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# Directional Deep Brain Stimulation for Parkinson's Disease: Results of an International Crossover Study With Randomized, Double-Blind Primary Endpoint

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**ABSTRACT**

**Objective:** Published reports on directional deep brain stimulation (DBS) have been limited to small, single-center investigations. Therapeutic window (TW) is used to describe the range of stimulation amplitudes achieving symptom relief without side effects. This crossover study performed a randomized double-blind assessment of TW for directional and omnidirectional DBS in a large cohort of patients implanted with a DBS system in the subthalamic nucleus for Parkinson's disease.

**Materials and Methods:** Participants received omnidirectional stimulation for the first three months after initial study programming, followed by directional DBS for the following three months. The primary endpoint was a double-blind, randomized evaluation of TW for directional vs omnidirectional stimulation at three months after initial study programming. Additional data recorded at three- and six-month follow-ups included stimulation preference, therapeutic current strength, Unified Parkinson's Disease Rating Scale (UPDRS) part III motor score, and quality of life.

**Results:** The study enrolled 234 subjects ( $62 \pm 8$  years, 33% female). TW was wider using directional stimulation in 183 of 202 subjects (90.6%). The mean increase in TW with directional stimulation was 41% ( $2.98 \pm 1.38$  mA, compared to  $2.11 \pm 1.33$  mA for omnidirectional). UPDRS part III motor score on medication improved 42.4% at three months (after three months of omnidirectional stimulation) and 43.3% at six months (after three months of directional stimulation) with stimulation on, compared to stimulation off. After six months, 52.8% of subjects blinded to stimulation type (102/193) preferred the period with directional stimulation, and 25.9% (50/193) preferred the omnidirectional period. The directional period was preferred by 58.5% of clinicians (113/193) vs 21.2% (41/193) who preferred the omnidirectional period.

**Conclusion:** Directional stimulation yielded a wider TW compared to omnidirectional stimulation and was preferred by blinded subjects and clinicians.

**Keywords:** Deep brain stimulation, directional programming, Parkinson's disease, therapeutic window

**Conflict of Interest:** Alfons Schnitzler, Jan Vesper, Pablo Mir, Leonardo Verhagen, and Matthew A. Brodsky are members of the PROGRESS Steering Committee. Alfons Schnitzler, Jan Vesper, Pablo Mir, Leonardo Verhagen, Nestor Tomczyk, Christian J. Hartmann, Sergiu Groppa, Ramiro Alvarez, Julie Pilitsis, Monika Pötter-Nerger, Stefan Jun Groiss, and Matthew A. Brodsky received compensation for professional services from Abbott. Alfons Schnitzler and Jan Vesper received speaker honoraria from Abbott. Florence Defresne, Edward Karst, and Binith Cheeran are employees of Abbott. Joohi Jimenez-Shahed received research support from Medtronic and Abbott, consulting fees from Medtronic and Boston Scientific, honoraria for lectures from Abbott and has served on an advisory board for the ADROIT registry with Abbott. Sean Nagel has received consulting fees from Abbott and honoraria for lectures from Medtronic. Sergiu Groppa has received honoraria for lectures from Abbvie, UCB, and Abbott. Dr. Groppa has also participated as an Adjudications Committee Member for Abbott and received IIT grants from Abbott, MagVenture, and Boston Scientific. Alfons Schnitzler has received grants from the German Research Council, Abbott, Medtronic, and Boston Scientific. Dr. Schnitzler has also received consulting fees from Abbott, Medtronic, Boston Scientific, and Zambon. Dr. Schnitzler has received payment or honoraria from Abbott, Medtronic, Boston Scientific, Abbvie, dPV, and BIAL. Leonardo Almeida has received consulting fees from Medtronic, Boston Scientific; honoraria for lectures from Medtronic, Boston Scientific, and the Movement Disorders Society. Nestor Tomczyk has received a grant for DBS for opioid use disorder and consulting fees from Abbott. Monika Pötter-Nerger has received governmental grants from DFG; consulting fees from Abbvie, Abbott, Medtronic, Boston Scientific, Licher, and Zambon. Dr. Pötter-Nerger has also received speaker honoraria from Abbvie and Abbott, travel support and participation as an advisory board member from Abbvie. Christian Hartmann has received grant support from Abbott and lecture honoraria from BSH medical communications (sponsored by Abbott). Pablo Mir has received honorarium for lecturing from Abbott, Allergan, Abbvie, Bial, Britannia, Italfarmaco, Merz, UCB, Teva, and Zambon and has received support for attending meetings and/or travel from Abbott, Abbvie, Bial, Teva, and Zambon. Dr. Carrillo has received honorarium for lecturing from Abbvie, Bial, Teva, and Zambon and has received support for attending meetings and/or travel from Abbott and Abbvie. Dr. Pilitsis reports grants and other from Boston Scientific, grants and other from Nevro, grants and other from Abbott, grants and other from Medtronic, other from Saluda, grants and other from TeSera, grants from NIH 2R01CA166379-06, grants from NIH U44NS115111, other from Aim Medical Robotics, other from Karuna Labs, outside the submitted work. The remaining authors have no conflicts of interest to disclose.

**INTRODUCTION**

Deep brain stimulation (DBS) has been used clinically for a quarter century to treat symptoms of movement disorders such as Parkinson's disease, essential tremor, and dystonia<sup>1-7</sup> and is under investigation for additional indications.<sup>8-11</sup> For Parkinson's disease, leads are implanted in or near the subthalamic nucleus (STN) or, alternatively, the globus pallidus interna (GPi) for treatment of motor symptoms, dyskinesia reduction and to maximize good

quality on time.<sup>5,12-16</sup> The STN is a small (typical dimensions  $9 \times 7 \times 4$  mm), bi-convex nucleus in the basal ganglia surrounded by myelinated axons.<sup>17-19</sup> Conventional leads used in DBS have four circumferential electrodes and a diameter of approximately 1.3 mm, and typical accuracy of placement can be up to 3 mm from the planned target.<sup>20</sup> Potential side effects of chronic STN stimulation can include speech impairment, reduced verbal fluency, involuntary eye movement, muscle contraction, postural instability, and impaired cognition, because of proximity to other

neuronal circuits.<sup>21,22</sup> A recent analysis found that lead revisions or replacements may range from one-sixth to one-third of all procedures involving DBS.<sup>23</sup>

Recently, directional leads have been developed with the two middle rings divided into three segments. In contrast to conventional stimulation delivered to the entire ring, selection of a segment creates an axially asymmetric stimulation field. Directional stimulation therefore has the potential to focus stimulation energy at the target, while avoiding unwanted side effects that may occur due to current spread with omnidirectional stimulation. Selection of optimal stimulation contacts has the potential to improve battery lifespan and reduce the need for revision surgeries. Several single-center investigations have been conducted on directional leads: two initial studies reporting intraoperative experience with experimental lead designs<sup>24,25</sup> and three further studies implanting directional leads in seven to ten subjects.<sup>26–28</sup> All but one of the studies compared therapeutic window (TW), the range of stimulation amplitude that produces symptom relief without causing side effects, for conventional omnidirectional and directional stimulation. Therefore, a large prospective, international, multicenter, blinded-subject, blinded-assessor study was designed to compare the TWs of omnidirectional and directional DBS in a real-world setting.

## MATERIALS AND METHODS

The study was approved by an ethics review committee for each participating institution, conducted in accordance with the Declaration of Helsinki, and registered at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT02989610. All patients provided written informed consent.

### Study Design and Participants

PROGRESS (Post-MaRket Clinical FOLlow-Up EvaluatinG the Infinity Deep BRain Stimulation ImplantABLE PulSe Generator System) aimed to determine whether a wider TW could be achieved with directional stimulation, compared to omnidirectional stimulation delivered by the same lead. The primary endpoint was evaluated three months after initial study programming by recording TW for omnidirectional and directional stimulation sequentially, in randomized order determined by coin toss, as assessed by a blinded evaluator in blinded subjects off medication. The randomization was performed by the investigator at each study site. Subjects were blinded to the stimulation type for the first six months of the study.

Eligible patients had levodopa-responsive Parkinson's disease and were scheduled to receive, or had already received, a bilateral DBS system with directional leads implanted in the STN (Infinity DBS System, Abbott, Plano, TX). Patients provided written informed consent before enrollment. Subjects implanted before entering the study could be enrolled only if they had received omnidirectional programming since DBS implant. No previous directional programming was allowed.

The primary endpoint analysis of the study was conducted on 66 subjects, the statistically powered sample size used to complete a regulatory postmarket study requirement. The study aimed to study directional programming on a large cohort and enrolled a total of 234 subjects. Reported here are the results for the initial 66 subjects with complete data and the full study cohort of 234 subjects.

### Implant and Programming

Study sites followed routine DBS implantation procedure using stereotaxis and aimed to place contacts 2 and 3 in proximity to the target. Details on implant procedure were collected in the database. The study allowed for awake and asleep procedure, use of microelectrode recording, and intraoperative imaging.

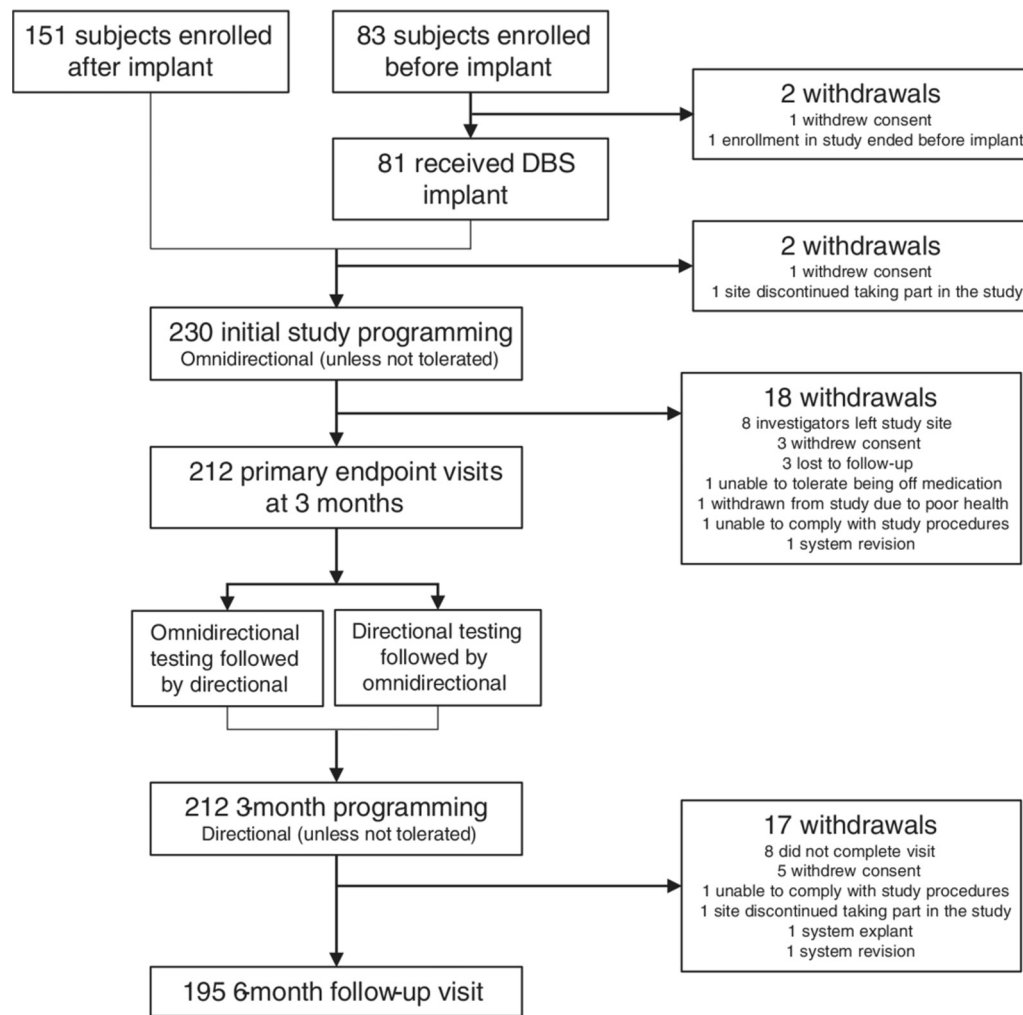
At initial study programming, subjects received three months of conventional, omnidirectional stimulation unless not tolerated. Subjects then received directional stimulation for the next three months and returned for evaluation of secondary endpoints at the six-month follow-up visit (Fig. 1). Stimulation adjustments were allowed throughout the study. Directional stimulation included both the use of a single segment and any combination of two segments. Bipolar stimulation was used in a small number of subjects. Subjects were instructed not to take medication for 12 hours prior to the baseline and three-month visits and to take medication as instructed during the visit.

### Data Collection

Data collection occurred at enrollment, and after 3, 6, and 12 months. Reported here are the primary and secondary endpoints and additional results from the first six months. TW was defined as the difference in amplitude resulting in a sustained side effect that lasted at least for 30 sec minus the minimum therapeutic current resulting in symptom relief. TW was evaluated acutely three months after initial study programming for each of the three directional contacts, combinations of two contacts, and the optimal full ring. The primary endpoint was collected three months after initial study programming, with the subject off medication. A blinded assessor performed the clinical assessments for benefit and side effects, while an unblinded programmer gradually increased stimulation amplitude for each electrode configuration tested in randomized order. The blinded assessor also assessed the Unified Parkinson's Disease Rating Scale (UPDRS) part III motor examination at three- and six-month visits and was unaware of the subject's specific device settings at the time of the evaluation. UPDRS part III was collected on medication at baseline, three and six months, and off medication at baseline and three months. Quality of life was evaluated using the 39-question Parkinson's Disease Questionnaire (PDQ-39), and activities of daily living were measured using UPDRS part II (on medication) at baseline, three and six months. Subject and clinician preference were recorded at six months after subjects had received omnidirectional and directional stimulation for three months each. Serious adverse events and device-related adverse events were collected through the duration of the study and recorded in an adverse event form.

### Statistical Analysis and Sample Size

The primary endpoint was based on the proportion of subjects that achieved a wider TW with directional stimulation at the three-month evaluation. The criterion for superiority would be met if more than 60% of subjects had a wider TW on one or both leads with directional stimulation. The criterion for noninferiority would be met if more than 40% of subjects had a wider TW on one or both leads with directional stimulation. The analysis was carried out by calculating a one-sided 95% lower confidence bound (LCB) on the proportion of subjects with wider TW for directional stimulation using the Clopper–Pearson exact method and demonstrating that



**Figure 1.** Study flow diagram. There were 212 subjects who completed the primary endpoint visit, of which 202 had complete assessments of TW for omnidirectional and directional stimulation on both leads.

it exceeded 60% to satisfy the superiority endpoint and 40% to satisfy the noninferiority endpoint.

The secondary endpoint for UPDRS part III compared the on-medication score at three months after omnidirectional stimulation to six months using directional stimulation. It was hypothesized that UPDRS would be lower with directional stimulation than with omnidirectional stimulation. The analysis was carried out by calculating the one-sided 95% LCB on the change in UPDRS part III using a paired *t*-test, and would be satisfied if the difference was greater than zero. Additional prespecified comparisons were for therapeutic current strength (the minimum current required to achieve symptom relief) and side effect threshold (the current that generates a sustained side effect). The outcome measures were also combined as TW percentage, the ratio of TW to therapeutic current strength expressed as a percentage.

A level of significance of 0.05 was used to evaluate primary and secondary endpoints and for all additional statistical comparisons. Results are summarized using mean and standard deviation for continuous variables and number and percentage for categorical variables. Pairwise comparisons of TW and current thresholds, which have nonparametric distributions, are conducted using the

Wilcoxon signed-rank test. Paired *t*-tests were used for other comparisons.

Sample size was calculated with an assumption that 75% of participants would have a wider TW with directional stimulation, compared to a threshold of 60% to show superiority. It was determined that 62 participants would be required to satisfy the superiority criterion at 80% power and a level of significance of 0.05. Accounting for expected 5% attrition, a minimum sample size of 66 was required to perform the primary endpoint analysis. Statistical analysis was conducted using SAS version 9.3.

## RESULTS

PROGRESS enrolled 234 participants between January 2017 and January 2019 at 37 sites in Europe, United States, and Australia. Subject characteristics and medication usage of the 234 enrolled subjects are presented in Table 1. Age at enrollment was  $61.7 \pm 8.4$  years; 157 of 234 subjects (67.1%) were male. In total, 151 subjects (64.5%) had an existing STN DBS implant with omnidirectional stimulation upon enrollment in the study. The characteristics of subjects enrolled before and after implant are presented

**Table 1.** Basic Characteristics.

	All subjects (N = 234)	Enrolled before implant (n = 83)	Enrolled after implant (n = 151)
Age in years	61.7 ± 8.4	59.8 ± 7.8	62.8 ± 8.6
Female	77 (32.9%)	24 (28.9%)	53 (35.1%)
Male	157 (67.1%)	59 (71.1%)	98 (64.9%)
Parkinson symptoms, time in years	11.7 ± 7.6	12.0 ± 10.6	11.5 ± 5.2
Years since initial diagnosis	10.2 ± 7.4	10.5 ± 10.5	10.0 ± 4.8
<b>Medications</b>			
Levodopa	222 (95.7%)	82 (98.8%)	140 (93.3%)
Dopamine agonist	141 (60.8%)	51 (61.4%)	91 (60.7%)
COMT inhibitor	37 (15.9%)	24 (28.9%)	13 (8.7%)
MAO-B inhibitor	90 (38.8%)	41 (49.4%)	49 (32.7%)
Amantadine	60 (25.9%)	25 (30.1%)	35 (23.3%)
Levodopa equivalent dose	1234 ± 670 mg	1285 ± 625 mg	1217 ± 711 mg

Values shown are mean ± standard deviation for continuous variables; count (percentage) for discrete variables.

in Table 1. Subjects with existing implants were enrolled in the study an average of 130 days after implant. A total of 163 subjects had a DBS system implanted during an awake procedure and 69 subjects were implanted under general anesthesia.

There were 230 subjects who had initial study programming. Out of 212 subjects who completed the three-month visit, there were 202 with complete primary endpoint data. After the three-month visit, 17 additional subjects were withdrawn or did not return for the next scheduled follow-up visit, leaving a total of 194 subjects who completed the six-month visit (Fig. 1).

No intracranial hemorrhages or infections were reported. There were 11 serious adverse events (0.05 per subject) related to a DBS device, procedure or stimulation, and 34 non-serious device-related events (0.14 per subject). For the 83 subjects enrolled prior to implant, there were 6 serious device-related events (0.07 per subject), 15 non-serious device-related events (0.18 per subject), and 5 non-device-related serious adverse events (0.06 per subject). Three of the four stimulation-related serious adverse events occurred during the first three months when omnidirectional stimulation was used. Out of 28 non-serious stimulation-related events, 20 (71%) were reported during the omnidirectional period and 8 (29%) during the directional period. Table 2 contains a complete list of adverse events recorded for the 234 subjects from enrollment to six-month follow-up visit.

The primary endpoint analysis of TW was performed three months after initial study programming to avoid a possible stun effect. Out of the first 66 subjects with complete data, 59 had a wider TW with directional programming (89.4%). This result, which had a lower confidence bound of 81.0%, satisfied the primary endpoint by exceeding the threshold of 60% for superiority ( $p < 0.001$ ) and the 40% threshold for non-inferiority ( $p < 0.001$ ). In the full cohort of 202 subjects with complete primary endpoint data, 183 (90.6%) had a wider TW with directional stimulation (LCB 86.5%,  $p < 0.001$  for superiority). While the primary endpoint evaluated directional stimulation from a single segment or two segments, it was also found that for 86.6% of subjects (175/202), a wider TW could be achieved with only a single segment activated compared to omnidirectional stimulation. Also, 62.2% of subjects had a wider TW with a single segment activated compared to two segments; 21.6% of subjects had equal TW with single-segment or two-segment activation.

In the full cohort of 234 subjects, TW increased 41% using directional stimulation ( $2.98 \pm 1.38$  mA) compared to omnidirectional

stimulation ( $2.11 \pm 1.33$  mA) (Fig. 2, panel a). Using the contact with lowest therapeutic current strength, directional stimulation could reduce current required to achieve symptom relief by 39% ( $1.11 \pm 1.00$  mA) compared to omnidirectional stimulation ( $1.83 \pm 1.52$  mA) (panel b). TW percentage, the ratio of TW to therapeutic current strength, had a median value of 312% with directional stimulation, compared to 167% with omnidirectional stimulation (panel c). If directional stimulation was chosen to optimize side effect threshold, the amplitude that first introduced side effects could be increased by 0.58 mA or 16% from  $3.48 \pm 1.17$  mA with omnidirectional stimulation to  $4.06 \pm 1.28$  mA with directional stimulation (panel d). Stimulation amplitude, pulse width, and frequency did not differ significantly at three and six months. Amplitude was  $2.29 \pm 0.96$  mA at three months and  $2.36 \pm 0.97$  mA at six months; pulse width was  $61.5 \pm 10.8$   $\mu$ sec at three months and  $61.9 \pm 12.1$   $\mu$ sec at six months; frequency was  $135.4 \pm 170$  Hz at three months and  $136.6 \pm 16.5$  Hz at six months. Among 212 subjects who completed the three-month visit, there were 25 subjects (11.8%) who could not tolerate omnidirectional programming and were programmed with directional stimulation for the first three months. There were also 36 of 195 subjects (18.5%) who remained on omnidirectional settings after the three-month follow-up.

There were no significant differences in UPDRS motor examination score at three months compared to six months. The paired difference of scores at three and six months with medication on and stimulation on was  $-2.7$ , indicating slightly higher motor score at six months. Baseline motor score on medication before DBS was  $18.6 \pm 10.6$  and was significantly lower at three and six months with stimulation on. When stimulation was turned off, on-medication motor scores were significantly increased over time to  $25.2 \pm 12.8$  at three months and  $30.8 \pm 14.1$  at six months. There were significant reductions in paired on-medication motor score for stimulation on vs off at three and six months: by 42.4% at three months from  $25.1 \pm 12.5$  to  $14.4 \pm 7.8$  and by 43.3% at six months from  $30.9 \pm 13.9$  to  $17.5 \pm 10.0$  (Fig. 3).

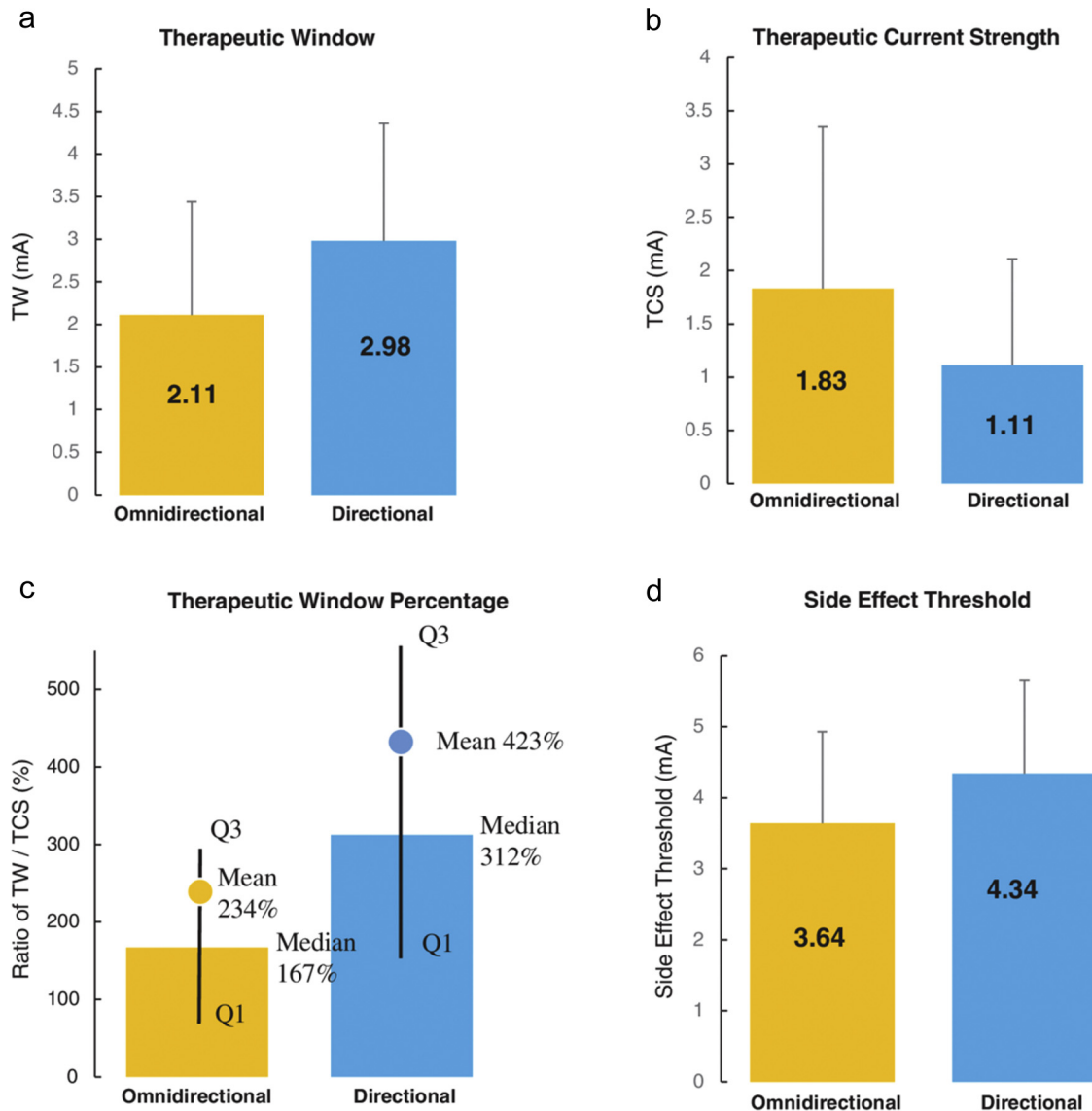
There was improved quality of life using PDQ-39 summary index from baseline ( $31.6 \pm 16.2$ ) to three months ( $25.8 \pm 15.1$ ) and six months ( $24.4 \pm 14.2$ ) ( $p < 0.001$  for each pairwise comparison). All eight components of PDQ-39 were improved at six months; only communication showed no significant change at three months (Table 3). There were no significant differences in paired comparisons of UPDRS part II indicating activities of daily living, which averaged  $9.2 \pm 6.6$  at baseline,  $10.0 \pm 6.1$  at three months ( $p = 0.08$ ),



**Table 2.** List of Adverse Events.

Stimulation-related serious adverse events	Occurred in omnidirectional or directional period?	Event outcome	Status	Events	Subjects
Cognitive impairment: Confusion*	Omnidirectional	Medication	Resolved without sequelae	1	1
Speech or language impairment: Aphasia*	Omnidirectional	No action	Resolved without sequelae	1	1
Speech or language impairment: Dysphagia*	Omnidirectional	Medication	Unresolvable	1	1
Worsening of Parkinson's motor symptoms: Tremor*	Directional	Medication and reprogramming	Resolved without sequelae	1	1
Device-related serious adverse events	Occurred in omnidirectional or directional period?	Event outcome	Status	Events	Subjects
Battery depletion resulting in hospitalization	Directional	IPG replacement	Subject withdrawal (system revision)	1	1
Extension breakage in a swimmer*	Omnidirectional	Extension replacement, patient education	Resolved without sequelae	1	1
Lead fracture due to trauma	Directional	Lead replacement	Resolved without sequelae	1	1
Loss of therapeutic benefit: Lead migration	Omnidirectional	Surgical intervention, medication and reprogramming	Resolved without sequelae	1	1
Procedure-related serious adverse events	Occurred in omnidirectional or directional period?	Event outcome	Status	Events	Subjects
Cognitive impairment: Disorientation	Before PROGRESS initial programming	Patient education	Subject withdrawal before initial programming	1	1
Edema near site of lead	Omnidirectional	No action (infection excluded by lumbar puncture)	Resolved without sequelae	1	1
Erosion	Omnidirectional	Surgical intervention	Resolved without sequelae	1	1
Stimulation-related adverse events	Period	Event outcome	Status	Events	Subjects
Worsening of Parkinson's motor symptoms: Dyskinesia (4*)	Omnidirectional (5) Directional (1)	Decreased stimulation (1), medication (2), reprogramming (4), patient education (1)	Resolved without sequelae (6)	6	5
Worsening of Parkinson's motor symptoms: Tremor (2*)	Omnidirectional (4)	Reprogramming (4)	Resolved without sequelae (4)	4	4
Decreased therapeutic response*	Directional (3)	Reprogramming (3)	Resolved without sequelae (3)	3	2
Cognitive impairment: Emotional lability (1*)	Omnidirectional (2)	No action required (1), medication and reprogramming (1)	Resolved without sequelae (2)	2	2
Sensory disturbance or impairment: Neuralgia*	Directional (2)	Medication (1), reprogramming (1)	Subject withdrawal (withdrew consent)	2	1
Sensory disturbance or impairment: Sensory deficit (1*)	Omnidirectional (2)	Medication (1), reprogramming (1)	Resolved without sequelae	2	2
Undesirable changes in stimulation	Omnidirectional	Reprogramming	Resolved without sequelae	1	1
Worsening of Parkinson's motor symptoms: Abnormal gait	Omnidirectional (2)	Reprogramming (2)	Resolved without sequelae	2	2
Worsening of Parkinson's motor symptoms: Bradykinesia	Omnidirectional (2)	Reprogramming (2)	Resolved without sequelae	2	2
Cognitive impairment: Hallucination*	Directional	Medication	Resolved without sequelae	1	1
Dystonia*	Directional	Reprogramming	Resolved without sequelae	1	1
Sensory disturbance or impairment: Neuropathy *	Omnidirectional	Reprogramming	Resolved without sequelae	1	1
Speech or language impairment: Dysarthria*	Omnidirectional	Device reprogramming	Resolved without sequelae	1	1
Device-related adverse events	Period	Event outcome	Status	Events	Subjects
Undesirable changes in stimulation*	Directional	Software update	Resolved without sequelae	1	1
High impedance*	Directional	Reprogramming	Resolved without sequelae	1	1
Impaired wound healing: Incision site drainage	Omnidirectional	Medication	Resolved without sequelae	1	1
Procedure-related adverse events	Period	Event Outcome	Status	Events	Subjects
Erosion	Omnidirectional	No action	Resolved without sequelae	1	1
Skull discoloration	Omnidirectional	No action	Unresolvable	1	1
Suboptimal placement of lead corrected during IPG implant	Omnidirectional	Surgical intervention	Resolved without sequelae	1	1

\*Indicates subject was enrolled after DBS system implant.



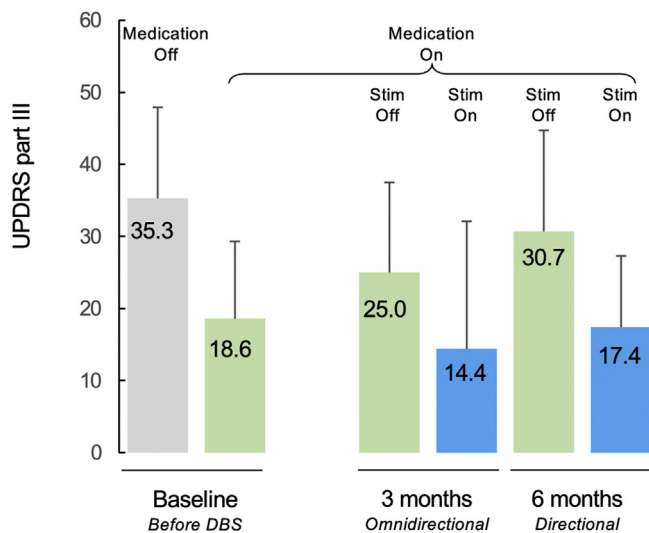
**Figure 2.** Stimulation testing results at the primary endpoint visit. a. TW;  $p < 0.001$ . b. Therapeutic current strength;  $p < 0.001$ . c. TW percentage;  $p < 0.001$ . d. Side effect threshold;  $p < 0.001$ .

and  $10.0 \pm 5.7$  at six months ( $p = 0.08$ ). Quality of life was improved similarly in subjects implanted before or after enrollment.

After six months during which subjects were blinded to stimulation type, 102 of 193 subjects (52.8%) preferred the three-month period when directional stimulation was used, compared to 50 (25.9%) who preferred the first three months when omnidirectional stimulation was used (Fig. 4, panel a). Forty-one subjects (21.2%) expressed no preference. Clinicians preferred the period of directional stimulation for 113 of 193 subjects (58.5%) (Fig. 4, panel B). The reason clinicians cited for the preference was symptom relief in 96 subjects and side effect avoidance in 11. The period with omnidirectional stimulation was preferred by clinicians for 41 subjects (21.2%), and there was no preference for 39 (20.2%).

In a subgroup analysis, TW increased with directional stimulation for subjects implanted after enrollment as well as those who had existing implants (Fig. 5, panel a). TW increased by 0.88 mA (44%) with directional stimulation for previously implanted subjects

( $2.88 \pm 1.38$  mA vs  $2.00 \pm 1.36$  mA), and 0.80 mA (35%) in subjects implanted after being enrolled in PROGRESS ( $3.09 \pm 1.38$  mA compared to  $2.29 \pm 1.26$  mA). Directional stimulation also required less current to achieve symptom relief in both groups (Fig. 5, panel b). Improvements in UPDRS III motor scores were reported with no significant differences between the two cohorts (Table 4). In subjects enrolled before DBS implant, PDQ-39 summary index improved from  $32.9 \pm 16.9$  at baseline to  $25.7 \pm 16.1$  at three months and  $23.4 \pm 14.3$  at six months. In subjects enrolled after DBS implant, PDQ-39 summary index improved from  $29.9 \pm 15.3$  at baseline to  $25.7 \pm 14.5$  at three months and  $25.1 \pm 14.1$  at six months. Among the subjects already implanted before starting the study, 59 (48.8%) subjects preferred directional stimulation while 34 (28.1%) subjects preferred the period with omnidirectional stimulation. Of those with no prior DBS, 43 (59.7%) preferred the directional period and 16 (22.2%) preferred the omnidirectional period.



**Figure 3.** UPDRS part III motor score. Baseline score off and on medication before receiving DBS, and on medication at three and six months. Paired improvement 42.4% at three months with omnidirectional stimulation; 43.3% at six months with directional stimulation.

## DISCUSSION

In the largest prospective study of STN DBS for Parkinson's disease to date, 90.6% of subjects had a wider TW using directional stimulation of the STN compared to omnidirectional stimulation. The double-blind randomized comparison showed that directional stimulation achieves a superior TW compared to conventional omnidirectional stimulation. TW was increased by an average of 41% using directional stimulation, and directional contacts could be selected depending on treatment goals either to reduce the amplitude required to relieve symptoms, or to increase the threshold for side effects. Blinded motor examination showed similar improvements in motor score with omnidirectional and directional stimulation of the STN. Disease-specific quality of life was also significantly improved with DBS. Approximately 20% of clinicians and subjects had no preference for stimulation paradigm, but of those who expressed a preference, twice as many subjects and three times as many clinicians preferred directional stimulation.

The study enrolled subjects before implant as well as those who had already received omnidirectional DBS. There is a significant benefit of directional stimulation on TW in both groups. Whether subjects were implanted after enrollment or had the DBS system for a longer time, there was a similar benefit from directional stimulation. The acute evaluation at three months suggests that directional settings could also allow a decrease in required current to achieve symptom relief. As expected, there was slightly smaller TW in subjects who had received DBS for a longer period. The PROGRESS study collects data at 12 and 36 months after initial study programming and will assess how TW evolves over time with directional programming.

Previous open-label, single-center investigations on small numbers of patients similarly observed wider TW with directional stimulation.<sup>24,26,27</sup> In the first intraoperative comparison, Pollo and colleagues found a similar 41% increase in TW and a 43% decrease in therapeutic current required for the optimal directional

**Table 3.** Quality of Life and Activities of Daily Living.

	PDQ-39 Parkinson's Disease Quality of Life		
	Baseline	Three months	Six months
Mobility	42.5 ± 27.3 (149)	34.8 ± 25.3 (202)	34.3 ± 26.4 (191)
ADL	42.1 ± 25.0 (149)	29.5 ± 20.6 (202)	26.9 ± 20.3 (191)
Emotional well-being	31.8 ± 22.5 (149)	27.8 ± 21.1 (203)	25.5 ± 20.1 (192)
Stigma	29.8 ± 26.9 (149)	17.3 ± 21.1 (202)	15.4 ± 18.6 (192)
Social support	16.3 ± 20.0 (132)	13.0 ± 20.0 (170)	11.8 ± 17.6 (162)
Cognition	25.9 ± 19.2 (149)	23.7 ± 17.2 (202)	22.6 ± 18.1 (192)
Communication	27.3 ± 25.0 (149)	28.0 ± 22.2 (203)	26.4 ± 21.3 (192)
Bodily discomfort	39.1 ± 24.6 (148)	35.3 ± 23.6 (202)	34.8 ± 22.7 (192)
Summary Index	31.6 ± 16.2 (149)	25.8 ± 15.1 (203)	24.4 ± 14.2 (192)
UPDRS Part II Activities of Daily Living			
	Baseline	Three months	Six months
UPDRS part II	9.2 ± 6.6 (121)	10.0 ± 6.1 (121)	10.0 ± 5.7 (112)

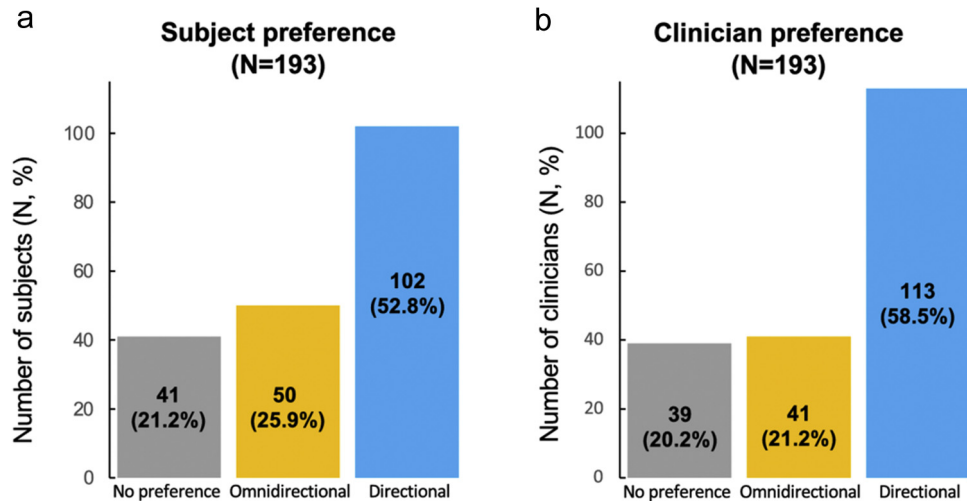
Values shown are mean ± standard deviation (number with complete data).

contact.<sup>26</sup> Rebelo and colleagues observed that directional DBS of the ventral intermediate nucleus for tremor could improve TW by 91% using the optimal contacts and therapeutic current strength could be reduced by 31%.<sup>28</sup> The single-center studies highlighted promising effects of directional DBS on limited numbers of subjects with a brief follow-up period. Vitek et al conducted a randomized multicenter study assessing the safety and efficacy of a new DBS system. The authors confirmed that DBS increases on time, improves motor scores, and adds to quality of life, but did not report extensively on programming capabilities.<sup>29</sup>

Although both omnidirectional and directional stimulation were used for three months, only 29% of stimulation-related adverse events occurred in the directional period. Subjects received three months of omnidirectional followed by three months of directional stimulation, with only the acute primary endpoint evaluation randomized. Since adverse events are known to occur more commonly in the first months after DBS and decrease over time, it cannot definitively be concluded if the reduction in events was due to stimulation type or time since implant.<sup>30</sup> All stimulation-related adverse events were resolved without sequelae except for the dysphagia event, which required hospitalization and subsequent outpatient care. Out of the total of 32 stimulation-related events, there were two events (worsening of tremor and abnormal gait) that could be resolved by switching from omnidirectional to directional stimulation. Two other events were instances of tremor that were resolved by switching from directional to omnidirectional stimulation.

There are several limitations of this study. Omnidirectional stimulation was used the first three months followed by an acute, randomized, primary endpoint evaluation, since directional stimulation had not been thoroughly studied at the time this study was designed. Comparisons between the first three months with omnidirectional stimulation and the following three months with directional stimulation may be affected by the time since surgery, in addition to the type of stimulation. Direct comparisons in the group implanted after study enrollment should be interpreted with caution, since resolution of the microlesion effect, post-operative events, and titration of medication occur largely during the first period. Subjects implanted after enrollment were 2.7 times as likely

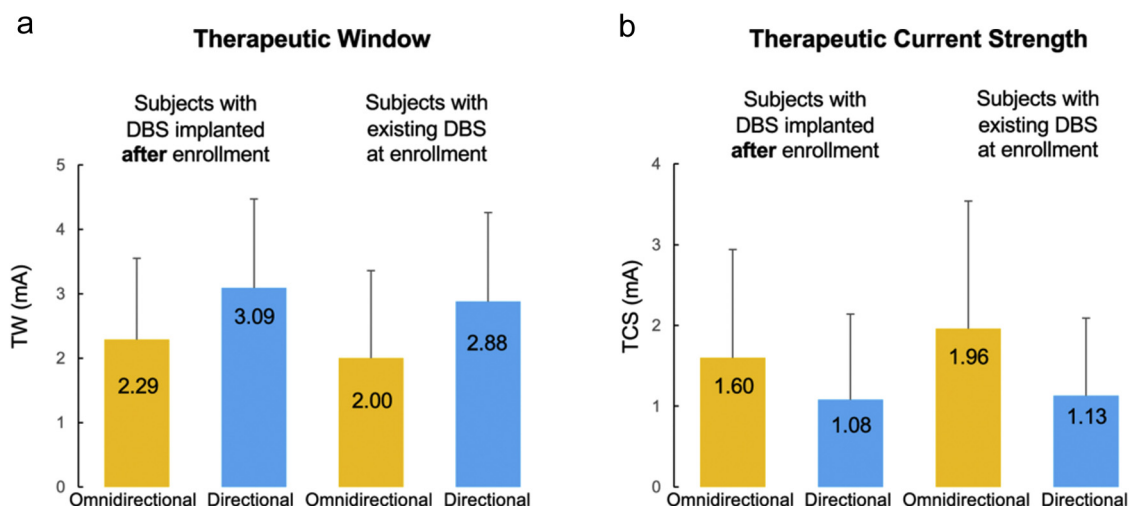




**Figure 4.** Subject and clinician stimulation preference at six months. a. Blinded subject preference, expressed as percentage in each category. b. Clinician stimulation preference, expressed as percentage in each category.

to favor the directional period compared to the omnidirectional period, while those with existing DBS implants at the time of study enrollment were 1.7 times as likely to favor the directional period. Although adverse event rates were quite modest compared to previous studies, 151 patients (64.5%) were enrolled after already having a successful implant.<sup>30</sup> Assessor blinding for certain secondary endpoints such as preferred stimulation type may be compromised, as the details of stimulation could be inferred based on knowledge of the study design. A recency bias could also occur for the preference evaluations, since there was a sequential administration of the two stimulation types (omnidirectional first and then directional stimulation). On the other hand, disease progression might have occurred over the course of the study favoring the omnidirectional period, particularly for subjects who were already implanted at enrollment. These sources of bias do not affect the randomized comparison of TW during the primary endpoint visit.

TW is a composite measurement that accounts for symptom control provided by the therapy and any side effects that could emerge with increased amplitude. TW was selected as the primary endpoint, since direct clinical outcome measures (such as UPDRS motor score) do not adequately consider stimulation-induced side effects.<sup>31</sup> DBS programming often involves tradeoffs between symptom relief and common side effects such as mild dysarthria and can account for patient and clinician preference for a particular stimulation setting. Moreover, TW can be expected to narrow over time, as the therapy current strength increases or the side-effect threshold decreases.<sup>32</sup> It is likely that a wider TW in early stages of DBS is associated with more favorable long-term outcomes. However, there are only limited variations in near-term DBS clinical outcomes for well-selected and treated patients. Both omnidirectional and directional stimulation significantly improved UPDRS motor score compared to stimulation off, confirming previous findings that STN DBS is an effective treatment for



**Figure 5.** TW (a) and therapeutic current strength (b) in subjects enrolled before and after DBS implant.

**Table 4.** UPDRS III Motor Scores.

	Baseline	Three months	Six months
Medication on/Stimulation on			
All subjects		14.5 ± 7.9 (201)	17.5 ± 9.9 (193)
Enrolled before implant		15.6 ± 7.0 (74)	18.2 ± 9.4 (73)
Enrolled after implant		13.9 ± 8.3 (127)	17.0 ± 10.2 (120)
Medication on/Stimulation off			
All subjects	18.8 ± 10.9 (227)	25.2 ± 12.5 (198)	30.9 ± 13.9 (192)
Enrolled before implant	19.4 ± 10.0 (83)	26.9 ± 12.2 (74)	31.5 ± 14.3 (73)
Enrolled after implant	18.5 ± 11.4 (144)	24.1 ± 12.6 (124)	30.5 ± 13.6 (119)
Medication off/Stimulation on			
All subjects		22.4 ± 10.4 (209)	
Enrolled before implant		22.7 ± 9.8 (80)	
Enrolled after implant		22.2 ± 10.7 (129)	
Medication off/Stimulation off			
All subjects	36.3 ± 12.9 (225)	36.9 ± 12.7 (208)	
Enrolled before implant	37.0 ± 11.1 (83)	37.1 ± 11.9 (79)	
Enrolled after implant	35.9 ± 13.8 (142)	36.9 ± 13.2 (129)	

Parkinson's disease.<sup>2-5</sup> UPDRS III motor score on medication off stimulation increased over time, as STN DBS presumably allowed medication reduction to occur while still achieving symptom relief. Medication data were not collected until 12 months after initial study programming. A preliminary data set from 12-month follow-ups suggests levodopa equivalent dose was reduced by approximately 43%, potentially contributing to longer on time during the day, reduced side effects such as dyskinesias and better quality of life. PDQ-39 improved with DBS compared to baseline, but activities of daily living and UPDRS motor score did not. Major studies of DBS have shown a clinical benefit is improved good-quality on time, which does not necessarily translate to UPDRS changes.<sup>2-5,29</sup> An item analysis of activities of daily living revealed that tremor and factors related to independence, such as cutting food, dressing, hygiene, and turning in bed showed the greatest improvement with DBS. These factors may help to explain improved quality of life but unchanged overall UPDRS part II and III. It is also possible that the preference for directional DBS reflected further improvement in individual symptoms, even if this difference was not detected by standard multisymptom questionnaires.

In PROGRESS, more than 90% of patients experienced a wider TW with directional stimulation. In 56 leads, there was a TW of no more than 0.5 mA for omnidirectional stimulation. Although such leads might require revision without other programming options, 36 (64%) could be programmed to achieve TW of 1 mA or greater using directional stimulation. For some patients, there might be a desire to optimize battery longevity. Others may benefit from a restricted stimulation field that minimizes side effects. Tailoring settings to each individual was beyond the scope of this study but could theoretically involve selecting amplitude at a different point within the TW to achieve individual goals. Directional programming may introduce additional complexity, but a strategy identifying the best segmented level and testing the segments of a single level can approach the efficiency of conventional ring-only programming. It was also found in a post hoc evaluation from PROGRESS that fewer stimulation-related adverse events were reported in the period when directional programming was used. By selecting settings to avoid side effects during in-clinic testing, it may also be possible to reduce future adverse events requiring reprogramming. The clinical

improvements from directional leads may lie in flexibility in programming, reflected in wider TW and lower stimulation-related adverse events in the near term, as well as the possibility for improved long-term DBS outcomes as the disease progresses.

In conclusion, this large prospective study found that directional stimulation could achieve a superior TW compared to conventional omnidirectional stimulation and was preferred by blinded subjects and clinicians. Further investigation will be needed to determine whether wider TW predicts improved long-term clinical outcomes of DBS.

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## Authorship Statements

Alfons Schnitzler contributed to the conception and execution of the study, review, and critique of the statistical analysis and writing and review of the manuscript. Pablo Mir, Matthew A. Brodsky, Sergiu Groppa, Julie G. Pilitsis, Monika Pötter-Nerger, Joohee Jimenez-Shahed, and Leonard Verhagen contributed to the execution of the study, review, and critique of the statistical analysis and writing and review of the manuscript. Ramiro Alvarez, Andrew Evans, Marta Blazquez, Sean Nagel, Winona Tse, Leonardo Almeida, Nestor Tomycz, Witold Libionka, Fatima Carrillo, Christian J. Hartmann, and Martin Glaser contributed to the execution of the study and review and critique of the manuscript. Stefan Jun Groiss contributed to the conception and execution of the study and writing and review of the manuscript. Florence Defresne and Edward Karst contributed to the execution, review and critique of the statistical analysis and writing of the manuscript. Binith Cheeran contributed the writing

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### REFERENCES

- Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry*. 1999;66:289–296.
- Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006;355:896–908.
- Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol*. 2010;9:581–591.
- Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2010;362:2077–2091.
- Okun MS, Gallo BV, Mandylbur G, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol*. 2012;11:140–149.
- Wharen RE, Okun MS, Guthrie BL, et al. Thalamic DBS with a constant-current device in essential tremor: a controlled clinical trial. *Parkinsonism Relat Disord*. 2017;40:18–26.
- Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013;368:610–622.
- Holtzheimer PE, Husain MM, Lisanby SH, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry*. 2017;4:839–849.
- Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010;51:899–908.
- Baldermann JC, Schuller T, Huys D, et al. Deep brain stimulation for Tourette syndrome: a systematic review and meta-analysis. *Brain Stimul*. 2016;9:296–304.
- Rowland NC, Sammartino F, Tomaszczyk JC, Lozano AM. Deep brain stimulation of the fornix: engaging therapeutic circuits and networks in Alzheimer disease. *Neurosurgery*. 2016;63:1–5.
- Butson CR, Cooper SE, Henderson JM, Wolgamuth B, McIntyre CC. Probabilistic analysis of activation volumes generated during deep brain stimulation. *Neuroimage*. 2011;54:2096–2104.
- Herzog J, Fietzek U, Hamel W, et al. Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. *Mov Disord*. 2004;19:1050–1054.
- Okun MS, Foote KD. Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. *Expert Rev Neurother*. 2010;10:1847–1857.
- Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology*. 2012;79:55–65.
- Odekerken VJ, Boel JA, Schmand BA, et al. GPi vs STN deep brain stimulation for Parkinson disease: three-year follow-up. *Neurology*. 2016;86:755–761.
- Richter EO, Hoque T, Halliday W, Lozano AM, Saint-Cyr JA. Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson disease. *J Neurosurg*. 2004;100:541–546.
- Daniluk S, Elias SA, Novak P, Nazzaro JM. Assessment of the variability in the anatomical position and size of the subthalamic nucleus among patients with advanced Parkinson's disease using magnetic resonance imaging. *Acta Neurochir*. 2010;152:201–210 [discussion: 210].
- van Dijk KJ, Janssen ML, Zwartjes DG, et al. Spatial localization of sources in the rat subthalamic motor region using an inverse current source density method. *Front Neural Circuits*. 2016;10:87.
- Hamid NA, Mitchell RD, Mocoft P, Westby GW, Milner J, Pall H. Targeting the subthalamic nucleus for deep brain stimulation: technical approach and fusion of

- pre- and postoperative MR images to define accuracy of lead placement. *J Neurol Neurosurg Psychiatry*. 2005;76:409–414.
- Wodarg F, Herzog J, Reese R, et al. Stimulation site within the MRI-defined STN predicts postoperative motor outcome. *Mov Disord*. 2012;27:874–879.
  - Hamani C, Richter E, Schwab JM, Lozano AM. Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature. *Neurosurgery*. 2005;56:1313–1321 [discussion: 1321–1324].
  - Rolston JD, Englot DJ, Starr PA, Larson PS. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: analysis of multiple databases. *Parkinsonism Relat Disord*. 2016;33:72–77.
  - Pollo C, Kaelin-Lang A, Oertel MF, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain*. 2014;137:2015–2026.
  - Contarino MF, Bour LJ, Verhagen R, et al. Directional steering: a novel approach to deep brain stimulation. *Neurology*. 2014;83:1163–1169.
  - Steigerwald F, Muller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: a pilot study using a novel neuro-stimulation device. *Mov Disord*. 2016;31:1240–1243.
  - Dembek TA, Reker P, Visser-Vandewalle V, et al. Directional DBS increases side-effect thresholds—a prospective, double-blind trial. *Mov Disord*. 2017;32:1380–1388.
  - Rebelo P, Green AL, Aziz TZ, et al. Thalamic directional deep brain stimulation for tremor: spend less, get more. *Brain Stimul*. 2018;11:600–606.
  - Vitek JL, Jain R, Chen L, et al. Subthalamic nucleus deep brain stimulation with a multiple independent constant current-controlled device in Parkinson's disease (INTREPID): a multicentre, double-blind, randomised, sham-controlled study. *Lancet Neurol*. 2020;19:491–501.
  - Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*. 2009;301:63–73.
  - Maier F, Lewis CJ, Eggers C, et al. The deep brain stimulation impairment scale (DBS-IS) - response to Jahanshahi. *Parkinsonism Relat Disord*. 2017;41:133–134.
  - Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*. 1998;339:1105–1111.

### COMMENTS

The authors present a large, multicenter prospective study of patients who underwent implantation of directional deep brain stimulation (DBS) systems for treatment of Parkinson's disease symptoms and provide a comparison of outcomes using omnidirectional stimulation vs directional stimulation. In acute testing sessions, the therapeutic window was demonstrated to be significantly greater and the therapeutic current significantly lower for directional stimulation, but clinical outcomes (UPDRS II, III, and PDQ-39) and average stimulation parameters (amplitude, pulse width, frequency) did not differ between the two stimulation paradigms at 3- and 6-month follow-up. Side effects were more common during omnidirectional stimulation, and clinicians and patients tended to prefer directional stimulation, but, as the authors point out, these differences could reflect time post-implant because subjects were not randomized to stimulation paradigm. Omnidirectional stimulation was delivered during the first 3 months post-implant, when subjects were typically recovering from the surgery/microlesion effect and medication/stimulation therapies were being adjusted; whereas, directional stimulation was delivered during the subsequent 3 months when patients were more likely to have recovered from surgery and medication/stimulation therapy had been optimized and stabilized. The observation that greater therapeutic window and lower therapeutic current of directional stimulation demonstrated in acute testing did not translate clearly to the clinical arena might reflect that the study was performed early in the availability of directional stimulation, during which time clinicians might not have been versed in programming directional stimulation to full advantage. We can reasonably expect that clinicians will learn with time and experience how to use directional stimulation to maximum benefit, which can, in turn, provide better outcomes for DBS patients.

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The authors present a 6-month follow-up of a randomized double-blind study of patients implanted with directional DBS leads – specifically, patients were programmed in non-directional “ring” mode for the initial 3 months of the study, and were then switched to directional stimulation for the next 3 months. Their primary findings are that the therapeutic window is significantly greater with directional stimulation. However, overall UPDRS motor scores were no different between the groups. They also report that more patients and physicians “preferred” the period with directional stimulation as compared with the earlier non-directional period. While the concept of a directional lead makes intuitive sense (haven’t we all seen the video of the directional lead making focal lesions in egg whites?), clear data demonstrating the benefit of this advanced (and more expensive)

technology has been lacking. I will note that with identical UPDRS scores between the groups, I cannot ascribe much significance to patient preference or to clinician preference, as they are likely tainted by recency bias – in other words, DBS programming is a work in progress of a period of months to years, and thus it would be expected that as time progresses, symptoms will be optimized and thus the “preference” would be for the most recent settings. Does directional stimulation increase generator longevity? Does it reduce the incidence of lead revision? Will it, in the long run, improve the quality of life for these patients? This paper provides intriguing evidence that the above may in fact be true – the DBS community awaits longer-term follow-up to confirm its true benefit.

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