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Effects of deep brain stimulation on rest tremor progression in early stage Parkinson disease

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Abstract

Objective

To evaluate whether the progression of individual motor features was influenced by early deep brain stimulation (DBS), a post hoc analysis of Unified Parkinson's Disease Rating Scale–III (UPDRS-III) score (after a 7-day washout) was conducted from the 2-year DBS in early Parkinson disease (PD) pilot trial dataset.

Methods

The prospective pilot trial enrolled patients with PD aged 50–75 years, treated with PD medications for 6 months–4 years, and no history of dyskinesia or other motor fluctuations, who were randomized to receive optimal drug therapy (ODT) or DBS plus ODT (DBS + ODT). At baseline and 6, 12, 18, and 24 months, all patients stopped all PD therapy for 1 week (medication and stimulation, if applicable). UPDRS-III “off” item scores were compared between the ODT and DBS + ODT groups ($n = 28$); items with significant between-group differences were analyzed further.

Results

UPDRS-III “off” rest tremor score change from baseline to 24 months was worse in patients receiving ODT vs DBS + ODT ($p = 0.002$). Rest tremor slopes from baseline to 24 months favored DBS + ODT both “off” and “on” therapy ($p < 0.001$, $p = 0.003$, respectively). More ODT patients developed new rest tremor in previously unaffected limbs than those receiving DBS + ODT ($p = 0.001$).

Conclusions

These results suggest the possibility that DBS in early PD may slow rest tremor progression. Future investigation in a larger cohort is needed, and these findings will be tested in the Food and Drug Administration–approved, phase III, pivotal, multicenter clinical trial evaluating DBS in early PD.

Classification of evidence

This study provides Class II evidence that for patients with early PD, DBS may slow the progression of rest tremor.

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From the Departments of Neurology (M.L.H., M.T., L.E.H., A.L.M., A.D.C., T.L.D., F.T.P., P.H., D.C.) and Neurosurgery (P.E.K.), Vanderbilt University Medical Center, Nashville, TN; Department of Neurology (M.R.D.), Emory University School of Medicine, Atlanta, GA; Laboratory of Molecular Immunology (L.E.H.), National Institute of Allergy and Infectious Diseases, Bethesda, MD; Movement Disorders and Neuromodulation Center (J.L.O.), Department of Neurology, University of California San Francisco; Department of Neurology (K.R.C.), Walter Reed National Military Center, Bethesda; and Department of Epidemiology (L.T.D., A.L.S., D.M.S., J.T.), Johns Hopkins University, Baltimore, MD.

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Glossary

CI = confidence interval; DBS = deep brain stimulation; FDA = Food and Drug Administration; HR = hazard ratio; LEDD = levodopa equivalent daily dose; ODT = optimal drug therapy; PD = Parkinson disease; STN = subthalamic nucleus; UPDRS-III = Unified Parkinson's Disease Rating Scale, part III.

Deep brain stimulation (DBS) is an effective adjunctive therapy for mid-stage and advanced stage Parkinson disease (PD), improving motor symptoms and quality of life while reducing medication-associated complications.^{1,2} The demonstrated efficacy of DBS in later PD stages and preclinical data supporting its earlier application^{3–5} warrant clinical trials to explore whether DBS applied in very early stage PD could extend or even enhance its benefits. Vanderbilt University completed a prospective, randomized, controlled clinical trial investigating subthalamic nucleus (STN) DBS in early PD.⁶ This pilot trial was designed to evaluate safety and tolerability of DBS in early PD, and the Food and Drug Administration (FDA) limited enrollment to 30 patients. The trial met its primary safety endpoint,⁶ and the FDA has approved the conduct of a pivotal, multicenter trial of DBS in early PD (IDE G050016). A key design feature of the pilot was implementation of week-long washouts of all PD therapy (medication and stimulation, if applicable) every 6 months during the 2-year trial. This 7-day washout was conducted in order to capture the underlying state of early motor symptoms. A secondary analysis of the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) total motor examination “off” score favored DBS plus optimal drug therapy (ODT) over ODT but did not reach statistical significance.⁶ This study's objective was to evaluate whether progression of individual motor features was influenced by early DBS.

Methods

Standard protocol approvals, registrations, and patient consents

The DBS in early PD pilot was a prospective, randomized, controlled, single-blind clinical trial (NCT00282152) that was approved by the FDA (IDEG050016) and Vanderbilt institutional review board (IRB040797).

Patients

Thirty patients with idiopathic PD aged 50–75 years, taking PD medications for 6 months–4 years at enrollment, Hoehn & Yahr II “off” medication, and without history of dyskinesia or motor fluctuations were enrolled in the study. For this analysis, 2 patients were excluded: 1 ODT patient dropped out after baseline; 1 DBS + ODT patient was discovered after the trial concluded to have not met the inclusion criteria for the duration of medication treatment.

Study procedures

The pilot study design and methods were previously described.⁶ Patients were admitted to the clinical research center for a week-long inpatient washout at baseline and every 6 months during

the 2-year trial. At baseline, the UPDRS-III examination was videotaped on day 1 “on” therapy (“on” medication), and patients then discontinued PD therapy for 1 week. On day 8, the UPDRS-III examination was videotaped again “off” therapy (“off” medication). After baseline evaluations, patients were then randomized 1:1 to receive ODT or bilateral STN DBS + ODT.⁷ All follow-up visits (6, 12, 18, and 24 months) were also videotaped on day 1 “on” therapy (“on” medication and stimulation, if applicable) and on day 8 “off” therapy (“off” medications and stimulation, if applicable). After the study concluded, all videotapes were de-identified with respect to treatment assignment, follow-up duration, and “on”/“off” status and scored in random order by an independent, blinded neurologist certified in scoring the UPDRS.⁶ The UPDRS-III total score reported includes all motor examination items except rigidity, which cannot be assessed by videotape. DBS + ODT patients did not begin active treatment until ~6 weeks after baseline assessments in order to allow time for preoperative planning and postoperative healing.⁶

Medication and stimulation management

Patients' medication and stimulation adjustments were made by their treating neurologist (not the principal investigator). Monopolar stimulation with case positive and the optimal contact negative was utilized for all patients (model 3389 leads; Medtronic, Minneapolis, MN).⁷ Patients were initially programmed per standard of care for DBS, and the optimal contact was titrated to efficacy alongside medication adjustments 4 weeks after surgery.⁶ DBS and medications could then be adjusted by the patient's treating neurologist as needed over the trial. Stimulation pulse width and frequency were fixed at 60 μ s and 130 Hz, respectively. Levodopa equivalent daily dose (LEDD)⁸ and voltages are reported as mean \pm SD.

Patient satisfaction survey

A survey was conducted to collect information regarding patient experiences and satisfaction participating in the trial. Twenty-seven respondents completed the written survey ($n = 14$ ODT, $n = 13$ DBS + ODT), which addressed their decision to participate, experience with the expanded informed consent process, study procedures, and poststudy reflections. DBS + ODT patients completed additional questions designed to explore their DBS experience.

Statistical analysis

This analysis was conducted to provide Class II evidence of the effect of DBS on the progression of individual motor features of early stage PD. Patients were analyzed in the treatment group to which they were randomized. Statistical

analyses were performed using IBM SPSS Statistics 23.0 (IBM, Armonk, NY), STATA 13.1 (StataCorp LP, College Station, TX), and SAS 9.3 (SAS Institute, Inc., Cary, NC). *p* Values comparing the 2 groups on changes from baseline to 24 months in UPDRS-III “off” items (i.e., individual motor examination items) were determined from Wilcoxon rank-sum tests; using a Bonferroni multiple comparisons correction,⁹ *p* < 0.0038 (0.05/13 items) was considered statistically significant.

A multiple linear regression model with generalized estimating equations and robust variance estimation¹⁰ was used to assess the magnitude and statistical significance of the between-treatment group difference in item trends (difference in slopes) over 24 months. The model adjusted for baseline score and accounted for within-patient correlations in the repeated measures (changes in score from baseline to 6, 12, 18, and 24 months); exchangeable correlations within patients were assumed. Separate models for score change were fit for the “off” and “on” treatment states. Each model included a binary term for treatment group, a continuous term for time, and a term for the treatment group by time interaction, as well as a baseline score term. The *p* value for the difference in the DBS + ODT vs ODT score trends was determined from a 2 degrees of freedom χ^2 test of the null hypothesis that both the treatment and treatment by time interaction terms were zero.

A Cox proportional hazards model¹¹ with a binary term for treatment group was used to estimate the between-group hazard ratio for the time to at least a 2-point worsening in UPDRS-III “off” rest tremor score. A 2-point worsening of the rest tremor item was selected because the minimum clinically important difference for the entire UPDRS-III (combination of all motor items) is 2.3.¹² The *p* value for difference between the treatment groups for risk of at least 2-point worsening was determined from the log-rank test.

The number of limbs affected by rest tremor (face, right hand, left hand, right leg, left leg) was evaluated for each patient at baseline and 24 months, and mean change from baseline to 24 months was compared between groups using a 2-sample *t* test with equal variances. Each patient was also evaluated for rest tremor development in previously unaffected limbs. De novo development was defined per limb as having no baseline rest tremor present (question 20 UPDRS-III “off” item score = 0) and a non-zero 24-month rest tremor item severity score. Patients with rest tremor onset in at least one limb at 24 months were categorized as having developed rest tremor de novo. Fisher exact test was used to assess the difference between treatment groups in the risk of de novo rest tremor development (development vs no development). *p* < 0.05 Was considered to be significant.

Data availability

The individual de-identified participant data and related study documents are not being publicly shared at this time as they

are currently being used for the development of a proprietary, multicenter, phase III, pivotal clinical trial (IDE G050016).

Results

Baseline characteristics

Twenty-eight out of the 30 patients enrolled in the pilot trial were included in this analysis (1 ODT patient dropped out after baseline; 1 DBS + ODT protocol violation). At baseline, the groups were similar in sex, age, Hoehn & Yahr, medication

Table Baseline characteristics

Characteristic	ODT (n = 14)	DBS + ODT (n = 14)
Sex		
Male	12	13
Female	2	1
Age, y		
Mean	60.5 ± 6.6	61.3 ± 6.4
Range	50.2–69.5	53.6–73.9
Mean disease duration, y	2.1 ± 1.6	1.9 ± 1.5
Hoehn & Yahr		
“On”	1.8 ± 0.4	1.7 ± 0.5
“Off”	2.0 ± 0.0	2.0 ± 0.1
Medicine use		
Mean duration, y	1.9 ± 1.0	2.0 ± 1.4
Mean L-dopa equivalents, mg/d	490.7 ± 216.2	409.0 ± 316.5
Total UPDRS		
“On” (day 1) ^a	33.4 ± 13.3	37.2 ± 15.0
“Off” (day 8) ^b	42.7 ± 12.7	44.6 ± 11.4
UPDRS-III		
“On” (day 1) ^a	21.3 ± 9.2	24.8 ± 12.0
“Off” (day 8) ^b	29.5 ± 8.7	29.2 ± 9.5
PD phenotype^c		
Tremor-dominant	9	8
Postural instability/gait difficulty	2	2
Mixed	3	3
Unknown ^b	0	1

Abbreviations: DBS = deep brain stimulation; ODT = optimal drug therapy; PD = Parkinson disease; UPDRS-III = Unified Parkinson’s Disease Rating Scale, part III.

Total UPDRS “on” = UPDRS I + UPDRS II “on” + UPDRS III “on” + UPDRS IV. Total UPDRS “off” = UPDRS I + UPDRS II “off” + UPDRS III “off” + UPDRS IV.

^a 1 ODT patient was missing baseline blinded “on” data for the UPDRS.

^b 1 DBS + ODT patient was missing baseline blinded “off” data for the UPDRS.

^c “Off” scores used to calculate PD phenotype using method described by Stebbins et al.⁴¹

duration, UPDRS-III “off” score, and PD phenotype distribution (table). The DBS + ODT group had lower LEDD and worse “on” scores for total UPDRS and UPDRS-III at baseline, but these differences did not reach statistical significance in this small study.

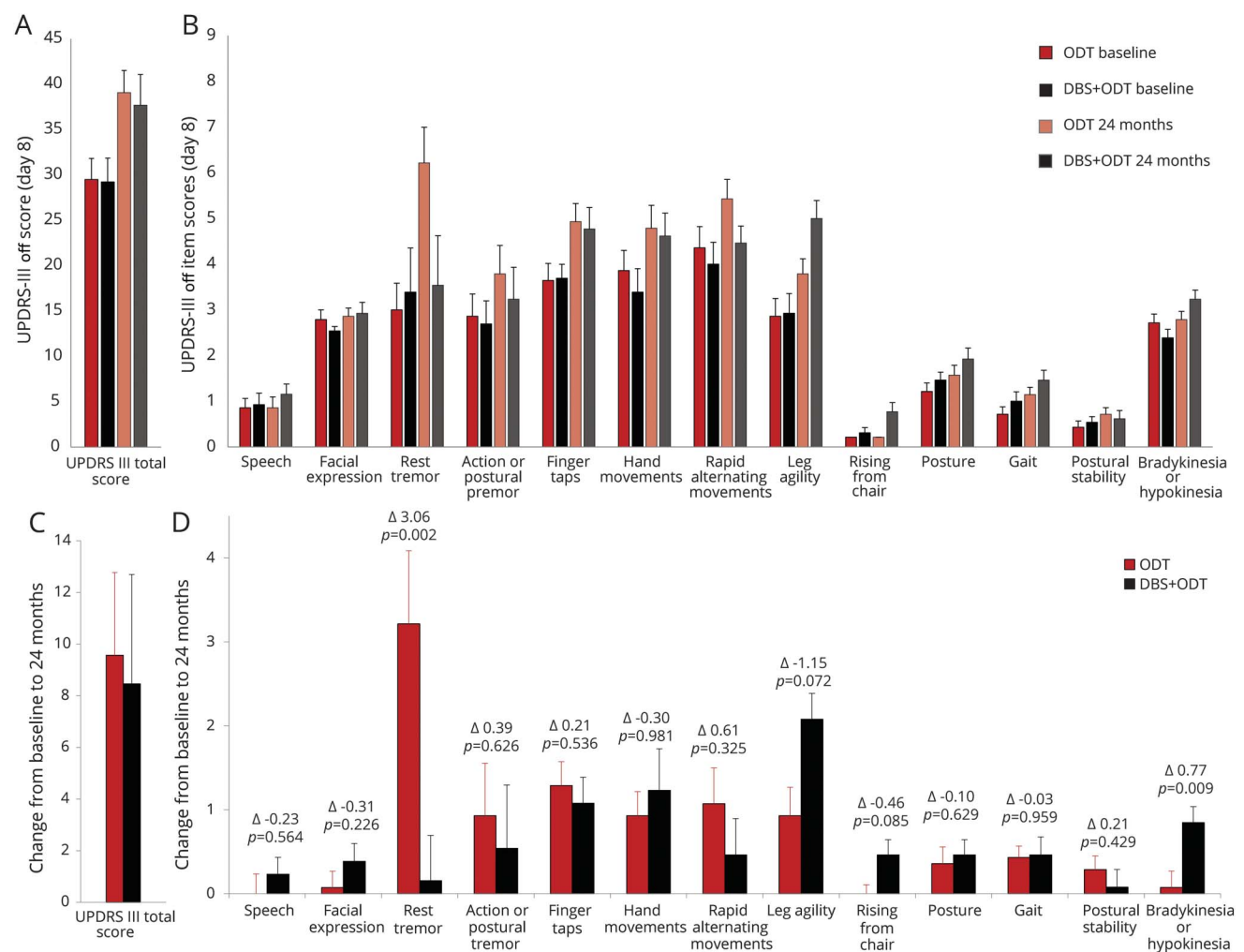
UPDRS-III motor items “off” therapy

Mean UPDRS-III total “off” scores worsened for both groups from baseline to 24 months (figure 1, A, C). Figure 1B shows mean baseline and 24-month scores for individual UPDRS-III “off” items, and change scores from baseline to 24 months were compared between groups (figure 1D). Rest tremor “off” change scores were 3.1 points better for the DBS + ODT group than the ODT group, and this was the only UPDRS-III item that reached statistical significance after adjusting for multiple comparisons ($p = 0.002$).

Rest tremor “off” therapy

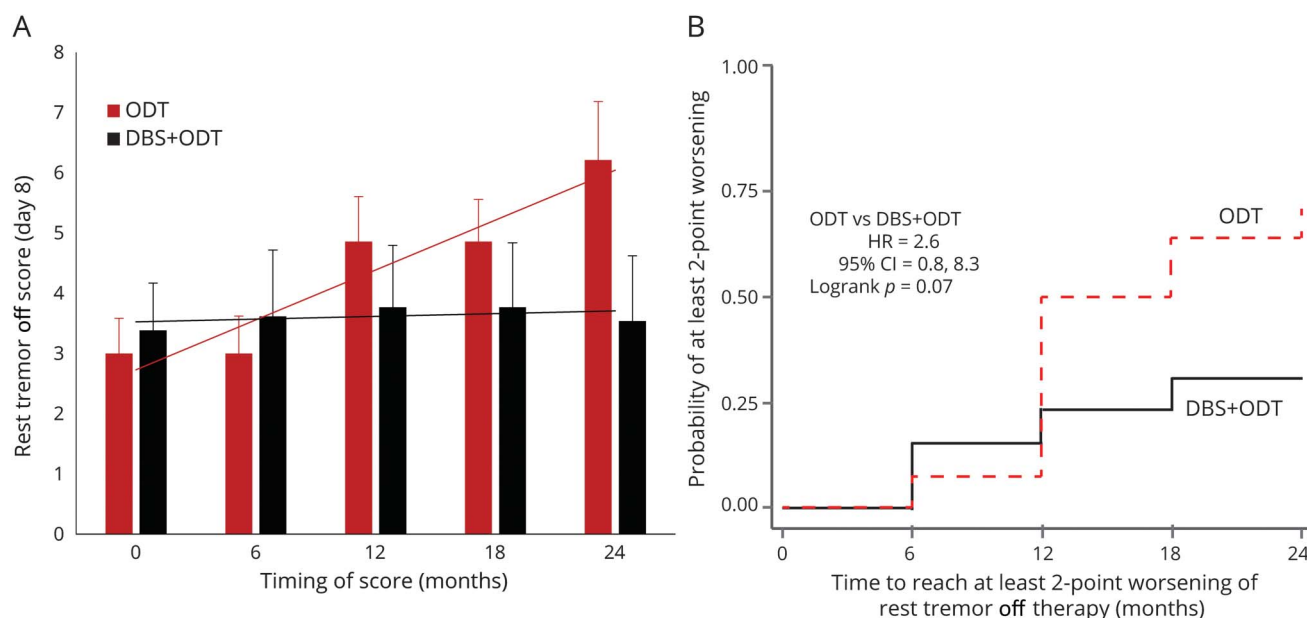
Mean rest tremor “off” score worsened 3.2 points for the ODT group over 2 years, with minimal change (+0.2 points) in the DBS + ODT group (figure 2A). The difference in rest tremor “off” score slopes favored DBS + ODT (DBS + ODT vs ODT = -2.0 points/y; $p < 0.001$). A Cox proportional hazards model revealed that the risk of at least 2-point worsening in rest tremor “off” score was 2.6 times greater in the ODT group compared to the DBS + ODT group (figure 2B; hazard ratio [HR], ODT vs DBS + ODT = 2.6; 95% confidence interval [CI] 0.8–8.3; log-rank $p = 0.07$). Seventy-one percent of the ODT group (10/14) and 31% of the DBS + ODT group (4/13) experienced at least a 2-point worsening in their rest tremor “off” score by 24 months (figure 2B). In a sensitivity analysis, the Cox proportional hazards model was repeated including the DBS + ODT patient with

Figure 1 Unified Parkinson’s Disease Rating Scale, part III (UPDRS-III) motor examination “off” item scores



Mean \pm SEM UPDRS-III scores after a 7-day washout (day 8) by treatment group ($n = 14$, optimal drug therapy [ODT]; $n = 13$, deep brain stimulation [DBS] + ODT) and mean \pm SEM changes in scores from baseline to 24 months. (A) UPDRS-III total score (excludes rigidity) at baseline and 24 months. (B) UPDRS-III item scores at baseline and 24 months. (C) Change in UPDRS-III total score (excludes rigidity) from baseline to 24 months. (D) Change in UPDRS-III item scores from baseline to 24 months. $\Delta =$ ODT minus DBS + ODT difference in change from baseline to 24 months; p values determined from Wilcoxon rank-sum test; $*p < 0.0038$ (0.05/13) was considered significant for this analysis.

Figure 2 Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) motor examination "off" rest tremor



UPDRS-III rest tremor score after 7-day washout (day 8) by treatment group ($n = 14$, optimal drug therapy [ODT]; $n = 13$, deep brain stimulation [DBS] + ODT). (A) Mean \pm SEM rest tremor "off" score at baseline and 6, 12, 18, and 24 months by treatment group, with regression lines showing the trend in score over time for each group. The p value for the DBS + ODT vs ODT difference in rest tremor "off" score trends (difference in slopes = -1.97 points/y) is determined from a 2 degrees of freedom χ^2 test from analysis of covariance of the change in score from baseline, adjusting for the baseline score and within-patient correlations and was significant at the 0.01 level ($p < 0.001$, exchangeable correlations). Model for change in rest tremor "off" score over time: change in rest tremor "off" score = $1.93 \times \text{time (y)} + 1.04 \times \text{DBS} - 1.97 \times \text{DBS} \times \text{time (y)} - 0.05 \times \text{Baseline rest tremor "off" score} - 0.53$. (B) Time to reach at least 2-point worsening in rest tremor score "off" therapy. The hazard ratio (HR) and 95% confidence interval (CI) were derived from a Cox regression model with treatment group as the single model variable; the p value was determined by the log-rank test.

a protocol violation, which yielded similar results (HR, ODT vs DBS + ODT = 2.8; 95% CI 0.9–9.1; log-rank $p = 0.047$).

De novo rest tremor development

The mean number of limbs per patient affected by rest tremor at baseline was 1.4 ± 0.8 and 1.6 ± 1.3 for the ODT and DBS + ODT groups, respectively (figure 3A). The mean number of limbs per patient affected by rest tremor at 24 months doubled in the ODT group (2.8 ± 1.3) and decreased slightly in the DBS + ODT group (1.5 ± 1.3), with the change from baseline to 24 months favoring DBS + ODT ($p = 0.001$). Furthermore, 86% of ODT patients developed rest tremor in previously unaffected limbs from baseline to 24 months (12/14), compared to 46% of patients receiving DBS + ODT (figure 3B; 6/13; odds ratio 7.0, 95% CI 1.10–45.45, $p = 0.046$). Seven DBS + ODT patients did not develop rest tremor in any previously unaffected limb, and 4 of those patients had rest tremor present in a limb at baseline that resolved by 24 months. Of note, rest tremor disappeared from all affected limbs for 1 DBS + ODT patient (rest tremor item score: baseline = 4, 24 months = 0).

Rest tremor "on" therapy

Mean rest tremor scores were also analyzed "on" treatment (figure 4A). At baseline, the DBS + ODT group was 1.3 points worse than the ODT group, and in this small study, this difference was not significant ($p = 0.18$). The DBS + ODT group mean rest tremor "on" score improved over the 2-year

period (-1.5 points), while the ODT group mean score worsened ($+0.9$ points). The difference in rest tremor "on" change score favored the DBS + ODT group (difference in slopes = -0.74 points/y; $p = 0.003$).

Treatment measures

The DBS + ODT group took less medication on average at each visit than the ODT group (figure 4B). Mean stimulation voltage was modest over the 2-year period, beginning at 1.6 ± 0.2 V at 6 months and increasing to 1.9 ± 0.3 V at 24 months (figure 4C).

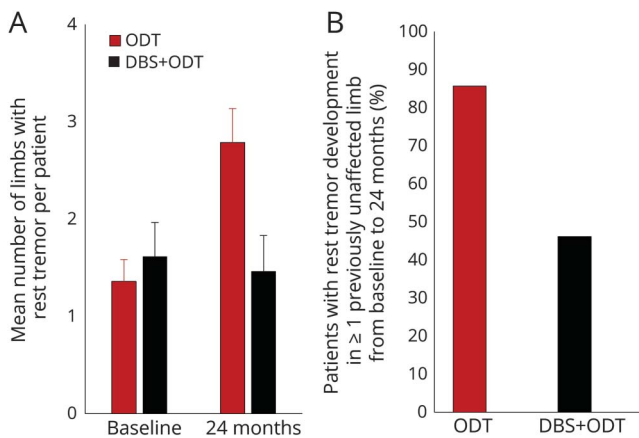
Patient survey responses

A patient satisfaction survey was conducted after the trial concluded. DBS + ODT patients were asked the open-ended question, "What has been the greatest benefit of undergoing DBS surgery?" Responses were categorized, and 6/13 patients treated with DBS + ODT identified tremor improvement as the greatest DBS benefit. Additional responses were related to quality of life improvement ($n = 2$), symptom reduction ($n = 2$), PD progression slowed ($n = 1$), research to help patients with PD sooner ($n = 1$), and making friends with PD ($n = 1$).

Discussion

This study was conducted to evaluate changes in individual UPDRS-III motor examination items collected following a 7-day therapeutic washout in the pilot trial of DBS in early

Figure 3 De novo development of rest tremor



(A) Mean \pm SEM number of limbs affected by rest tremor at baseline and 24 months. Difference between groups in change from baseline to 24 months, $p = 0.001$. p Value determined by the 2-sample t test with equal variances. (B) Proportion of patients who developed rest tremor in previously unaffected limbs from baseline to 24 months. Optimal drug therapy [ODT] $n = 14$, deep brain stimulation [DBS] + ODT $n = 13$. Odds ratio 7.0, 95% confidence interval 1.10–45.45, $p = 0.046$. p Value determined using the Fisher exact test was used to assess the difference between the ODT and DBS + ODT groups in the risk of de novo development of rest tremor (development vs no development). $p < 0.05$ was considered significant for this analysis.

PD. Rest tremor was identified as a motor feature that may be slowed by early DBS. As expected in early PD, mean rest tremor “off” score for the ODT group progressively worsened, whereas there was virtually no worsening for the DBS + ODT group. Rest tremor development or spread to previously unaffected limbs occurred in the majority of ODT patients (86%) compared to only 46% of DBS + ODT patients. The spread of motor features from limbs affected at diagnosis to previously asymptomatic areas is a hallmark feature of PD. These data suggest that patients with early PD treated with ODT alone are 7 times more likely to develop rest tremor in previously unaffected limbs after 2 years than patients treated with DBS + ODT. Furthermore, rest tremor “on” treatment improved in early DBS + ODT patients compared to ODT patients, similar to the benefit expected with STN-DBS in more advanced PD stages.¹³ Taken together, these findings suggest that DBS in early PD not only improves rest tremor in the treated state but that early STN stimulation may also slow rest tremor progression.

Tremor is highly variable and is often not the single overriding symptom associated with disability and the need for long-term care in advanced PD. There are even reports of tremor disappearing late in the disease.¹⁴ Nevertheless, tremor is a highly visible feature of PD,¹⁵ is often distressing, and evokes feelings of embarrassment and stigma for patients.^{16,17} While the importance of PD tremor is sometimes downplayed,¹⁷ up to 75% of patients are affected by this cardinal motor feature.¹⁸ Tremor is especially distressing in the early stages of the disease due to challenges faced in vocational and social settings.^{19,20} The importance of tremor control in early PD is also reflected by DBS patients in this study, with nearly half

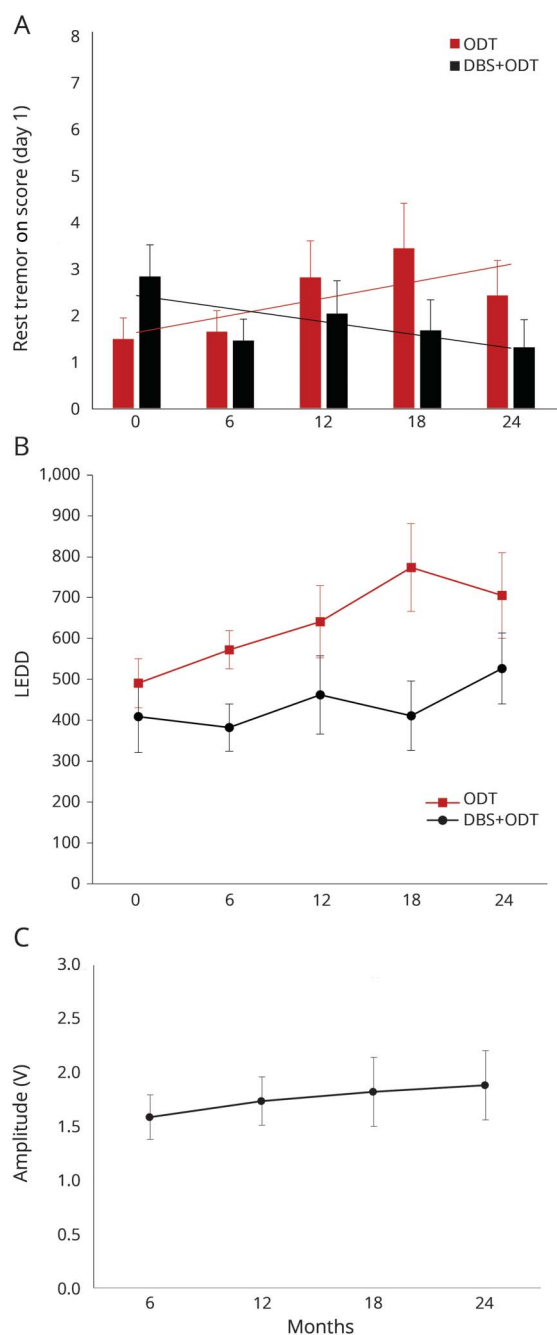
responding that the greatest benefit of undergoing surgery was management of their tremor.

These results should be interpreted with caution due to limitations of this study including its post hoc comparisons, small sample size, and open-label design. This single-blind UPDRS-III subanalysis excludes rigidity, which cannot be evaluated by videorecording, and the effect of early DBS on the 2-year progression of this cardinal feature therefore remains unknown. Medication-refractory tremor is known to respond well to STN-DBS²¹; however, this was not assessed during the pilot trial. In addition, without an objective PD biomarker to monitor disease progression, clinical trials such as this one must utilize currently available clinical scales. For the pilot, single-blind UPDRS-III scores were assessed after a 7-day washout to evaluate underlying motor symptoms. While the UPDRS-III is a validated evaluation method, there is a subjective element to this clinical assessment, and, in lieu of a biomarker, future investigations may benefit from objective data collection technology. The open-label pilot study was also vulnerable to potential placebo/lessebo effects.²² However, UPDRS-III videos were rated after the study concluded by an independent neurologist blinded to treatment, “on”/“off” status, and study visit chronology.⁶

This study’s design also restricts distinction between benefits due to DBS surgery (implantation + stimulation) vs stimulation alone. Microlesion-induced motor symptom improvement after surgery is well-documented,²³ but this phenomenon is reported to resolve within weeks to months after surgery and likely correlates with resolving edema.²⁴ A recent neuroimaging study indicates that microlesion benefits are not only transient (deteriorate within 1 month) but they also occur through a different mechanism (brainstem-mediated), distinguishable from that of STN stimulation (thalamocortical-mediated).²⁵ That study also found that clinical microlesion signs had no effect at 1 year postsurgery. In one advanced PD study where microlesion benefit was reported to last up to 6 months, the effect was not specific to tremor, with improvements also observed in bradykinesia and rigidity.²⁶ Nevertheless, this study cannot rule out influence of a microlesion effect, and future investigations of DBS in PD should include designs to better understand microlesioning effects and their correlation with long-term clinical benefit. Preoperative and postoperative baseline assessments are included in the study design for the FDA-approved pivotal trial of DBS in early PD.

The pilot’s 7-day washout produced one of the most robust longitudinal “off” datasets collected in a prospective, randomized PD trial. While PD medication washout durations are highly variable,^{27,28} it is important to note that ODT patients received more medications on average than the DBS + ODT group throughout this study.^{6,29} Therefore, any lasting benefit of medications after the washout is expected to favor ODT. Although lack of tremor progression with DBS in advanced PD reported by others may suggest long-lasting

Figure 4 Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) motor examination "on" rest tremor and treatment use



(A) Mean \pm SEM UPDRS-III rest tremor score "on" therapy (day 1) by treatment group (n = 13, optimal drug therapy [ODT]; n = 14, deep brain stimulation [DBS] + ODT) over time with regression lines showing the trend in score over time for each group. The *p* value for the DBS + ODT vs ODT difference in rest tremor "on" score trends (difference in slopes = -0.74 points/year) is determined from a 2 degrees of freedom χ^2 test from analysis of covariance of the change in score from baseline, adjusting for the baseline score and within-patient correlations and was significant at the 0.01 level (*p* = 0.003, exchangeable correlations). Model for change in rest tremor "on" score over time: change in rest tremor "on" score = $0.58 \times \text{time (y)} - 0.90 \times \text{DBS} - 0.74 \times \text{DBS} \times \text{time (years)} - 0.34 \times \text{baseline rest tremor "on" score} + 0.84$. (B) Mean \pm SEM levodopa equivalent daily dose (LEDD) for ODT (n = 14) and DBS + ODT (n = 14) over the 24-month study period. (C) Stimulation measures (rate 130 Hz, pulse width 60 ms). Mean \pm SEM stimulation amplitude for the DBS + ODT group (n = 14). Amplitude shown as average of left and right leads. V = voltage. Amplitude range = 1.0–2.4 V.⁵

stimulation effects,³⁰ STN-DBS washout times are reported to be much faster than for medications, with 90% of motor symptoms worsening within 2 hours of discontinuing STN-DBS³¹ and resting-state beta-band local field potentials becoming stable within seconds after STN-DBS withdrawal.³² While long-lasting stimulation benefit remains possible, it is less likely given reports of the rapid return of tremor within minutes after stopping stimulation—much faster than other motor signs.^{31,33}

Another important point is that the STN-DBS effect on rest tremor in this study was achieved with modest stimulation. Therefore, the effect could potentially have been more pronounced if stimulation measures were maximized. While typical stimulation voltage for advanced PD ranges from 2.5 to 3.5 V,³⁴ patients in this early PD trial were managed at much lower voltages (mean 1.6–1.9 V). Treating neurologists in this study were instructed to program per standard of care for DBS such that stimulation was titrated to clinical efficacy alongside medication adjustments.⁷ Future studies could consider trial designs focused on higher initial amplitude of stimulation to determine if greater benefit could be achieved with increased stimulation.

Tremor pathophysiology is well-established to be distinct from other PD motor features, notable for pronounced cerebellar influence and lack of correlation with striatal dopaminergic depletion. Tremor progression does not correlate with other motor symptoms,³⁵ and patients with tremor-dominant PD typically have a better prognosis and slower disability progression than non-tremor-dominant patients.³⁶ Ultimately, the identification of rest tremor as a feature that may progress more slowly after STN-DBS in early PD could further reflect the unique, still poorly understood circuitry and pathophysiology of this cardinal motor feature. Although there is not yet a clear mechanism for rest tremor in PD,^{37,38} there is increasing evidence for subcortical basal ganglia and cerebellar interactions that may be influenced by early STN-DBS.^{39,40} It is worth noting that leg agility and bradykinesia scores from baseline to 24 months favored ODT over DBS + ODT by 1.2 and 0.8 points, respectively, although these differences were not statistically significant in this small study after accounting for multiple item comparisons. A larger cohort is needed to adequately investigate potential beneficial or harmful effects on motor progression resulting from early DBS.

The DBS in early PD pilot trial suggests that STN stimulation may slow rest tremor progression. More investigation is needed in a larger cohort, and the FDA has approved the conduct of a multicenter, pivotal clinical trial testing STN-DBS in early PD.

Authors contributions

M.L.H.: research project: conception, organization, execution; statistical analysis: review and critique; manuscript preparation: writing of the first draft. M.R.D.: research project: conception; statistical analysis: design and review and

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