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Single Electrode and Multiple Electrode Guided Electrical Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease

OBJECTIVE: It is still debated to what extent intraoperative electrophysiological techniques contribute to the outcome of subthalamic nucleus (STN) deep brain stimulation (DBS). Intraoperative electrophysiological recordings for identification of the STN can be made with one electrode or with multiple, simultaneously implanted electrodes. The latter provide more detailed information about the electrophysiological boundaries of the STN; however, implantation of several electrodes at one time might increase the risk of bleeding. Here we report the results of a study of patients with advanced Parkinson's disease, in which one group of patients underwent bilateral STN DBS with electrophysiological recordings from a single electrode, and the other group received STN DBS with multiple (five or fewer) simultaneously implanted electrodes.

PATIENTS AND METHODS: Fifty-five patients suffering from advanced Parkinson's disease who underwent bilateral STN stimulation were included in this study. Thirty-two patients underwent STN DBS guided by a single semi-microelectrode, and 23 patients underwent STN DBS guided with simultaneously implanted multiple microelectrodes. All patients were examined preoperatively and 3 and 12 months postoperatively with regard to activities of daily living, motor functions, and neuropsychological functions.

RESULTS: We found that the simultaneous implantation of multiple electrodes does not increase the risk of bleeding or any other major intracranial complication. The use of multiple electrodes resulted in better motor results when compared with patients who underwent STN DBS guided with a single recording electrode. There were significantly more improvements in patients' tremor and rigidity, and as a consequence, a better total Unified Parkinson Disease Rating Scale, Part III score was identified during the medication-off phase. Despite better motor effects, patients treated with multiple electrodes showed subtle deterioration in neuropsychological functions, particularly in memory function.

CONCLUSION: STN DBS performed with multiple electrophysiological recording electrodes resulted in better motor outcome but induced specific mild declines in neuropsychological functions.

KEY WORDS: Deep brain stimulation, Microelectrode recording, Parkinson's disease, Subthalamic nucleus

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Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is presently widely performed for the treatment of patients suffering from advanced Parkinson's disease (PD). Many studies have appeared describing the short- and long-term effects of bilateral STN DBS for patients with PD (2, 4, 8–11, 13–15, 21). These studies consistently show that patients with PD significantly benefit from this procedure. However, the results vary between centers (7). It is likely that these differences in outcome are at least partly related to differences in surgical procedure. Even at present there is no standard procedure, and the imaging technique for localization of the target and the use of intraoperative electro-

physiological recordings and test stimulations often depend on the surgeon's preferences and experience.

It has been suggested that electrophysiological identification of the STN is an important tool in the correct placement of stimulating electrodes (3). Presently, it is still debated to what extent intraoperative electrophysiological techniques contribute to the outcome of STN DBS. A recent study showed that patients who underwent implantation of STN electrodes with intraoperative electrophysiological recordings had significantly better results with regard to Parkinsonian motor disability than patients who underwent the same surgery without these techniques (5). Intraoperative electrophysiological recordings for identification of the STN can be made with one electrode or with multiple simultaneously implanted electrodes. The latter provide more detailed information about the electrophysiological boundaries of the STN, but implantation of several electrodes at one time might increase the risk of bleeding. The key question is whether this supposed increase in risks is counterbalanced by a better clinical outcome. Here we report the results of a study of patients with advanced PD, in which one group of patients underwent bilateral STN DBS with electrophysiological recordings from a single electrode, and the other group received STN DBS with multiple (five or fewer), simultaneously implanted electrodes.

PATIENTS AND METHODS

Patients

Between November of 1999 and June of 2005, patients were selected for STN stimulation if they had clinical findings consistent with idiopathic PD and, despite optimal pharmacological treatment, severe response fluctuations and/or dyskinesias. Good initial L-dopa response was an absolute criterion. The one exception to this was the inclusion of patients who demonstrated L-dopa-resistant rest tremor. Exclusion criteria consisted of significant atrophy, multiple white-matter lesions, or other focal brain abnormalities on magnetic resonance imaging, Hoehn and Yahr Stage 5 at the best moment of the day, a score of less than 24 on the Mini-Mental State Examination, psychosis, and general contraindications for surgery such as severe hypertension or blood coagulation disorders. Informed consent was obtained from all patients, and STN DBS was approved by the local ethics committee.

In the first group of consecutive patients (Group A), surgery was performed using a single recording electrode. In the second group of consecutive patients (Group B), surgery was performed using multiple recording electrodes.

Surgery

The patient was withdrawn from antiparkinsonian drugs for 36 hours before the scheduled surgery. While the patient received a local anesthetic, the stereotactic procedure was performed using a CRW stereotactic frame (NeuroPlan; Radionics, Ghent, Belgium). The target was determined from fused computed tomographic (CT) and magnetic resonance images with the following coordinates: 11 to 12 mm lateral to the anterior commissure-posterior commissure line, at the mid-commissural point, and 4 mm inferior to the intercommissural line. Special attention was given to the trajectory planning for all patients to avoid blood vessels during electrode installation. After making a precoronal burr hole, recording electrodes were introduced.

In Group A patients, a single semi-microelectrode (Model RAD SME-E; Radionics) was introduced 10 mm above the presumed target for electrophysiological recordings (Neuromap; Radionics). Recordings were performed in steps of 0.5–1 mm, usually to 4 or 5 mm below the target. The STN was characterized by a neuronal firing pattern consisting of increased baseline activity and a strong increase in high-voltage spikes, which were usually present over a length of 4 to 5 mm (*Fig. 1A*). Subsequently, the electrode was withdrawn and another electrode for test stimulation was introduced (Model TC 112; Radionics).

Intraoperative macrostimulation was initiated with a frequency of 100 Hz and a stimulus duration of 0.1 millisecond. This was continued stepwise every 2 mm, from 4 mm above the target to 4 mm below the target. At each step, the stimulus intensity was increased at increments of 0.5 V until the desired response was achieved or until unwanted side effects occurred. At each point of test stimulation, the clinical response was evaluated by the neurologist. The following clinical parameters, using the Unified Parkinson Disease Rating Scale (UPDRS), were scored: tremor (if present) and rigidity in all four extremities, finger taps, hand movements and/or handgrips, and leg agility. If a clinical response was not present at or several millimeters below the target, the electrode was withdrawn, and a second target through a different trajectory was chosen, 2 mm anterior, posterior, medial, or lateral to the

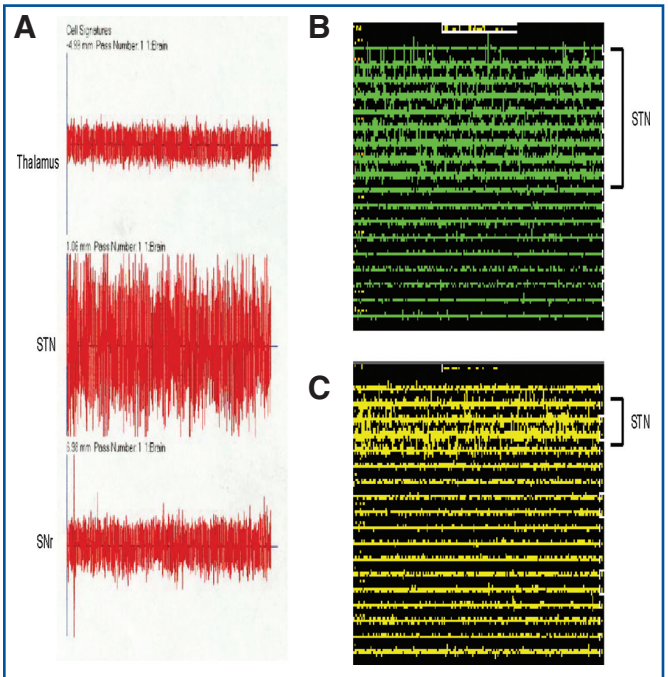

FIGURE 1. A, *a representative image of electrophysiological activity measured by a single semi-microelectrode during STN DBS surgery. The upper trace is 4 mm above target (thalamic activity), the middle trace is 1 mm under target (typical STN activity), and the lower trace is 7 mm below target (substantia nigra pars reticulata [SNr] activity).* **B** *and* **C**, *representative images of electrophysiological activity measured by five simultaneously implanted microelectrodes; central electrode (***B***) and posterior electrode (***C***). In both trajectories, STN activity is indicated (*black line*). Typically, STN activity is characterized by a neuronal firing pattern consisting of increased baseline activity and a strong increase in high-voltage spikes, which are usually present over a length of 3 to 6 mm.*

initial target. When a good effect was identified with the absence of side effects, the test electrode was replaced by the final quadripolar electrode (Model 3389; Medtronic, Minneapolis, MN), with the second-deepest pole at the level of the best clinical result.

In the patients of Group B, normally five microelectrodes were simultaneously implanted (Leadpoint; Medtronic). When the trajectory planning had shown it to be impossible to avoid a blood vessel when using five electrodes, then four or, if necessary, fewer electrodes were used. Recordings were performed in 0.5–1-mm steps from 10 mm above the target, usually until 4 to 5 mm below the target. The electrode with the most typical STN pattern (*Fig. 1, B* and *C*) over the longest distance was selected for test stimulation. This microelectrode was retracted until its tip was hidden, and the tip of its outer cannula, designed for test stimulation, was installed at 4 mm above the target. The other four (or fewer) electrodes were left in place but retracted for 20 mm. Stimulation was performed in the same way as for Group A. When we obtained a positive clinical result without unwanted side effects, the electrode was withdrawn and replaced by the quadripolar electrode while the other four electrodes were temporarily left in place to maximize the correct positioning ("anchoring effect") of the final electrode. When we encountered an unsatisfying clinical effect, another electrode was chosen for test stimulation.

In both patient groups, the position of the final electrodes was verified using fluoroscopy. This electrode was finally fixed in the burr hole with methylmethacrylate and connected to an extension cable, which was externalized at a distance of approximately 7 cm from the burr hole, and connected to an external pulse generator (Model 3625; Medtronic). The same procedure was performed on the contralateral side. On the second postoperative day, all patients underwent CT imaging to evaluate the relative position of the electrodes and to detect (a)symptomatic bleedings or other complications. The images were evaluated by an independent neuroradiologist. When 1 week of evaluation with test stimulation showed a clear effect on parkinsonian symptoms, a second operation was performed under general anesthesia, to implant the pulse generator infraclavicularly or abdominally (Itrell III or Kinetra; Medtronic).

To compare the duration of surgery for both groups, we recorded this information for all patients.

Motor Evaluations

Disease stage was assessed using Hoehn and Yahr scores, activities of daily living (ADL) were evaluated using the UPDRS, Part II, and motor performance was evaluated using the UPDRS, Part III. The complications of drug therapy were evaluated using the UPDRS, Part IV score. These scores were evaluated preoperatively, 3 months postoperatively, and 1 year postoperatively. Evaluations were performed in the best medication-on and practically defined medication-off phases, with both stimulators on and off for 12 hours as described by the Core Assessment Program for Intracerebral Transplantation for PD (12). This resulted in four experimental conditions. All data were collected by the same investigators in the same sequence, and the patient as well as the investigator were aware of the status of the medication and stimulation.

Medication

Medication intake was defined by the L-dopa equivalent dose, which equals 100 mg of L-dopa or 133 mg of L-dopa modified-release preparations or 1 mg of pergolide, 10 mg of bromocryptine, 1 mg of cabergoline, 6 mg of ropinirole, 1 mg of lisuride, 1 mg of pramipexol, or 20 mg of apomorphine. A stable level of medication was maintained for at least 2 months before surgery.

Neuropsychological and Psychiatric Evaluations

All patients underwent neuropsychological and psychiatric evaluation preoperatively and at 3 months and 1 year postoperatively in the on-phases. The neuropsychological evaluation was based on a selection of standard neuropsychological tests often performed on patients with PD. If available, alternate forms were used at follow-up time points to reduce practice effects. The selection included the following tests.

Controlled Oral Word Association Test

The Controlled Oral Word Association Test (18) consists of three word-naming trials. During 1 minute, the patient must name as many words as possible beginning with a given letter. The total score is the number of correct words provided in 3 minutes. Alternate versions were used at follow-up.

Semantic Fluency

In the Semantic Fluency test (16), the patient must name as many words as possible belonging to animal and occupational categories within 1 minute. The total score is the number of correct words provided in 2 minutes.

California Verbal Learning Task (Dutch Version)

The California Verbal Learning Task (6) affords an analysis of learning and retention and is specifically designed to assess the use of semantic associations. In the present study, raw scores are used and are based on five learning trials of a 16-word list, including four categories (total score per trial, 1–5), a free trial for long delay (delayed reproduction), and recognition of the target words presented with distractors, including words from an interference list. We used alternate forms of this test at follow-up.

Recognition Memory Test

We used the nonverbal form of the Recognition Memory Test (22), which contains 50 stimulus items (male faces) followed by a recognition trial that pairs the target with 50 distractors. Retention is assessed immediately after the presentation. Raw scores range from 0 to 50.

Stroop Color Word Test

The Stroop Color Word Test (19) measures perceptual interference, response inhibition, and selective attention by having the subject 1) read color names, 2) name colors, and 3) name the ink color used on words that are printed in a nonmatching color (the interference trial). The test is scored by measuring the time to complete each trial and the number of errors in the interference trial.

Psychiatric evaluations involved open interviews with the patient and family members to discuss and observe clinically significant changes in behavior. Additionally, the Dutch version of the Beck Depression Inventory (2nd edition) (1) was completed to assess the existence and severity of depression. This edition of the Beck Depression Inventory includes a self-report measure of 21 items. Each item deals with a particular aspect of depression and contains four statements of graded severity (four-point scale ranging from 0 for absence to 3 for most severe). Total scores range from 0 to 63, with scores higher than 20 indicating moderate to severe depression.

Statistical Analysis

Data are presented as means and standard deviations. The changes in motor parameters between baseline (preoperative), 3 months postoperatively, and 1 year postoperatively were analyzed using repeated-measures analysis of variance with time as the within-subjects factor

and group as the between-subjects factor. For assessments performed in on- and off-phases, these analyses were repeated for each phase for each clinical parameter. For neuropsychological parameters, change scores were calculated by distracting the scores at baseline from those at 3 months and 1 year postoperatively. These scores were analyzed using nonparametric tests (Mann-Whitney *U* test). A *P* value of less than 0.05 was considered to be statistically significant for all analyses. All data were analyzed using SPSS-pc, version 12.0.1 software (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

Fifty-five patients suffering from advanced PD who underwent bilateral STN stimulation were included in this study (*Table 1*). Group A consisted of 32 patients (21 men and 11 women) and Group B consisted of 23 patients (15 men and 8 women). The mean age of the patients at the time of surgery was 59.4 years in Group A and 64.6 years in Group B. The mean disease durations were 13.1 and 11.3 years for Groups A and B, respectively. The preoperative Hoehn and Yahr stage in the medication-on phase was similar in both groups.

In Group A, three patients died due to an unrelated cause, and in Group B, one patient died and one patient went for follow-up to another hospital.

Details of Surgery

While making the electrophysiological recordings, we observed typical STN activity on the right side over a length of 4.7 ± 1.5 mm in Group A and of 4.8 ± 1.5 mm in Group B. On the left side, the heights of STN activities were 4.1 ± 1.5 mm and 4.8 ± 0.9 mm in Groups A and B, respectively. The differences between the groups were not statistically significant (*F test*, <3.6; not significant).

In Group A, a mean of 1.5 ± 1.0 trajectories (range, 1–5 trajectories) for the right STN and 1.3 ± 0.8 trajectories (range 1–5 trajectories) for the left STN were necessary to find a satisfactory effect on macrostimulation. In Group B, five microelectrodes were used for simultaneous electrophysiological recordings except for three patients. In these patients, one electrode (typically the medial electrode) was excluded because of a blood vessel that was observed during trajectory planning and could not be avoided despite adjustment of the stereotactic angles. In the right STN, the trajectory chosen for implantation of the final quadripolar electrode was the central trajectory for 36% of the patients (8 patients), the anterior trajectory for 27% of the patients (6 patients), the lateral trajectory for 23% of the patients (5 patients), the posterior trajectory for 9% of the patients (2 patients), and the medial trajectory for 5% of the patients (1 patient). For implantation of the final quadripolar electrode in the left STN, we chose the central trajectory in 32% of the patients (7 patients), the anterior trajectory in 27% of the patients (6 patients), the lateral trajectory in 18% of the patients (4 patients), the posterior trajectory in 14% of the patients (3 patients), and the medial trajectory for 9% of the patients (2 patients).

All patients experienced at least a 50% improvement of their key symptom(s) (akinesia, rigidity, or tremor) during intraoperative macrostimulation.

TABLE 1. Patient characteristics for 55 patients suffering from advanced Parkinson's disease who were included in the study

Characteristic	Group A	Group B
Sex (no.)		
Male	21	15
Female	11	8
Age at surgery (yr)		
Mean ± standard deviation	59.4 ± 7.0	64.6 ± 9.6
Range	43–75	43–79
Disease duration (yr)		
Mean ± standard deviation	13.1 ± 5.1	11.3 ± 5.6
Range	8–21	3–21
Hoehn and Yahr stage, preoperative, medication-on		
Mean ± standard deviation	2.7 ± 1.2	2.7 ± 0.6
Range	2–5	2–5

Duration of Surgery

The duration of surgery was equal in both groups (*F test*, 1.20; not significant). In Group A, the mean duration of surgery from skin incision to skin closure was 5.38 hours ± 52.5 minutes (range, 3.43–7.05 hours), and in Group B, mean duration was 5.37 ± 1.37 hours (range, 2.43–8.47 hours).

Activities of Daily Living

Bilateral STN stimulation improved the total UPDRS, Part II score by 36.2% in Group A (*F test*, 22.39; $P < 0.01$) and by 35.4% in Group B (*F test*, 22.44; $P < 0.01$) in the medication-off phase at 3 months postoperatively. At 1 year postoperatively, these improvements were 31.7% (*F test*, 14.34; $P < 0.01$) and 44.0% (*F test*, 9.93; $P < 0.05$) in Groups A and B, respectively. The changes in the UPDRS, Part II score after 3 months and 1 year were not different between Groups A and B (*F tests*, < 0.80; not significant) in the medication-off phase (*Tables 2 and 3*).

In the medication-on phase, there were small improvements in the total UPDRS, Part II score in both groups at 3 months and 1 year postoperatively (*Tables 2* and *3*). These improvements were not statistically significant (*F tests*, 2.2; not significant).

Motor Functions: UPDRS, Part III

Bilateral STN stimulation improved the total UPDRS, Part III score in the medication-off phase by 44.5% (*F test*, 28.7; $P < 0.01$) in Group A and by 56.5% (*F test*, 46.1; $P < 0.01$) in Group B at 3 months postoperatively (*Tables 2* and *3*). The improvements at 1 year postoperatively in the medication-off phase were 40.9% (*F test*, 28.2; $P < 0.01$) and 55% (*F test*, 107.3; $P < 0.01$) in Groups A and B, respectively. The total UPDRS, Part III score was significantly more improved in patients of Group B compared with patients in Group A at 1 year postoperatively (*F test*, 4.2; $P < 0.05$).

TABLE 2. Changes in Unified Parkinson Disease Rating Scale scores for Group A with bilateral subthalamic nucleus deep brain stimulation[a]

Scoring factor	Baseline Score	3 Months Postoperatively		1 Year Postoperatively	
		Score	*P* value	Score	*P* value
Medication-off					
UPDRS, Part II	22.1 ± 7.2	14.1 ± 7.4	<0.01	15.1 ± 8.6	<0.01
UPDRS, Part III total	41.1 ± 13.9	22.7 ± 14.7	<0.01	24.3 ± 13.6	<0.01
Tremor	3.4 ± 4.2	2.6 ± 3.8	ns	2.7 ± 3.8	ns
Rigidity	8.8 ± 5.2	5.1 ± 4.4	<0.05	4.8 ± 3.3	<0.01
Akinesia	15.4 ± 5.5	7.7 ± 4.8	<0.01	8.8 ± 5.5	<0.01
Bradykinesia	2.5 ± 1.2	1.4 ± 1.3	<0.01	0.9 ± 1.2	<0.01
Freezing	2.3 ± 2.1	0.8 ± 0.9	<0.01	1.2 ± 1.9	<0.05
Gait	2.2 ± 0.9	1.2 ± 1.2	<0.01	0.8 ± 1.2	<0.01
Medication-on					
UPDRS, Part II	10.5 ± 7.7	8.7 ± 4.6	ns	10.3 ± 4.7	ns
UPDRS, Part III, total	18.5 ± 10.2	11.1 ± 6.0	<0.01	14.4 ± 6.8	<0.05
Tremor	1.7 ± 3.9	0.8 ± 1.4	ns	0.9 ± 1.5	ns
Rigidity	4.7 ± 3.8	2.5 ± 2.4	<0.05	2.5 ± 2.9	<0.01
Akinesia	6.2 ± 3.8	3.1 ± 2.7	<0.01	5.0 ± 4.3	ns
Bradykinesia	0.9 ± 0.8	0.5 ± 0.6	<0.01	0.5 ± 0.7	<0.05
Freezing	0.6 ± 0.8	0.3 ± 0.6	ns	0.4 ± 0.8	ns
Gait	0.9 ± 0.6	0.6 ± 0.8	ns	0.5 ± 0.8	ns
UPDRS, Part IV	6.6 ± 3.5	1.7 ± 1.6	<0.01	1.2 ± 1.6	<0.01
Medication: L-dopa	840.2 ± 400.1			490.5 ± 339.2	<0.01

[a] UPDRS, Unified Parkinson Disease Rating Scale; ns, not significant.

Concerning the individual items in the UPDRS, Part III score, at 3 months postoperatively there were significant improvements in rigidity (Group A: *F test*, 8.07; $P < 0.05$; Group B: *F test*, 28.81; $P < 0.01$), akinesia (Group A: *F test*, 29.35; $P < 0.01$; Group B: *F test*, 14.35; $P < 0.01$), bradykinesia (Group A: *F test*, 18.31; $P < 0.01$; Group B: *F test*, 23.40; $P < 0.01$), freezing (Group A: *F test*, 19.24; $P < 0.01$; Group B: *F test*, 6.12; $P < 0.05$), and gait (Group A: *F test*, 49.65; $P < 0.01$; Group B: *F test*, 6.26; $P < 0.05$) in both groups in the medication-off phase. However, reduction in tremor was only significant in Group B (*F test*, 5.31; $P < 0.05$). At 1 year postoperatively, again rigidity (Group A: *F test*, 32.19; $P < 0.01$; Group B: *F test*, 33.78; $P < 0.01$), akinesia (Group A: *F test*, 11.62; $P < 0.01$; Group B: *F test*, 13.96; $P < 0.01$), bradykinesia (Group A: *F test*, 25.79; $P < 0.01$; Group B: *F test*, 16.67; $P < 0.01$), freezing (Group A: *F test*, 4.75; $P < 0.05$; Group B: *F test*, 6.58; $P < 0.05$), and gait (Group A: *F test*, 45.08; $P < 0.01$; Group B: *F test*, 9.26; $P < 0.05$) were significantly improved in the medication-off phase. Improvement of tremor was only significant in Group B (*F test*, 12.25; $P < 0.01$). The improvements in tremor (*F* tests > 4.74; $P < 0.05$) and rigidity (*F* tests > 3.86; $P < 0.05$) were significantly greater in Group B compared with Group A at both 3 months and 1 year postoperatively.

In the medication-on phase, the total UPDRS, Part III score improved by 40.0% (*F test*, 13.56; $P < 0.01$) and by 33.7% (*F test*, 13.31; $P < 0.01$) at 3 months postoperatively in Groups A and B, respectively. At 1 year postoperatively, these improvements were 22.2% (*F test*, 4.86; $P < 0.05$) and 28.9% (*F test*, 6.86; $P < 0.05$) in Groups A and B, respectively. These improvements were similar in both groups (*F* tests < 2.85; not significant).

In the medication-on phase, bilateral STN stimulation improved rigidity (Group A: *F test*, 5.41; $P < 0.05$; Group B: *F test*, 22.99; $P < 0.01$), bradykinesia (Group A: *F test*, 7.77; $P < 0.01$; Group B: *F test*, 4.92; $P < 0.05$), and akinesia (Group A: *F test*, 9.33; $P < 0.01$; Group B: *F test*, 13.62; $P < 0.05$) at 3 months postoperatively. Tremor was significantly reduced only in Group B (*F test*, 10.78; $P < 0.01$). At 1 year postoperatively, the items rigidity (Group A: *F test*, 15.22; $P < 0.01$; Group B: *F test*, 7.52; $P < 0.05$) and bradykinesia (Group A: *F test*, 4.92; $P < 0.05$; Group B: *F test*, 9.48; $P < 0.05$) showed a significant improvement. Tremor was similar to 3 months postoperatively, only significantly reduced in Group B (*F test*, 16.04; $P < 0.01$).

Complications of Drug Therapy: UPDRS, Part IV

The total UPDRS, Part IV score was improved by 74.8% (*F test*, 57.24; $P < 0.01$) and 80.7% (*F test*, 17.23; $P < 0.01$) at 3

TABLE 3. Changes in Unified Parkinson Disease Rating Scale scores for Group B with bilateral subthalamic nucleus deep brain stimulation[a]

Scoring factor	Baseline Score	3 Months Postoperatively		1 Year Postoperatively	
		Score	*P* value	Score	*P* value
Medication-off					
UPDRS, Part II	19.8 ± 7.0	19.6 ± 10.6	<0.01	11.1 ± 7.7	<0.05
UPDRS, Part III total	45.1 ± 13.7	19.6 ± 10.6	<0.01	20.3 ± 10.2	<0.01
Tremor	5.6 ± 4.4	3.3 ± 2.2	<0.05	3.9 ± 1.2	<0.01
Rigidity	11.1 ± 5.9	3.0 ± 2.9	<0.01	2.8 ± 3.7	<0.01
Akinesia	14.1 ± 6.1	7.1 ± 3.9	<0.01	8.6 ± 5.3	<0.01
Bradykinesia	2.3 ± 1.3	0.7 ± 0.9	<0.01	0.4 ± 0.7	<0.01
Freezing	1.9 ± 1.7	1.0 ± 1.3	<0.05	0.7 ± 1.1	<0.05
Gait	1.5 ± 1.3	0.8 ± 1.0	<0.05	0.8 ± 1.2	<0.05
Medication-on					
UPDRS, Part II	12.8 ± 5.8	11.5 ± 8.6	ns	11.1 ± 7.7	ns
UPDRS, Part III, total	24.9 ± 12.9	16.5 ± 8.4	<0.01	17.7 ± 9.4	<0.05
Tremor	5.9 ± 5.1	2.6 ± 2.4	<0.01	3.0 ± 1.5	ns
Rigidity	6.6 ± 4.6	1.9 ± 1.8	<0.01	2.3 ± 2.5	<0.01
Akinesia	9.6 ± 5.2	5.8 ± 3.9	<0.01	6.2 ± 4.9	ns
Bradykinesia	1.2 ± 1.1	0.6 ± 0.7	<0.05	0.3 ± 0.6	<0.05
Freezing	1.3 ± 2.1	0.8 ± 1.2	ns	0.6 ± 1.0	ns
Gait	1.0 ± 0.8	0.6 ± 0.9	ns	0.4 ± 0.8	ns
UPDRS, Part IV	6.2 ± 3.1	1.2 ± 1.5	<0.01	0.6 ± 0.7	<0.01
Medication: L-dopa	798.4 ± 475.2			364.9 ± 354.5	<0.01

[a] UPDRS, Unified Parkinson Disease Rating Scale; ns, not significant.

months postoperatively, and by 81.6% (*F test*, 17.23; $P < 0.01$) and 90.6% (*F test*, 14.28; $P < 0.01$) at 1 year postoperatively in Groups A and B, respectively (*Tables 2* and *3*). These improvements in Groups A and B were similar (*F* tests < 0.31; not significant).

Medication: L-dopa Equivalent Dose

Bilateral STN stimulation resulted in a profound decrease of the L-dopa equivalent dose of 49.8% (*F test*, 50.27; $P < 0.01$) and 41.7% (*F test*, 38.81; $P < 0.01$) in Group A and of 49.0% (*F test*, 26.26; $P < 0.01$) and 54.4% (*F test*, 15.29; $P < 0.01$) in Group B at 3 months and 1 year after surgery, respectively (*Tables 2* and *3*). These reductions were not statistically different between Groups A and B (*F* tests < 0.44; not significant).

Active Contacts and Stimulation Parameters

In 26 patients (81.1%) of Group A, the contact at the level of the target was activated on the right side (*Fig. 2*). In four (12.5%) patients, the contact above target, in one patient, the contact at two levels above target, and in one patient, the contact below target was activated on the right side. On the left side in Group A, the following was activated: in 24 patients (75%) the target contact, in 4 patients (12.5%) the contact above target, in 2 patients the contact at two levels above target, and in 2 patients the contact below target.

For Group B, these distributions on the right side were as follows: in 17 patients (73.9%), the contact at the level of the target, in 4 patients (17.3%), the contact above target, in 1 patient, the contact at 2 levels above target, and in 1 patient, the contact below target. On the left side, again in 17 patients (73.9%) the target contact was activated, in 4 patients (12.5%) the contact above target was activated, in one patient the contact at two levels above target was activated, and in one patient the contact below target was activated. The distribution of active contacts between the groups was not significantly different.

At 3 months postoperatively, the mean stimulation settings for patients in Group A were 180 and 180 Hz, 2.2 and 2.6 V, and 108.8 and 112.5 microseconds for channels 1 (left STN) and 2 (right STN), respectively. The majority of the patients received monopolar stimulation. For Group B, these settings were 156.9 and 156.9 Hz, 2.2 and 2.4 V, and 90 and 101.6 microseconds for channels 1 and 2, respectively. In this group, the majority of the patients received monopolar stimulation as well. At 1 year postoperatively, these parameters were generally comparable to the settings used at 3 months (*Table 4*). There were no statistically significant differences between the

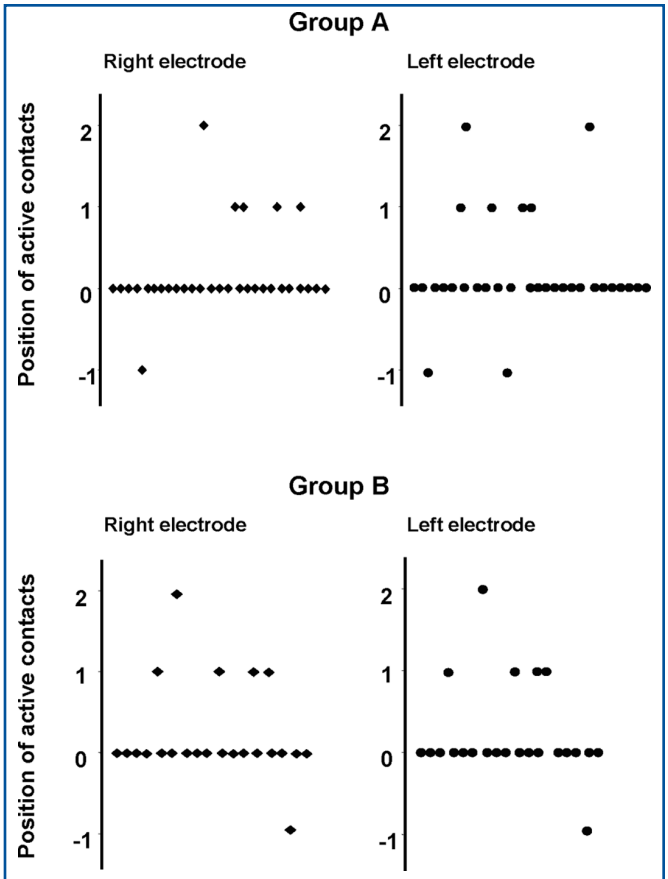

FIGURE 2. *Distribution of active electrode contacts in Groups A and B on the right and left sides. The contact at the level of the target is indicated by 0; 1 is the electrode contact above target, 2 is the electrode contact at two levels above target (the most proximal electrode contact of the 3389 electrode), and –1 is the contact below target (the most distal electrode contact of the 3389 electrode).*

groups with respect to stimulation settings (F tests < 0.72; not significant).

Behavior: Neuropsychological and Psychiatric Evaluations

Fifty patients completed neuropsychological assessment at baseline and at 3 months follow-up, and 45 patients completed follow-up assessment at 1 year after surgery. The groups did not differ in education level (median, 5; range, 1–7), but patients in Group A were younger than those in Group B (Z, –2.05; $P < 0.05$). The neuropsychological tests scores of both groups are shown in *Table 5*. There were no significant differences at baseline on the neuropsychological tests except for letter fluency, with Group A scoring higher than Group B (Z, –2.14; $P < 0.05$).

At 3 months after surgery, significant differences were identified between the groups in changed scores on tests for mental speed and verbal memory, including the total score on the five-trial presentation of a 16-word list and the delayed (free) reproduction. Patients in Group B needed more time to name colors than those in Group A (Z, –2.64; $P < 0.05$). With respect to verbal memory, patients in Group A showed an increase in number of words learned, whereas patients in Group B showed a decrease in number of words learned (Z, –3.25; $P < 0.01$). Also for the delayed reproduction, Group A showed an increase in number of words reproduced, whereas Group B showed a decrease in number of words reproduced (Z, –3.25; $P < 0.01$).

One year after surgery, there were significant differences between the groups in changes from baseline on both verbal and nonverbal memory tests. Patients in Group A again showed an increase in the number of words learned and reproduced, whereas patients in Group B showed a decrease in both number of words learned (Z, –3.48; $P < 0.01$) and reproduced (Z, –2.92; $P < 0.01$). At 1 year follow-up, there was also a significant difference in the recognition trial, with patients in Group A showing an improvement and patients in Group B showing a decline in the number of words recognized (Z, –2.69; $P < 0.05$). Finally, patients in Groups A and B differed significantly in changes from baseline on a nonverbal memory test. Patients in Group A showed an increase in the number of faces recognized, whereas patients in Group B showed a decrease in number of faces recognized (Z, –2.54; $P < 0.05$). Subsequent analysis revealed that the above-mentioned differences between Groups A and B were not related to the age differences.

There was no significant difference in changes from baseline, both at 3 months and one year postoperatively, on a self-report questionnaire for depression. The patients in Group A, however, showed a trend toward a decrease in self-reported depression at 1 year after surgery compared with patients in Group B (Z, –1.92; $P = 0.06$).

Individual psychiatric evaluation revealed clinically significant changes in behavior. After surgery, seven patients (22%) in Group A and four patients (19%) in Group B suffered from depressive symptoms, and one patient (3%) in Group A and four patients (19%) in Group B experienced (hypo)manic symptoms. Furthermore, in Group A, one patient (3%) reported symptoms of hypersexuality, and another patient reported aggressiveness. Three patients in Group B (14%) reported symptoms of passiveness.

Surgery- and Hardware-Related Complications

There were no postoperative hemorrhages or epileptic attacks in patients of Groups A or B. In the first three patients in Group B, the postoperative CT scan showed a pneumoencephalus with a thickness of more than 1 cm. One of these patients showed a decrease in consciousness for approximately 40 minutes at the end of the surgery, and improved at the time of the CT scan.The other two patients did not present with any sign of raised intracranial pressure. Two patients of Groups A and B developed a local hardware-related infection around the implanted pulse generator and the extension cable. Two were successfully treated with antibiotic therapy, whereas the other two required additional removal of the infected extension

TABLE 4. Mean stimulation settings for all patients at 3 months and 1 year postoperatively

Characteristic	Group A		Group B	
	3 Months	1 Year	3 Months	1 Year
Stimulation frequency (Hz)				
Channel 1	180.0 ± 0	172.2 ± 19.6	156.9 ± 25.9	161.8 ± 25.2
Channel 2	180.0 ± 0	171.3 ± 20.6	156.9 ± 25.9	161.8 ± 25.2
Stimulation amplitude (V)				
Channel 1	2.2 ± 1.0	2.4 ± 1.3	2.2 ± 0.8	2.5 ± 1.1
Channel 2	2.6 ± 1.2	3.4 ± 1.1	2.4 ± 0.9	2.7 ± 0.9
Pulse width (μs)				
Channel 1	108.8 ± 53.0	94.4 ± 12.0	90.0 ± 12.2	103.6 ± 38.8
Channel 2	112.5 ± 52.6	94.4 ± 12.0	101.6 ± 19.5	103.6 ± 28.0
Stimulation polarity, monopolar/bipolar				
Channel 1	26/6	25/7	19/4	21/2
Channel 2	24/8	24/6	21/2	19/4

cables and pulse generators. After subsequent antibiotic therapy, new pulse generators and extension cables were implanted. Nine patients (four from Group A and five from Group B) showed immediate postoperative confusion, which resolved with conservative treatment in several hours to days. We found no correlation between postoperative confusion and neuropsychological outcome.

DISCUSSION

After its first application in patients in 1993 (17), STN DBS is presently considered the treatment of choice for patients suffering from advanced PD (as outlined by the American Association of Neurological Surgeons). In the last 13 years, the technique of DBS in general and STN DBS in particular has undergone several adaptations, especially with regard to imaging and intraoperative neurophysiology, to enhance both efficacy and safety. The simultaneous implantation of five microelectrodes in the form of an orthogonal cross with the central electrode directed toward the target was developed to obtain a three-dimensional representation of the STN. The STN can be functionally divided into three parts, including an anterodorsolaterally located motor part, a more ventromedially located associative part, and a smaller, most medially located limbic part (20). The target for STN DBS in PD is located in the anterodorsolateral motor part, to obtain the best possible results for motor symptoms and reduce the risk for behavioral complications. An intraoperative, three-dimensional, neurophysiological mapping of the STN would lead to better identification of the borders of this small nucleus on the basis of the length of the typical STN pattern recorded by the five respective electrodes. This in turn will promote better identification of the anterodorsolateral part.

The results of the present study show that the simultaneous implantation of multiple electrodes does not increase the risk of bleeding or any other major intracranial complication. The first three patients we operated on with intraoperative, three-dimensional electrophysiological mapping showed a pneumoencephalus bifrontally with a thickness of more than 1 cm on the postoperative CT scan. Refining the burr hole (with a smaller diameter and a better positioning of the patient, at the highest level of the head), led to a disappearance of this complication in subsequent patients. We also found that this procedure does not necessarily increase the duration of surgery as compared to the procedure performed with a single recording electrode. This is important for the comfort of both the patient and the surgeon.

The use of multiple electrodes resulted in better motor results when compared with patients who underwent STN DBS guided with a single recording electrode. Patients in Group B had significantly more improvement of tremor and rigidity, and as a consequence they also had a better total UPDRS, Part III score during the medication-off phase as compared with patients in Group A. The fact that only in 32% (left side) and 36% (right side) of the patients was the central trajectory chosen for final electrode placement means that in the majority of the patients, less than optimal effect would have been obtained when only one recording or test electrode was used.

Despite better motor effects, patients in Group B showed deterioration in neuropsychological functions, and more specifically, deterioration in memory functions. At 3 months follow-up, patients in Group A improved on both verbal learning and delayed verbal reproduction, whereas patients in Group B showed deterioration on both measures. At 1 year follow-up, there was still a significant difference between the groups in the change from baseline on both learning and delayed reproduction in favor of Group A. Additionally, at this time point, we also found that patients in Group A showed an increase in recognition of both words and faces, whereas patients in Group B showed a decrease in verbal and nonverbal recognition. With respect to clinically significant psychiatric changes, in both groups, similar amounts of affective symptoms are reported. In

TABLE 5. Neuropsychological tests scores for both groups studied[a]

Characteristic	Group A	Group B	*P* value
Stroop			
Word(s)	50.5 ± 12.6	54.1 ± 12.6	
Change at 3 months	2.3 ± 8.6	6.2 ± 8.6	ns
Change at 1 year	4.0 ± 11.0	4.0 ± 15.2	ns
Color(s)	67.6 ± 15.2	69.5 ± 13.3	
Change at 3 months	2.3 ± 11.1	10.5 ± 8.8	<0.05
Change at 1 year	6.7 ± 16.1	12.0 ± 11.9	ns
Color word(s)	113.8 ± 30.9	127.7 ± 37.6	
Change at 3 months	10.4 ± 31.0	30.8 ± 49.1	ns
Change at 1 year	20.5 ± 34.3	25.4 ± 19.1	ns
Color word errors	2.4 ± 3.2	3.6 ± 5.2	
Change at 3 months	0.7 ± 2.9	4.5 ± 8.4	ns
Change at 1 year	1.5 ± 4.4	5.4 ± 8.74	ns
California Verbal Learning Task			
Total score from Trials 1–5	47.1 ± 10.0	47.5 ± 9.5	
Change at 3 months	1.6 ± 7.7	–7.5 ± 9.1	<0.01
Change at 1 year	4.7 ± 10.0	–6.8 ± 5.3	<0.01
Delayed reproduction	9.3 ± 3.2	9.5 ± 2.3	
Change at 3 months	1.5 ± 2.7	–1.4 ± 2.8	<0.01
Change at 1 year	1.6 ± 3.1	–1.2 ± 2.0	<0.01
Recognition	14.4 ± 1.6	15.1 ± 1.2	
Change at 3 months	0.4 ± 2.0	–0.4 ± 1.5	ns
Change at 1 year	0.6 ± 2.0	–0.9 ± 1.0	<0.05
Recognition Memory Test: faces	41.1 ± 4.9	39.0 ± 4.4	
Change at 3 months	1.1 ± 4.6	–0.3 ± 4.4	ns
Change at 1 year	3.0 ± 4.0	–0.9 ± 4.4	<0.05
Controlled Oral Word Association Test			
Letter fluency	37.8 ± 11.3	33.2 ± 11.1	
Change at 3 months	–3.3 ± 8.6	–5.1 ± 8.9	ns
Change at 1 year	–3.9 ± 10.2	–3.6 ± 9.3	ns
Category fluency	37.8 ± 11.4	33.9 ± 8.8	
Change at 3 months	–4.0 ± 5.9	–4.6 ± 6.7	ns
Change at 1 year	–3.0 ± 7.9	–3.9 ± 6.5	ns
Beck Depression Inventory	11.8 ± 6.6	9.2 ± 7.1	
Change at 3 months	–4.4 ± 8.2	–3.1 ± 6.9	ns
Change at 1 year	–3.7 ± 6.9	1.4 ± 8.2	ns

[a] ns, Not significant.

Group B, however, more patients suffered from (hypo)manic features and passiveness. A microlesion effect could be a possible explanation for the difference in neuropsychological functioning, in favor of the single-electrode group; when five electrodes at a time are implanted within the STN, the chance is greater that at least one will be located in the non-motor part and thus can give rise to a postoperative lesion effect related to associative and limbic functions. There are two counterarguments for this microlesioning effect. First, this reduced neuropsychological functioning in Group B is still present after 1 year, and second, the tips of the microelectrodes are so small (diameter, 20–25 μm), that a lesioning effect is unlikely. One could argue that the use of two or three simultaneously placed microelectrodes could prevent the deterioration of neuropsy-

chological functions. This would be a compromise between the two techniques. In the present study, only in 1 out of 23 patients in Group A were 3 simultaneously placed microelectrodes used for electrophysiological recording. The other patients had five, and few had four simultaneously placed microelectrodes. Future investigation is necessary to determine whether such a compromise could be made and be effective in preventing neuropsychological decline.

The nonrandomized nature of this study may be a possible limitation. A randomized setup of the study would be preferred from a methodological point of view. However, when we started this study, the use of electrophysiology was strongly debated, and we first wanted to confirm the safety of electrophysiology in DBS. Therefore, we operated on the first group of patients using electrophysiological recordings through a single electrode, and we did not perform a randomized trial. After the process appeared to be safe, we proceeded to multiple-electrode-guided DBS and compared the effects as outlined here.

An important question is, to what extent do these neuropsychological results undermine the motor effects, in other words, to what extent are these neuropsychological results clinically relevant? We performed open interviews with patients and partners. Mainly symptoms of depression, (hypo)mania, and passiveness were reported as relevant by the patient and family. Nevertheless, patients and caregivers should be aware of all of these behavioral changes, even if the clinical impact of some appears to be small.

CONCLUSION

The use of simultaneously implanted multiple electrodes for electrophysiological recording to guide STN DBS is a safe procedure and produces improved motor outcome. The subtle changes in neuropsychological function need special consideration.

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COMMENTS

This article compares the outcome and complications of subthalamic nucleus (STN) deep brain stimulation (DBS) in two groups of patients, including one who received limited microelectrode recording (MER) and one who underwent simultaneous five-channel MER recording. Temel et al. show that motor outcomes are slightly better in the latter, but that neuropsychological side effects at 1 year are slightly worse. This study adds information to the debate regarding optimal strategy for MER. There are methodological issues inherent to nonrandomized studies; for example, the effect of surgeon experience could account in part for the results. Nevertheless, the results are thought-provoking. Multiple simultaneous MERs are relatively safe from the standpoint of hemorrhagic stroke, as reported in this as well as other studies. However, more brain penetrations cannot be made with total impunity. This motivates the search for methods of DBS implantation that reduce the number of brain penetrations while preserving high levels of accuracy and precision.

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Temel et al. address an interesting question in this article, namely, in patients undergoing placement of electrodes for DBS, is there a dif-

ference in terms of efficacy and safety between the use of single or multiple microelectrodes?

This study included only patients with medically refractory Parkinson's disease who had bilateral STN electrodes placed. This facilitated matching of the two groups and the data analysis. There were 55 patients overall; of these, 32 patients (Group A) had surgery guided by a single semi-microelectrode, whereas in Group B (23 patients) an array of (usually) 5 microelectrodes was placed simultaneously. Patients were assessed before surgery and at 3 and 12 months after surgery, with assessments of overall Unified Parkinson's Disease Rating Scale (UPDRS) as well as components of the UPDRS relating to activities of daily living (UPDRS II), motor functions (UPDRS III), and complications of medical therapy (UPDRS IV). Psychiatric and neuropsychiatric evaluations were also done. Patients were assessed for any changes in postoperative medication requirements and for stimulation parameters.

Surgical technique and duration were essentially the same in both groups, except for the difference in the microelectrodes. In Group A, a mean of 1.5 electrode passes were made (range, 1–5). In Group B, in about one-third of the patients, an electrode other than the central one was used (in conjunction with macrostimulation control) to choose the path of the implanted electrode. This indicates that the multiple electrode array was of use in identifying the ideal final target. Postoperative computed tomography scans ruled out significant hemorrhage in all patients.

UPDRS evaluations showed improvements in activities of daily living, motor function, medication requirements, and complications of drug therapy in both groups. Stimulation parameters were equivalent. Comparison between the two groups showed a relative benefit for Group B only in tremor and rigidity in the medication-off phase. Neurospsychiatric testing identified a decrease in verbal and nonverbal memory in Group B. These patients were also 5 years older on average, although their disease duration was 2 years shorter. Similar numbers of patients had depression after surgery, whereas there was a trend toward increased hypomania in Group B.

Temel et al. have added evidence to the literature indicating that microelectrode recording affects placement of subthalamic stimulators and is not associated with an increased risk of hemorrhage. The mixed clinical outcomes (improved motor scores with a decline in neuropsychiatric testing results) clearly warrant additional study and prevent this article from being a ringing endorsement of multiple microelectrode arrays for DBS placement.

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Temel et al. compared their results from 32 patients who underwent surgery guided by a single semi-microelectrode and 23 patients who had surgery guided by simultaneously implanted multiple microelectrodes. They found that there was no difference in complication rates. Patients with simultaneously implanted multiple microelectrodes had significantly better medication-off motor outcomes as assessed by UPDRS III, but worse neuropsychological outcomes on tests of verbal and nonverbal memory at 1 year. The multiple microelectrode systems are attractive because of the potential time-saving ramifications, although the authors show no difference in operating room time between the groups. The article is well written and timely, as more systems that simultaneously implant multiple microelectrodes are becoming commonplace and available (1, 7, 8). The results of this study warn of the potential for greater impairment on neuropsychological tests of memory in the group that underwent multiple simultaneous MERs. Design problems, statistical weaknesses, and lack of bias controls enfeeble the veracity of the conclusions.

It is important to note that the patients who had surgery with the semi-microelectrode were earlier patients in the series, and those with multiple simultaneous microelectrode tracks were the later patients. This makes any late improvements more difficult to interpret. Was the improvement in motor outcome secondary to the new technique or was it a result of better patient selection and targeting based on previous experience? It also makes findings concerning the risk of bleeding difficult to assess. Specifically, was there no increased risk of bleeding in the second group of patients because multiple tracks do not increase risk or because the blood pressure and perioperative medications with anticoagulant properties were more tightly controlled with the authors' increased experience and recognition of risk factors that may be associated with intracranial hemorrhage (2)?

The negative findings, i.e., greater impairment on memory testing in the later group of patients, is more noteworthy, as these patients benefited from the authors' earlier experiences yet still had the effect. Why this occurred remains unclear. The second group was older, yet covariate analysis excluded age as a confounding variable. Age has been shown to correlate with a decline in executive functions in these patients (5). Other possibilities include increased injury with multiple tracks to the limbic and associative areas of the STN or to the substantia nigra (4). The mean number of penetrations in Group A was 1.5, whereas 20 of 23 patients had 5 tracks in Group B. There is mounting evidence that STN DBS may lead to impaired performance on cognitive testing (4, 6, 9). Multiple microelectrodes that pass through the sensorimotor areas of the STN have not been reported to show significant injury in autopsy specimens (3). It is possible that multiple tracks through the caudate or in the associative region of the STN may be the source of these adverse effects. It is also possible that this finding is an epiphenomenon.

As systems capable of multiple simultaneous MERs become increasingly available, the question becomes, how many tracks are truly warranted? Advocates of MER presently determine the number of tracks based on intraoperative data collected. The decision of subjecting patients to five tracks automatically, especially in light of the potential effects on cognitive outcome, should not be taken lightly. As the authors note, one potential compromise that we prefer is the use of three tracks rather than five. Of course, clinicians would need to determine which three tracks and the relative positioning of those tracks based on variable orientations of the *x*–*y* stage. This article is a timely contribution to the literature and provides data that may influence daily practice.

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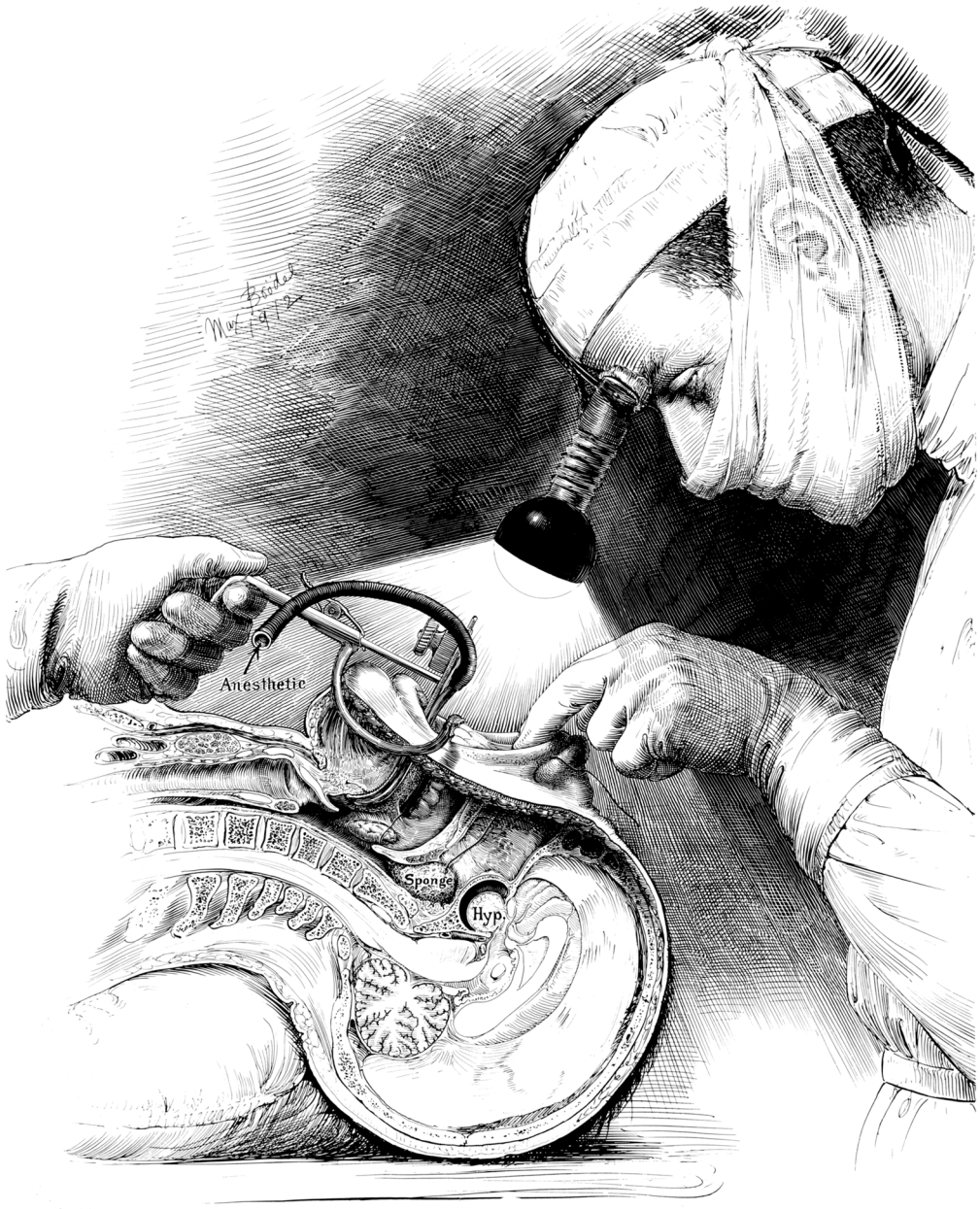

Illustration of a transsphenoidal procedure for pituitary disorders (1912), by Max Brödel for Cushing's publication, "Surgical Experiences with Pituitary Disorders," in *The Journal of the American Medical Association, Volume LXIII, 1914*. From Crosby RW, Cody J: *Max Brödel: The Man who put Art into Medicine*. New York, Springer-Verlag, 1991.