then, >100 cases have been published in which DBS has shown great potential for treatment-refractory TS; DBS was often able to exert a positive effect on comorbid disorders as well (8). Although its underlying mechanisms are not yet fully understood, DBS is assumed to exert its effect by modulating neural activity within dysregulated circuits. In 1986, Alexander *et al.* (9) formulated a model according to which several so-called basal-ganglia-cortex-loops are organized in parallel with a different function ascribed to each of them. However, the idea of such separate neural entities turned out to be simplistic. Instead, these different loops seem to form a multitude of interconnections, and applying electrical stimulation to any of the neural structures involved can probably promote diverse motor or behavioral changes (10). This idea might especially apply to the complex anatomy of the thalamus and relate to the frequently witnessed side effects of DBS on behavioral patterns and the patient's affective state.

The aim of the present study is to portray the clinical effect of DBS of ventral anterior and ventrolateral thalamic regions receiving pallidal, nigral, and cerebellar input as well as probably limbic input on TS symptoms, psychiatric comorbidity, quality of life, and side effects in a sample of eight patients with treatment-refractory TS. Because concerns regarding a potentially adverse effect of DBS on personality are continuously being voiced, special attention has been paid to the expression of, or rather the change of, personality traits.

METHODS AND MATERIALS

To document clinically the course of TS symptoms, possible comorbidities, side effects, personality parameters, and the patients' self-perceived quality of life under thalamic DBS, patients underwent psychiatric baseline and postsurgical follow-up examinations.

Patients

During the period 2009–2012, eight patients (three female, five male) 19–56 years old (mean, 33.25; SD, 11.46) fulfilling diagnostic criteria of TS according to ICD-10 (11), DSM-IV-TR (12), and the Tourette Syndrome Diagnostic Confidence Index (13) criteria were recruited at the University Hospital of Cologne, Germany. Table 1 presents demographic data. Although sampling started before the European guidelines for DBS in TS (14) had been published, the on-site interdisciplinary defined inclusion criteria were largely in line with these guidelines. Inclusion in the study was based on a nonresponse to at least three antipsychotic agents of known efficacy in tic disorder and ideally to the alpha$_2$-adrenergic agonist clonidine; a substantial reduction of quality of life and psychosocial functioning; no acute suicidal tendencies at time of operation; and no other severe medical, neurologic, psychiatric, or cognitive disorders that would inordinately increase the risk of anesthesia, the operative procedure, and DBS. Patient no. 3, whose baseline Yale Global Tic Severity Scale (YGTSS) score fell below the recommended cutoff (minimum YGTSS total score = 60, minimum YGTSS tic score = 30), was the only exception. The severity of this patient's mainly one-sided motor tics was not adequately reflected by the YGTSS but became evident after assessment of the patient's modified Rush Video-Based Rating Scale (mRVRS) score (15) [see associated video in Kuhn *et al.* (15)]. All patients gave written informed consent before surgery.

Table 1. Demographic Data

	Patient No.									
	1	2	3	4	5	6	7	8	Mean	SD
Sex	M	M	F	M	F	M	F	M		
Age at DBS	39	24	26	31	33	38	56	19	33.25	11.46
Years of Education	14	10	10	12	13	25	19	9	14	5.45

DBS, deep brain stimulation; F, female; M, male.

Study Design

This open-label trial followed a longitudinal within-subjects design with patients undergoing repeated psychiatric assessments at baseline (T0) and 6 (T1) and 12 (T2) months after stimulation onset. Approval by the Ethics Committee of the University of Cologne was obtained before patient recruitment. Patients were to be consecutively entered into the study.

Material

Assessment of the clinical course of TS symptoms at T0, T1, and T2 was based on the YGTSS (16) and the mRVRS (17). The Yale-Brown Obsessive Compulsive Scale (18), the Beck Depression Inventory (19), and the State-Trait Anxiety Inventory (STAI) (20) were used to assess comorbidity at T0, T1, and T2. The Dimensional Assessment of Personality Pathology–Basic Questionnaire (DAPP-BQ) (21) was used to monitor possible alterations of personality parameters at T0 and T2. The DAPP-BQ is a well-validated and widely used tool for dimensional personality characterization that is ideally suited to assess personality traits ranging in expression from mild to extreme. Both the Global Assessment of Functioning (12) (T0, T1, T2) and the Modular System for Quality of Life (22) (T0, T2) were used to obtain an estimate of patients' self-perceived quality of life. In addition, the Symptom Checklist-90-Revised was administered to obtain a broad range of preoperative psychopathologic parameters that were to be entered as predictors of tic reduction in correlational analysis. Given the already very time-consuming test battery, assessment of this measure was restricted to T0.

Surgery

Based on good experience with former implantations at our site, surgical planning included stereotactically guided implantation of quadripolar electrodes (Medtronic 3387 in patient no. 3 and patient no. 4 and Medtronic 3389 in all other patients; Medtronic, Inc., Minneapolis, Minnesota) into ventral anterior