

Deep brain stimulation in movement disorders The applications reconsidered

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Abstract

In this study the role of DBS in advanced Parkinson disease (PD) is re-evaluated and new indications in the field of movement disorders are explored.

The authors performed unilateral pallidal stimulation in 26 patients with advanced PD. At long-term follow-up review, the motor effect is unsatisfying. The authors conclude that unilateral pallidal stimulation is not a favourable treatment option for patients with advanced PD.

Bilateral subthalamic nucleus stimulation was performed in twenty patients with advanced PD.

After a minimum follow-up of 4 years, there was still a significant improvement in motor function and functional performance in all patients. One side-effect of the stimulation was however rather concerning: four patients presented with stimulation-induced hypomanic to manic characteristics.

Bilateral subthalamic stimulation was performed in four patients with multiple system atrophy-parkinsonism. At long-term follow-up, the patients fared better with than without stimulation.

The authors finally present a completely new indication for DBS: Tourette syndrome (TS). They review the literature on surgical procedures performed in TS, all of which consisted of making lesions.

Three TS patients are presented on which bilateral thalamic stimulation was performed. At long-term follow-up, all major tics had disappeared, as well as associated behavioral disturbances.

Key words: Deep brain stimulation; Parkinson disease; Multiple system atrophy-parkinsonism; Tourette syndrome.

Since more than fifteen years, deep brain stimulation (DBS) is performed on a wide scale in patients with intractable movement disorders.

The benefit of thalamic stimulation to tremor patients has been broadly established since its first application (Pollak *et al.*, 1993; Benabid *et al.*, 1996; Kumar *et al.*, 1999; Schuurman *et al.*, 2000; Lozano, 2000; Krauss *et al.*, 2001). For PD, however, the situation seems to be different: starting with DBS of the thalamus, surgeons moved to the GPi aiming to reduce all Parkinson symptoms, and

eventually ended up at the STN. In this study the role of DBS in advanced Parkinson disease (PD) is re-evaluated and new indications in the field of movement disorders are explored.

DBS in Parkinson disease

This study commenced in January 1996.

In the pre-DBS era, unilateral pallidotomies were considered the treatment of choice in advanced Parkinson disease to alleviate all motor symptoms. Since high frequency stimulation mimics the effects of a lesion, but with far fewer complications, we decided to perform unilateral pallidal stimulation in selected patients with idiopathic Parkinson disease with unilateral or asymmetric distribution of symptoms and, despite optimal pharmacological treatment, severe response fluctuations and/or dyskinesias. Twenty-six patients (20 men and six women) were included in this study. The mean age of these patients at the time of diagnosis was 43.1 ± 10.5 years and the mean age at the time of surgery was 56.2 ± 8.6 years. The side chosen for stimulation was either contralateral to the side affected or, if both sides were affected, contralateral to the more affected side.

After the patient had received a local anesthetic agent, a quadripolar electrode (Medtronic model 3387) was implanted at the side opposite the side affected or, if both sides were affected, the side contralateral to the more affected side. No serious complications occurred. After 3 months, the total Unified PD Rating Scale (UPDRS) (Fahn, 1987) Part III score decreased by 50.7% while patients were in the off-medication state (from 26.5 ± 9.2 to 13.1 ± 6.1) and by 55.4% while they were in the on-medication state (from 10.6 ± 6.3 to 4.7 ± 4.4). Only during the on state was the contralateral effect clearly more pronounced. The UPDRS Part IVa score decreased by 75% (from 3.7 ± 2.5 to 0.9 ± 1.1), and the UPDRS Part IVb score by 54.7% (from 3.3 ± 1.3 to 1.5 ± 1.3).

At long-term follow-up review (32.7 ± 10.7 months), there was an 8.3% increase in the

UPDRS Part III score while patients were in the off state (from 26.5 ± 9.2 to 28.7 ± 7.6), and a 40.2% increase in this score while patients were in the on state (from 10.6 ± 6.3 to 14.9 ± 5.1). The UPDRS Part IVa score decreased by 28.1% (from 3.7 ± 2.5 to 2.7 ± 2.3), and the UPDRS Part IVb score increased by 3.5% (from 3.3 ± 1.3 to 3.4 ± 1.6). Based on these unsatisfactory results at long-term review, the authors conclude that unilateral pallidal stimulation is not an effective treatment option for patients with advanced PD (Visser-Vandewalle *et al.*, 2003).

Between June 1997 and September 1998, patients were selected for subthalamic nucleus (STN) stimulation if they had clinical findings consistent with idiopathic Parkinson disease with bilateral and/or axial symptoms.

We investigated the effects at long-term follow-up, with a minimum follow-up of 4 years.

Twenty patients (15 males, 5 females) were included in this study. Their mean age at time of surgery was 60.9 ± 8.1 years (range 45-76 years).

For the implantation of the electrodes, the target was defined on CT-images. No depth-recordings were performed. UPDRS II (ADL), III (motor performance), IVa (dyskinesias), IVb (motor fluctuations), and Schwab and England (Schwab & England, 1969) scores were evaluated preoperatively during the best on-medication state (on state) and the practically defined off-medication state (off state), at 3 months in the on and off state with the stimulators on, and at 4 years in the on and off state with the stimulators on and off, respectively. At 3 months follow-up, significant improvements were found in the total UPDRS III score, in the off state (from 42.3 ± 9.3 to 19.5 ± 6.4), as well as in the on state (from 18.6 ± 12.2 to 10.1 ± 5.9). All motor subscores improved significantly in the off state. The UPDRS IVa and IVb scores decreased significantly. At long-term follow-up review, there were still significant improvements in the total UPDRS III motor score (from 42.3 ± 9.3 to 24.2 ± 13.2), as well as in all motor subscores, in the off state, during stimulation. In the on state, the only significant improvement was seen in rigidity and akinesia. At 3 months and at long-term follow-up review, there was a significant decrease in the UPDRS II score in the off state as well as in the on state. The Schwab and England scores increased significantly at 3 months and at long-term. The LEU (levodopa equivalent dose) decreased significantly with 47.2% at the long-term follow-up review. Complications included hypomania to mania in four patients. In one, this became apparent only one year after surgery.

Our results indicate that HFS STN results in long-lasting improvement of the motor symptoms, ADL activities and functional performance in patients suffering from advanced PD. The stimula-

tion induced behavioral changes need special consideration.

DBS in multiple system atrophy-parkinsonism (MSA-P)

The third part of this study consisted of the exploration of STN DBS as a potential treatment of multiple system atrophy-parkinsonism (MSA-P). MSA-P is a highly incapacitating disease with a short life-expectancy and very few treatment options (Albanese *et al.*, 1995 ; Quinn, 1989). After a local anesthetic was administered, electrodes were stereotactically implanted bilaterally into the STN in four patients with MSA-P and predominantly akinetorigid symptoms. UPDRS scores were evaluated preoperatively, at 1 month, and at long-term follow-up.

At 1 month the median decrease in the UPDRS III motor score was 22 on the 56-point scale (decreases of 16, 13, 29, and 15 points compared with baseline for Cases 1, 2, 3, and 4, respectively). This was mainly due to an improvement in rigidity and akinesia. The median decrease in the UPDRS II score was 11 on the 52-point scale (respective decreases of 5, 7, 13, and 9 points). At 2 years (mean follow-up 27 months) there was a median decrease in the UPDRS III score of 12 (respective decreases of 18, 13, 21 and 9 points), and in the UPDRS II score of 5 (with respective decreases of 2, 2, 17, and 2), both compared with the stimulation off state.

At long-term follow up there was an increase in the individual Schwab and England scores of 10 to 15% in the stimulation on compared with the stimulation off condition.

There was a beneficial effect of STN HFS in these four patients on both a short-term and a long-term basis (Visser-Vandewalle *et al.*, 2003). A larger prospective study is justified.

DBS in Tourette syndrome

Whereas PD and MSA-P are mainly characterized by hypokinesia, we explored the possible role of DBS in a hyperkinetic disorder, namely Tourette syndrome (TS). TS is a chronic neurological disorder with onset in early childhood and characterized by tics. Tics are sudden, brief, intermittent, involuntary or semivoluntary movements (motor tics) or sounds (phonic or vocal tics). Frequently, TS is found to be a self-limiting disorder as the patient reaches adulthood whereas in a small proportion of the patients the tics continue into adult life and require long-term medication. In addition to motor and vocal tics, patients with TS often have a variety of behavioral symptoms, particularly those associated with attention deficit-hyperactivity disorder and obsessive-compulsive disorder (Cummings & Frankel, 1985 ; Jankovic, 2001 ; Robertson, 2000).

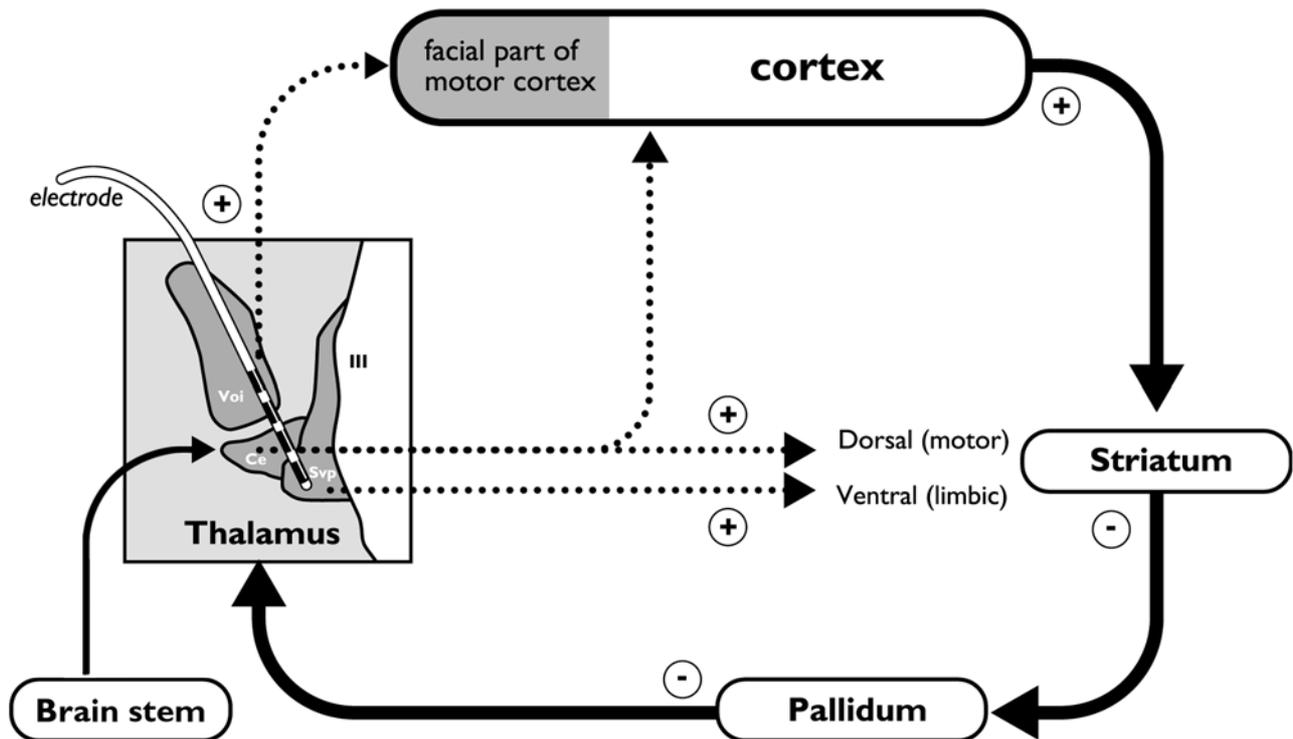


FIG. 1. — Schematic representation illustrating the target of stimulation. *Dotted lines* represent the output, hypothetically reduced by the stimulation, toward the main output structures of the targeted nuclei. Ce = centromedian nucleus ; Spv = substantia periventricularis ; Voi = nucleus ventrooralis internus ; III = third ventricle.

Behavioral therapy has not been proven to be effective at long term. Many different kinds of procedures have been performed on Tourette patients in the past, all of which consisted of making lesions in various parts of the brain (Temel & Visser-Vandewalle, 2004). Frontal lobe operations included prefrontal lobotomies and bimedial frontal leucotomies. The limbic system was targeted during limbic leucotomy and anterior cingulotomy. Thalamic operations included lesioning of the medial, intralaminar and ventrolateral thalamic nuclei. Infrathalamic lesions were performed at the level of Forel's fields (campotomies) and the zona incerta. Cerebellar surgery included dentatotomies. In an attempt to achieve total control of symptoms, more complex operations have been performed such as combined anterior cingulotomies and infrathalamic lesions.

The lack of rationale for choosing specific targets for these ablative procedures is striking and makes most of them hazardous from an ethical point of view, especially when the complications are taken into consideration. These vary from dystonia to even quadriplegia.

We introduce DBS as a new therapeutic approach in intractable TS. We performed the first DBS in a patient with intractable TS in 1997 (Vandewalle *et al.*, 1999), based on the results of thalamotomies described by Hassler in 1970

(Hassler & Dieckmann, 1970 ; Hassler, 1982). We present the long-term outcome of bilateral thalamic stimulation in three patients with TS.

Three male patients (42, 28, and 45 years of age) had manifested motor and vocal tics since early childhood. The diagnosis of Tourette syndrome was made according to the criteria of the Tourette Syndrome Classification Study Group (TSCSG). Any drug or alternative treatment had been either ineffective or only temporarily effective in all three patients. There was no serious co-morbidity.

The target for stimulation was chosen at the level of the centromedian nucleus, substantia periventricularis and nucleus ventro-oralis internus (Fig. 1). After 2 weeks of test stimulation, the pulse generators were implanted.

After a follow-up period of 5 years in the patient in Case 1, 1 year in the patient in Case 2, and 8 months in the patient in Case 3, all major motor and vocal tics had disappeared and no serious complications had occurred. When stimulation was applied at the voltage necessary to achieve an optimal result on the tics, a slight sedative effect was noted in all three patients. In the patients in Cases 1 and 3 there were stimulation-induced changes in sexual behavior (Temel *et al.*, 2004).

Chronic thalamic HFS may be an effective and safe treatment for medically intractable TS in adult patients (Visser-Vandewalle *et al.*, 2003). Unwanted stimulation-induced side-effects may occur.

After more than fifteen years of experience with DBS, we believe it is important to stay critical and to keep re-evaluating the effects in the long-term. Special attention should be paid to side-effects which are not apparent at first glance. STN DBS is since 1993 performed in patients with PD. Only the last few years, the attention is focussed on the stimulation-induced behavioral changes. These personality changes make the STN a less perfect target than it was first considered, based on the good motor results. This finding strengthens the statement "When one has an eye for something, one sees it better": the stimulation-induced behavioral changes after bilateral STN DBS often only become apparent when one specifically asks about them. Teamwork involving not only neurosurgeons and neurologists, but also neuropsychologists and psychiatrists, is of great importance in the field of DBS.

From our point of view, the safety offered by DBS makes the technique of creating permanent lesions in new indications unethical. Unwanted side-effects can occur, and may even appear when the patient is at home (cf. the changes in sexual behavior in the two TS patients) but these can be reversed in the case of DBS.

A final remark is that we believe we should further exploit the advantages and possibilities of DBS. Even in patients with a relatively short life-expectancy with symptoms which react less to DBS than in PD, DBS might be of great value resulting in their functional performance being considerably better than without stimulation.

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