Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Adaptive Deep Brain Stimulation Benefits: Younger Patients with Persistent Wearing-off Symptoms

Takuto Emura, MD, Naoki Tani, MD, PhD,* Koichi Hosomi, MD, PhD, Yuki Kimoto, MD, PhD, Takahiro Matsuhashi, MD, Takahiro Fujinaga, MD, Shimpei Miura, MD, Yuya Fujita, MD, PhD, Nobuhiko Mori, MHs, Hui Ming Khoo, MD, PhD, Satoru Oshino, MD, PhD, and Haruhiko Kishima, MD, PhD

Abstract: Background: Parkinson's disease (PD) often involves motor fluctuations and dyskinesia, which are difficult to manage with medication alone. Conventional deep brain stimulation (cDBS) effectively alleviates symptoms but has limitations, including the challenge of balancing therapeutic effects against potential side effects, as well as limited battery life. To address these issues, adaptive DBS (aDBS) systems, which dynamically adjust stimulation parameters based on real-time physiological feedback, have attracted growing interest.

Objectives: The aim of this study was to assess the efficacy, tolerability, and safety of aDBS in patients with advanced PD over a 1-year period, using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Parkinson's Disease Questionnaire-39 (PDQ-39).

Methods: This prospective, single-arm study involved 19 patients who transitioned from cDBS to aDBS. Baseline assessments were conducted under cDBS, and patients were re-evaluated 1 year after switching to aDBS.

Results: Sixteen patients completed 1 year of aDBS. Significant improvements in motor function, as measured by MDS-UPDRS Part III scores in the medication-off/stimulation-on condition, were observed. Patients with severe baseline wearing-off showed greater reductions in motor fluctuation (MDS-UPDRS Part IV) scores. Younger patients showed better quality of life (PDQ-39) and activity of daily living (MDS-UPDRS Part II) scores, though overall changes were not statistically significant.

Conclusions: aDBS shows promise in managing motor symptoms in PD, particularly in patients with pronounced wearing-off and younger patients, by dynamically adjusting stimulation parameters. Although further optimization and long-term studies are necessary, these findings underscore the potential of aDBS to offer personalized treatment options for advanced PD.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that significantly affects patients' quality of life (QoL). In advanced stages, patients with PD often develop motor fluctuations and drug-induced dyskinesia, which are difficult to manage with medication alone. Deep brain stimulation (DBS) is an effective treatment for carefully selected patients, with numerous high-quality studies demonstrating its superiority over optimal medical therapies.[1,2] However, conventional DBS (cDBS) has limitations, including balancing beneficial effects with potential side effects and limited battery longevity.[3,4] To address these, there is increasing interest in adaptive or closed-loop DBS systems, which automatically adjust the stimulation parameters in real time based on feedback signals reflecting the patient's clinical state.[5,6]

Recent technological advances have enabled the development of fully implantable bidirectional neural interfaces capable of sensing neural activity during stimulation and implementing feedback control.[7] These innovations have catalyzed research on

Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Japan

***Correspondence to:** Naoki Tani, Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Osaka 5650871, Japan. E-mail: n-tani@nsurg.med.osaka-u.ac.jp

Keywords: adaptive deep brain stimulation, Parkinson's disease, closed-loop system, local filed potential, beta oscillation.

Received 28 March 2025; revised 5 August 2025; accepted 12 August 2025.
Published online 00 Month 2025 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.70311

chronic invasive brain sensing and adaptive neurostimulation. Potential adaptive DBS (aDBS) inputs include basal ganglia local field potentials (LFP), cortical recordings, wearable sensors, and mobile health applications.[8–10]

In 2013, Little et al. demonstrated motor symptom improvement with closed-loop DBS compared to cDBS in patients with PD.[5] This approach utilizes the beta-band (13–30 Hz) LFP in the subthalamic nucleus (STN) as a biomarker for motor symptoms.[11]

Although aDBS shows promise, several barriers have hindered its widespread use. These include technical challenges in accurately sensing brain signals during ongoing stimulation and a lack of standardized algorithms for optimizing feedback control.[8,12] This study evaluated the clinical efficacy, tolerability, and safety of aDBS in real-world clinical practice without restricting stimulation parameters, allowing patients to benefit from optimized DBS settings while potentially addressing cDBS limitations. We report clinical outcomes in patients treated with aDBS for over 1 year.

Methods

This report presents the 1-year results of a single-center, prospective, single-arm interventional study of aDBS conducted at Osaka University Hospital. This study was approved by the Institutional Ethics Committee of Osaka University Hospital (approval no.: 20450-3). This study was conducted in accordance with the principles of the Declaration of Helsinki.[13] The trial was registered in the UMIN Clinical Trial Registry System (registration no.: UMIN000042900). All participants provided informed consent after being fully informed of the nature of the study, its potential risks, and its benefits.

Participants

This study included patients with advanced PD, defined as those experiencing significant impairment in activities of daily living (ADLs) due to wearing-off or dyskinesia, and exhibiting more than 30% diurnal variation in Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III scores. Eligible patients had undergone conventional STN DBS for at least 6 months prior to enrollment and were implanted with Medtronic's Percept PC neurostimulator. The implanted electrodes were either Medtronic 3389 quadripolar leads or SenSight directional leads (Model B33005). PD was diagnosed based on the 2015 criteria proposed by the International Parkinson and Movement Disorder Society.[14] The inclusion and exclusion criteria are described in Supplementary Materials (Supplementary Methods). *Consecutive patients who met the inclusion criteria were enrolled in the trial, including both those with well-controlled cDBS and those without. However, some eligible patients declined participation due to the requirement for inpatient evaluations.*

Surgical Procedure

At our institution, electrode placement and neurostimulator implantation are performed under general anesthesia in a single-stage procedure. Electrode targeting was guided by fusion images created from preoperative magnetic resonance imaging and stereotactic computed tomography scans obtained after Leksell frame placement, complemented by intraoperative microelectrode recording. The electrode was implanted with the most dorsal contact positioned just above the dorsal border of the STN, and the second contact located at the dorsal-most region within the STN.

Evaluation Methods

In this study, patients who underwent cDBS for over 6 months after electrode implantation transitioned to aDBS. There were no requirements for the stability of cDBS stimulation parameters prior to enrollment; settings could be adjusted as clinically indicated before study entry. Assessments included the Parkinson's Disease Questionnaire-39 (PDQ-39), MDS-UPDRS, Berg Balance Scale (BBS), and the 10-m Timed Up and Go Test (10-m TUG). The baseline evaluations used optimal cDBS settings. aDBS was initiated, and follow-up evaluations were conducted at 6 and 12 months. Each pre-DBS clinical score was retrospectively obtained from the medical records. The aDBS parameters were determined using Medtronic's Percept PC system with BrainSense technology. The process, conducted while the patients were in a medication-off state, involved the following steps:

1. Beta oscillation detection: BrainSense "Survey" measured STN LFPs, identifying beta frequencies (13–30 Hz) as therapeutic targets.
2. Stimulation protocol: Contact and amplitude settings from the cDBS were retained, whereas the frequency was adjusted within system constraints (55–180 Hz). Due to product limitations, the most dorsal and ventral contacts could not be used for stimulation, and bipolar, asymmetric double monopolar, and directional stimulation configurations were not permitted. Stimulation parameters, including contact selection, were initially retained from the cDBS settings. However, if appropriate sensing could not be achieved with the original cDBS settings, stimulation contacts were changed only when the resulting reduction in clinical benefit was considered acceptable.
3. Threshold setting: LFPs were measured at the minimum effective and maximum tolerable stimulation outputs to establish the upper and lower thresholds for adaptive adjustments.
4. Dual threshold mode: Stimulation intensity increased when beta power exceeded the upper threshold and decreased when it fell below the lower threshold.
5. Personalization: Thresholds and stimulation ranges were fine-tuned during follow-up visits, considering patient comfort and symptom fluctuations.

This approach ensures individualized therapy by leveraging the real-time sensing and adaptive modulation capabilities of the Percept PC system. Detailed LFP sensing and aDBS settings are described in the Supplementary Methods section.

MDS-UPDRS Part III was assessed under four conditions: stimulation-on/medication-on, stimulation-on/medication-off, stimulation-off/medication-on, and stimulation-off/medication-off. Stimulation-off evaluations occurred at least 5 minutes after turning off the stimulation, and medication-off evaluations followed a 12-hour washout of dopamine or agonists. For extended-release dopamine agonists, the previous morning dose was omitted, and dopamine agonist patches were removed the night before. Symptom evaluation and aDBS initiation were performed during hospitalization to ensure safety. Patients who did not consent to hospitalization were excluded from the study. Requests to revert to cDBS during the study period are also honored.

Stimulation Intensity and Levodopa-Equivalent Daily Dose Monitoring

To evaluate the variability of stimulation intensity in aDBS, we calculated the average stimulus intensity over the 30 days preceding each evaluation at 6 and 12 months. This average was derived from the mean stimulus intensity recorded every 10 minutes and stored in the implantable pulse generator (Percept PC). To assess the adequacy of the LFP threshold settings, we analyzed the daily fluctuations in stimulus intensity as follows:

1. The total time spent at each current intensity within a day was calculated.
2. These times were converted into percentages of the total stimulation time to determine the distribution of the intensities.
3. The 3 most frequently used intensities were identified based on these percentages.

A high percentage of the most frequent intensity indicated minimal variation, whereas a substantial percentage of subsequent intensities suggested greater variation. This process, repeated for all subjects, allowed us to quantify the current fluctuations, with a wider distribution indicating more dynamic changes. In addition, to quantify the variability in stimulation intensity over time, we calculated the standard deviation of the daily average stimulation intensities over a 30-day period for each patient. To assess changes in medication status following the initiation of a DBS, the levodopa-equivalent daily doses (LEDD) was calculated on each assessment day using the formula established by Schade et al.[15]

Statistical Analysis

Statistical analysis of clinical efficacy was performed by excluding participants who did not use aDBS continuously for 1 year. Although preoperative (pre-DBS) values were included in the figure for reference, they were not subjected to statistical analysis, as the primary aim of this study was to compare clinical outcomes between cDBS and aDBS. A linear mixed-effects model with an unstructured covariance matrix was used to assess longitudinal changes across the three main time points: baseline (under cDBS), 6 months, and 12 months (both under aDBS). Post hoc pairwise comparisons (baseline vs. 6 months and baseline vs. 12 months) were conducted using the Wilcoxon signed-rank test. To account for multiple comparisons, a Bonferroni correction was applied, adjusting the significance threshold to $\alpha = 0.025$. Pearson correlation coefficients were used to analyze the relationships between age at the start of aDBS and MDS-UPDRS Part II and PDQ-39 scores. This analysis was conducted because both the MDS-UPDRS Part II, which assesses ADLs, and the PDQ-39, which evaluates QoL, are expected to be influenced by age. Analyses were conducted using *JMP Pro 17*.

Results

Nineteen patients (11 females) were enrolled between October 2020 and March 2023. The mean age was 48.9 years (range, 35–64 years) at the onset of PD and 61.9 years (range, 40–73 years) at aDBS initiation (Table 1). The average time from implantation to aDBS initiation was 13.8 months (range, 5–64 months). Thirteen patients received Medtronic 3389 quadrupole leads, and 6 received Medtronic SenSight directional leads. Sixteen patients underwent new electrode implantation, whereas 3 underwent battery replacement with the Percept PC system. In our cohort, no patients used bipolar configurations or required bilateral end-contact stimulation. Directional stimulation was applied in several patients. Although directional configurations were allowed, some advanced options, such as vertical gradient programming, were not supported by the current aDBS system. Stimulation contacts were adjusted in a few patients (4 out of 21) when transitioning from cDBS to aDBS. These minor adjustments were based on clinical judgment following cDBS optimization and aimed at maintaining or slightly reducing stimulation efficacy, rather than enhancing it through contact reassignment. Importantly, although directional stimulation was employed, the directional settings themselves were not changed in any participant.

Individual DBS parameters for each patient are detailed in Table S1. No patients were excluded due to an inability to detect beta oscillations. When initial threshold calibration attempts were unsuccessful, adjustments to recording timing or contralateral sensing were employed. All enrolled patients achieved usable beta peaks through these adaptive strategies. For the 11 patients, the stimulus intensity was adjusted based on the LFP recordings from each electrode. In 8 patients, only 1 electrode (4 left and 4 right) exhibited the appropriate LFP power variations necessary for stimulus adjustment and was used as the feedback signal for bilateral stimulus adjustment (Table S2).

TABLE 1 Demographic and clinical characteristics of the study participants

Subject no	Sex	Duration from implantation to aDBS start (months)	Age at aDBS start	Age at onset	Pre-DBS evaluation						
					HY (on)	HY (off)	LEDD	MDS-UPDRS Part II	MDS-UPDRS Part III (on)	MDS-UPDRS Part III (off)	MDS-UPDRS Part IV
1	M	6	71	61	2	4	400	21	26	42	5
2	F	6	47	37	2	3	1185	20	34	56	15
3	F	6	55	40	3	4	710	26	28	52	15
4	M	64	45	35	2	5	1080	0	9	55	9
5	M	11	68	48	4	5	995	22	34	58	4
6	M	12	61	52	2	3	1290	33	24	42	6
7	M	6	60	44	3	4	1555	25	21	54	11
8	F	6	72	62	2	4	1015	20	37	59	17
9	M	6	63	46	3	4	800	11	24	52	8
10	F	6	63	46	2	3	922.5	22	26	41	13
11	M	11	63	54	2	4	1600	24	17	58	14
12	F	49	66	50	1	4	1075	24	13	44	18
13	F	5	73	64	2	3	895	13	17	41	10
14	F	8	70	55	2	5	450	27	34	65	15
15	F	8	71	59	2	4	1330	14	15	36	9
16	M	12	70	48	3	4	720	24	46	71	11
17	F	25	63	46	4	5	1310	33	43	65	18
18	F	6	42	39	2	4	1275	15	36	65	9
19	F	9	53	44	2	3	650	14	8	44	15

Abbreviations: No, number; aDBS, adaptive deep brain stimulation; HY, Hoehn and Yahr; LEDD, levodopa-equivalent daily dose; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; M, male; F, female.

Clinical Course

Of the 19 participants, 4 were excluded from the clinical effectiveness analysis. Three participants (participants 3, 5, and 6) were excluded because of their individualized use of either conventional or aDBS based on their specific clinical requirements. The remaining 16 patients (84% of the initial cohort) continued with aDBS throughout the 12-month study period (Fig. 1). One participant (participant 2) continued aDBS for 12 months but was excluded from the analysis due to missing follow-up assessments at both 6 and 12 months for personal reasons. Additionally, participant 19 declined the 6-month follow-up assessment.

Sensing Frequency

The average sensing frequencies (Hz) for electrodes using aDBS were as follows: at initiation, 18.95 ± 5.82 (left) and 18.03 ± 5.83 (right); at 6 months, 18.47 ± 6.03 (left) and 18.63 ± 6.26 (right); at 12 months, 18.21 ± 5.16 (left) and 18.10 ± 4.97 (right). Of the 31 hemispheres that underwent aDBS over the entire year, 9 exhibited changes in sensing frequency when the attending physician observed that the diurnal variation in LFP no longer correlated with symptom fluctuations following aDBS initiation (see Supplementary Materials, Table S2 for details).

Stimulation Intensity Monitoring

The median stimulation intensities (mA) (interquartile range [IQR]) at baseline were 2.15 (1.575–2.7) on the left and 2.15 (1.73–2.65) on the right. At 6 months, they were 2.20 (1.48–2.54) on the left and 2.30 (1.95–2.80) on the right, showing no significant difference from baseline (left: $P = 0.86$; right: $P = 0.10$). At 12 months, the intensities increased to 2.42 (1.76–2.67) on the left and 2.42 (2.07–2.80) on the right, which were significantly higher bilaterally than the intensities at baseline (left: $P = .02$; right: $P = .004$) (see Supplementary Materials, Fig. S1A).

The variation in the current intensity produced by the adaptive function within 30 days prior to the evaluation date differed significantly among participants (see Supplementary Materials, Fig. S2). The median range of variation was 0.4 mA (0–0.8) (min–max) at 6 months after the initiation of aDBS and 0.35 mA

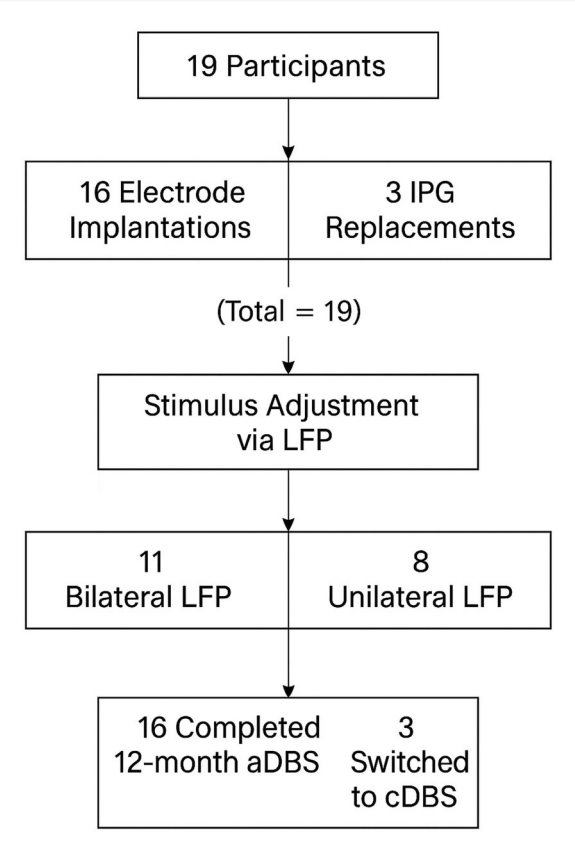

Fig. 1. Flowchart of the 12-month clinical course of the 19 participants. IPG, implantable pulse generator; LFP, local field potentials; aDBS, adaptive deep brain stimulation; cDBS, conventional deep brain stimulation.

(0.15–1.1) at 12 months. Similarly, the standard deviation of current intensity for each participant had a median of 0.11 mA (IQR: 0.08–0.16) at 6 months and 0.14 mA (IQR: 0.06–0.19) at 12 months, reflecting the extent of stimulation amplitudes variability during these periods. For the 14 participants for whom complete stimulus data were available 1 year after aDBS, the most frequently used current value was a median of 58 (41–85)% of the time at 6 months after initiation, and this pattern remained relatively stable at 12 months, with a median of 55 (40–66)%. For the second most frequently used current value, a significant increase in the frequency of use over time was observed. At 6 months, the median percentage of time this value applied was 18 (7–28)%, increasing to 25 (19–33)% at 12 months. This increase was statistically significant ($P = .0153$) (see Supplementary Materials, Fig. S3). These findings suggest a dynamic adaptation of the stimulation parameters during the treatment period, with a trend toward changes in current use over time.

LEDD

The LEDD remained stable throughout the study period, with no statistically significant changes. Median (IQR) LEDD values were 700 (470–898) mg at baseline, 645 (426.125–843.625) mg at 6 months ($P = 1.0$ vs. baseline, corrected), and 670 (512.5–898) mg at 12 months ($P = 1.0$ vs. baseline, corrected) (see Supplementary Materials, Fig. S1B).

Trends in UPDRS Subscores and PDQ-39

The following analysis was based on 15 participants who underwent aDBS for 12 consecutive months. This exclusion was solely made to determine the effect of aDBS. Motor function, assessed by MDS-UPDRS Part III under medication-off/stimulation-on conditions, showed a significant overall effect of time in the mixed model ($F[2,13.1] = 4.58$, $P = 0.031$). After the Bonferroni correction, the reduction from baseline to 12 months remained significant ($S = -43.5$, adjusted $P = 0.0226$), whereas the comparison between baseline and 6 months was nonsignificant (adjusted $P = 1.0$). The median score decreased from 33 (IQR: 28–38) at baseline to 26 (IQR: [23–32]) at 12 months. No significant changes were observed at 6 or 12 months under the other 3 conditions (Fig. 2). The median scores at 12 months and baseline, respectively, were 21 (IQR: 17.25–24.75) and 21.5 (IQR: 15.25–28.5) for medication-on/stimulation-on; 29.5 (IQR: 25.75–50.25) and 33 (IQR: 23–46) for medication-on/stimulation-off; and 52 (IQR: 40.75–57.75) and 53 (IQR: 42–57) for medication-off/stimulation-off.

Regarding MDS-UPDRS Part IV, which assesses motor complications, the median score at 12 months after initiating aDBS was 8 (IQR: 4–10), which was not significantly different from the baseline value of 7 (IQR: 4–9) (Fig. 3A). An additional analysis, not described in the Methods section, examined the effect of baseline wearing-off severity on motor fluctuations. In this context, Q3 and Q4 are specific items within the MDS-UPDRS Part IV that assess the severity and duration of wearing-off episodes. Spearman's rank correlation analysis revealed a significant moderate negative relationship between the baseline Q3 + Q4 scores and changes in Part IV scores at 12 months ($rs = -0.59$, $P = 0.021$). The equation (change in Part IV = 4.14–1.12 ⋆ baseline Q3 + Q4) indicates that higher baseline Q3 + Q4 scores were associated with greater reductions in Part IV scores (Fig. 3B). Specifically, patients with baseline Q3 + Q4 scores of 4 or higher experienced a significantly greater reduction in motor complications (median change: −1 [−3 to 1]) than those with scores below 4 (median change: 2 [1 to 3.5]; Wilcoxon rank-sum test, $P = 0.021$), suggesting that severe wearing-off predicts better improvement with aDBS (Fig. 3C).

The MDS-UPDRS Part I (non-motor symptoms), MDS-UPDRS Part II (ADLs), and PDQ-39 (QoL) scores were assessed at baseline and 6 and 12 months after the initiation of aDBS. Although no statistically significant differences were observed in these measures over time compared to baseline (Table 2), further analysis revealed interesting correlations between age at aDBS initiation and certain outcomes.

The correlation between age at aDBS initiation and baseline MDS-UPDRS Part II scores was 0.41, with a P-value of 0.13,

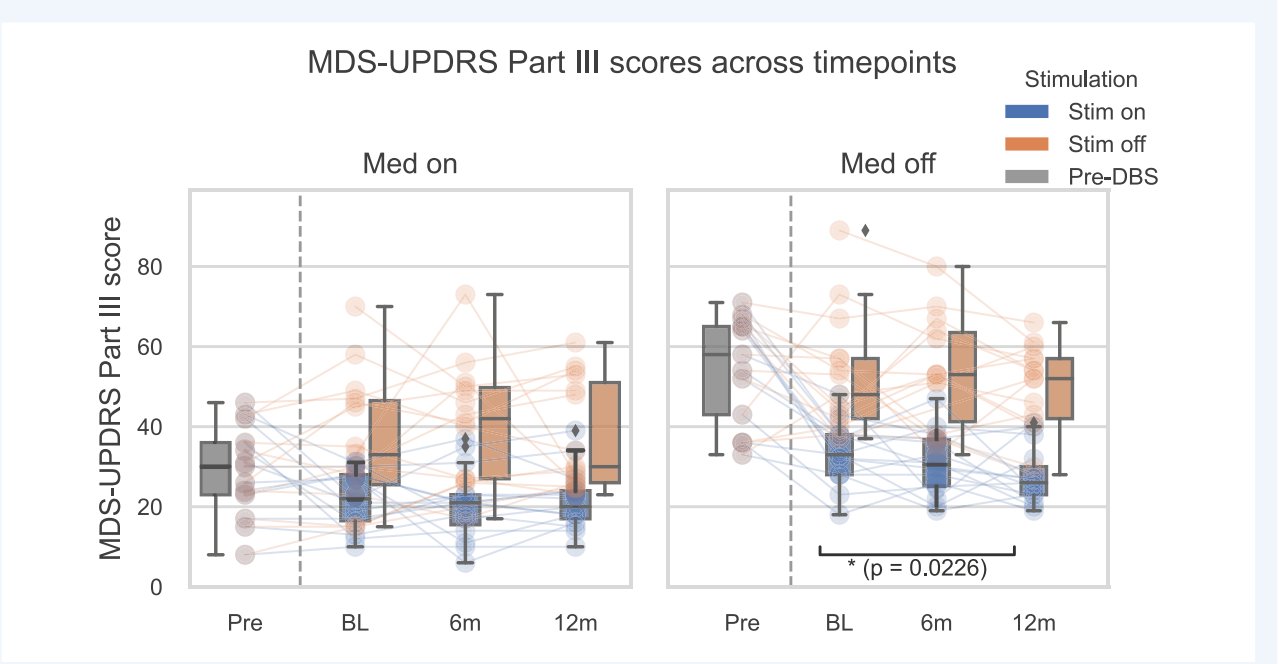

Fig. 2. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III scores at pre-DBS, baseline (BL), 6 months (6 m), and 12 months (12 m) under medication-on and off states. Boxplots and individual trajectories are shown by medication and stimulation condition. Significant improvement was observed only in the stim-on/med-off condition.

indicating no significant relationship (Fig. 4A). In contrast, a significant positive correlation was found between age at aDBS initiation and MDS-UPDRS Part II scores at 1 year, with a correlation coefficient of 0.74 ($P = 0.0016$) (Fig. 4B). However, the correlation between age at aDBS initiation and change in Part II scores over 12 months was 0.49 ($P = 0.064$), indicating a moderate trend toward a positive association, though not reaching statistical significance (Fig. 4C).

Similarly, for the PDQ-39 scores, there was no significant correlation between age at aDBS initiation and baseline scores (0.19, $P = 0.51$) (Fig. 4D). However, a significant positive correlation was found between age at aDBS initiation and PDQ-39 scores at 1 year, with a correlation coefficient of 0.74 ($P = 0.0014$) (Fig. 4E). The correlation between age at aDBS initiation and the change in PDQ-39 scores over 12 months was 0.62, with a *P*-value of 0.0145, indicating a statistically significant association (Fig. 4F).

Trends in BBS and 10-m TUG

BBS scores were assessed at baseline, 6 months, and 12 months after the initiation of aDBS in both the medication-on and medication-off conditions. No statistically significant changes were observed in either condition at 6 or 12 months compared to baseline.

The TUG test was used to assess functional mobility at baseline and at 6 and 12 months after aDBS initiation in both the medication-on and medication-off states. No statistically significant differences in walking time were observed between the baseline and follow-up time points in either medication state. At 6 months, 1 participant was unable to complete the test in the medication-on state and 3 in the medication-off state. At 12 months, 2 participants were unable to complete the test in the medication-on state and 3 in the medication-off state (Table 2).

Adverse Event

Adverse events occurred in 3 participants. Participant #5 developed urinary retention following 12-hour medication discontinuation, precluding further medication-off evaluations. Participant #6 experienced psychiatric symptoms 1 month after initiating aDBS and reverted to cDBS, leading to exclusion. Participant #3 also reverted to cDBS because of worsening dyskinesia. These adverse events primarily affected early enrollees, suggesting a learning curve in managing aDBS.

Discussion

DBS is crucial for managing advanced PD symptoms,[16] but managing motor fluctuations remains challenging.[4] This study highlights the efficacy and personalized benefits of aDBS.

Of 19 participants, 16 (84%) continued using aDBS for 1 year, supporting its practical utility. Three participants used cDBS either temporarily or continuously, primarily because of dyskinesia during the 12-month period.

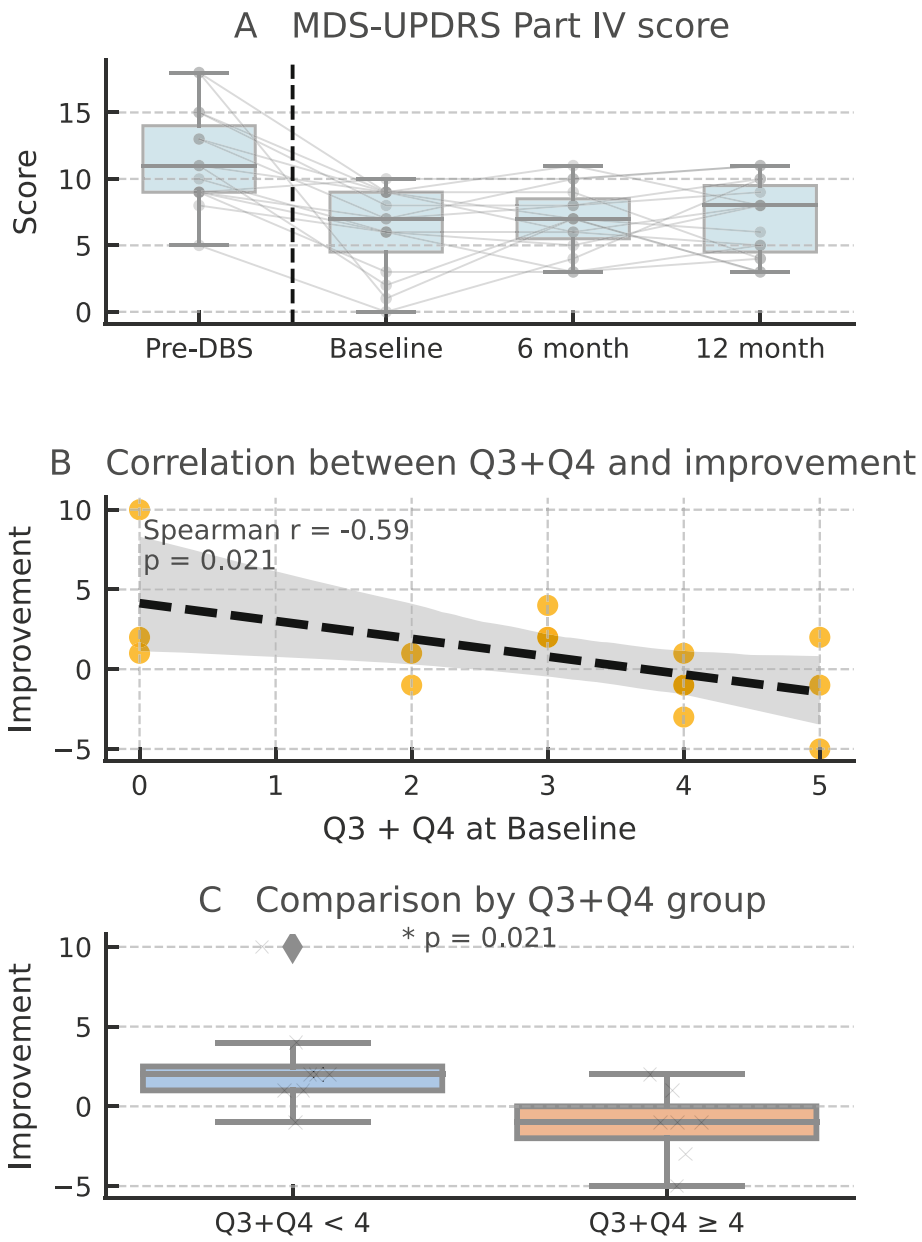

Fig. 3. Changes in Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part IV over 12 months. (**A**) Total score change. (**B**) Correlation between baseline Q3 + Q4 and total score changes (Spearman's $r = -0.59$, $P = 0.021$). (**C**) Comparison of the total score changes for groups with baseline Q3 + Q4 ≥ 4 and <4. Boxes show the median and interquartile range; whiskers indicate 1.5 * IQR.

Moreover, aDBS improved motor function in the medication-off state at 12 months compared to baseline cDBS among participants who used aDBS for 12 consecutive months. The lack of change in scores during the medication-on state, combined with improvements in the medication-off state, indicates that aDBS provides additional benefits in managing wearing-off phenomena beyond the effects of cDBS. Clinicians frequently encounter patients whose wearing-off symptoms are inadequately controlled with cDBS. The demonstrated ability of aDBS to further mitigate these symptoms underscores its potential as a promising therapeutic approach in the management of PD.

Although MDS-UPDRS Part IV, which assesses motor fluctuations, showed no overall improvement 12 months after initiating aDBS, patients with severe baseline wearing-off symptoms benefited from the therapy. A greater proportion of participants

TABLE 2 Clinical scores

			Pre-DBS (n = 15)	Baseline (n = 15)	6 months after aDBS (n = 13)	12 months after aDBS (n = 14)	*P*-value	
							6 months vs. baseline	12 months vs. baseline
MDS-UPDRS	Part I		14.5 (11.75–17)[a]	13 (8–15)	12 (9–14)	12 (8–13)	0.3403	0.9641
	Part II		24 (15–27)	18 (13–22)	16 (11–22)	19 (15–23)	0.1709	0.5703
	Part IV		11 (9–15)	7 (4–9)	7 (5–9)	8 (4–10)	0.1875	0.2678
PDQ-39			67 (53.5–75.5)[b]	50 (40–62)	48 (39–59)	59 (33–68)	0.4973	0.5892
TUG		Med on (seconds)	26.38 (23.32–43.24)	22.93 (18.45–35.96)	25.43 (19.13–47.29)	23.16 (17.65–41.74)	0.6221	0.3054
		Med on (N)	11/15	15/15	12/13	12/14		
		Med off (seconds)	29.3 (22.85–31.08)	22.85 (17.01–26.76)	24.735 (21.53–41.56)	24.16 (22.11–40.53)	0.6523	0.2637
		Med off (N)	11/15	15/15	10/13	11/14		
BBS		Med on	50.5 (15.25–53)[c]	53 (47–55)	52 (47.5–54.5)	51.5 (46.25–55)	0.3408	0.4570
		Med off	24 (24–40)[d]	51 (41–54)	49 (42.5–50)	50 (45.5–53.25)	0.9072	0.6758

Note: Scores are presented as median (interquartile range [IQR]).

Abbreviations: aDBS, adaptive deep brain stimulation; MDS-UPDRS, the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire-39; TUG, Timed Up and Go Test; BBS, the Berg Balance Scale; Med, medication; N, number of participants who completed the TUG.

[a]n = 14.

[b]n = 13.

[c]n = 12.

[d]n = 11.

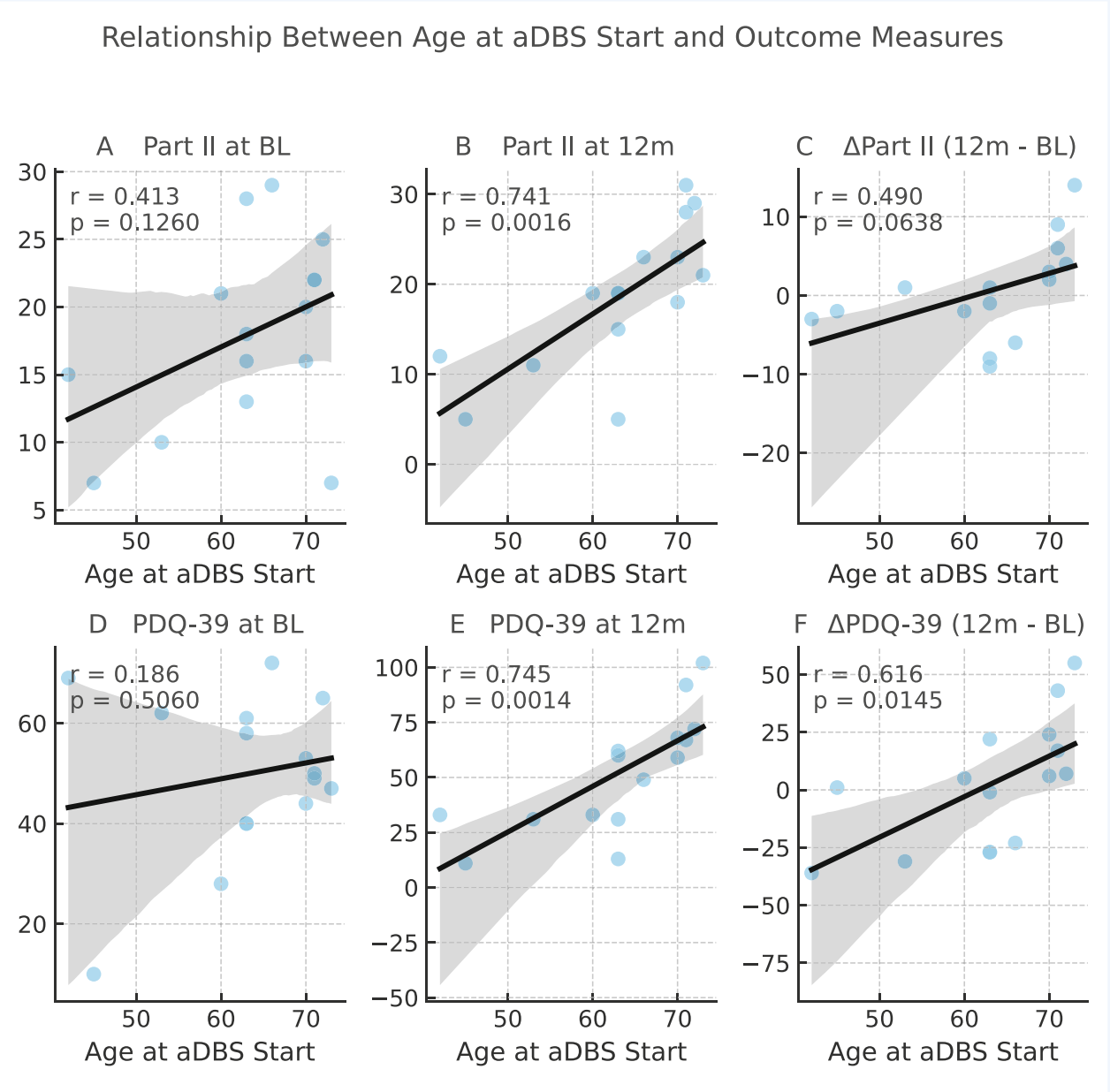

Fig. 4. Correlation between age at aDBS initiation and Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II or Parkinson's Disease Questionnaire-39 (PDQ-39) scores. Panels show baseline (**A**, **D**), 12-month (**B**, **E**), and change scores (**C**, **F**). aDBS, adaptive deep brain stimulation; cDBS, conventional deep brain stimulation.

with significant wearing-off may have yielded more pronounced overall improvements.

The study did not demonstrate significant improvements in MDS-UPDRS Part II (ADLs) or PDQ-39 (QoL). However, aDBS revealed age-related effects not observed with cDBS, as evidenced by correlations between age at aDBS initiation and both Part II and PDQ-39 scores at 1 year. Notably, younger patients tended to experience better outcomes, suggesting aDBS may be particularly effective for this demographic. To optimize treatment, adjusting stimulus intensity and speed based on patient age may be crucial. This approach aligns with the benefits of aDBS, which offers improved symptom management and QoL by adapting to patient needs.[17,18]

TUG scores remained unchanged after the initiation of aDBS. Similarly, the BBS showed no significant changes before or after aDBS implementation. Although these findings provide limited insights, they demonstrate that aDBS does not adversely affect gait or balance at least in the short term. Further studies are required to elucidate the long-term effects of aDBS on these parameters.

LEDD remained stable throughout the 12-month study period. Concurrently, we observed a gradual increase in the mean stimulus intensity, which was consistent with the typical progression observed in the initial years following DBS implantation. This pattern suggests that the impact of medication dosage and stimulus intensity on the assessment of clinical efficacy 12 months post-aDBS initiation is likely to be minimal. Nevertheless, these factors should be considered when interpreting our results and designing future long-term studies.

We successfully adjusted the stimulation intensity using beta power as a biomarker in the 30/38 hemispheres. The most frequent current levels were applied for approximately 60% of the day, with a median variation of 0.4 mA. Changes in current levels exhibited heterogeneous patterns among participants. Initially, some showed minimal variation, but adjustments to LFP thresholds led to changes. Notably, by 12 months, the use of the second most frequent current level increased compared to 6 months, indicating a more dynamic and adaptive stimulation pattern and suggesting that the system was better optimized over time. The average sensing frequency was approximately 18 Hz bilaterally, with 71% of hemispheres maintaining this frequency throughout the 12 months. This finding is consistent with previous reports indicating the stability of beta-band frequencies as reliable biomarkers of motor impairment in PD, as demonstrated by Neumann et al.,[19] and is further supported by studies validating beta-band activity for aDBS applications.[20]

Of the 19 participants, 3 discontinued the use of aDBS. One patient withdrew from the study because of cognitive decline after initiating aDBS, although the causal relationship remains unclear. Another participant withdrew because of worsening dyskinesia, which was likely attributable to the stimulation setting. The higher dropout rate among participants enrolled earlier in the study (as indicated by lower participant numbers) underscores the importance of physician experience in system adjustment. These results highlight the need to develop a standardized operational algorithm for aDBS to simplify its use and minimize complications. Despite these challenges, the overall complications were minimal, suggesting that aDBS is generally well tolerated.

Limitations

Our study had several limitations. As this was a single-arm, nonblinded observational study, we did not directly compare the efficacy of aDBS with that of cDBS. Nevertheless, this study provides preliminary insights that could inform future double-blind randomized controlled studies (RCTs). aDBS introduces new parameters, such as beta-power threshold settings and stimulation intensity ranges, which require labor-intensive optimization. Consequently, the optimal conditions may not have been fully achieved. It is essential to pool and analyze clinical data to develop effective algorithms. Although our cohort did not experience screening exclusions for beta-peak detection, the requirement for repeated calibration sessions may limit generalizability to centers without specialized programming expertise. We acknowledge that the adjustment of sensing frequency in 9 hemispheres introduces an additional variable that may affect outcome comparisons. However, these adjustments reflect real-world clinical practice and were made to optimize therapeutic efficacy. Furthermore, stimulation contacts were not fixed between cDBS and aDBS in all participants. Although such changes could potentially influence clinical outcomes, the adjustments were minimal, clinically justified, and not intended to enhance efficacy beyond the cDBS condition. Directional settings remained unchanged throughout the study, thereby minimizing confounding effects related to directional modulation. These contact adjustments, if anything, may have biased results conservatively against aDBS. Additionally, assessing whether fluctuations in beta power truly correlate with variations in motor symptoms during patients' daily activities is exceedingly challenging due to the lack of suitable wearable devices for such evaluations.

Furthermore, our study was limited by a small sample size of 19 participants, with 4 patients excluded from the efficacy analysis: 3 due to the use of cDBS during the study and 1 due to missing data. The results are presented on a per-protocol basis, which may not fully capture the potential differences in outcomes between aDBS and cDBS. This limitation underscores the need for larger comparative studies to clearly delineate the benefits of aDBS compared to conventional approaches.

Significant improvements in motor function (MDS-UPDRS Part III) scores in the medication-off state were observed among participants who used aDBS continuously for 1 year, suggesting its potential to effectively address wearing-off symptoms. The ability to dynamically adjust the stimulus intensity using beta power as a biomarker is a key finding that underscores the practical application of this system in clinical settings.

Our results also suggest that aDBS may be particularly beneficial for patients who have experienced an insufficient improvement in wearing-off symptoms with cDBS, as well as for younger patients. Despite some limitations, aDBS represents a significant advancement in DBS therapy, offering a more personalized approach through real-time patient-specific stimulus adjustments, which may lead to improved symptom management and reduced side effects.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique.

N.T.: 1A, 1B, 1C; 2A, 2B, 2C, 3A
T.E.: 1C, 2B, 3A
K.H.: 1C
Y.K.: 1C
T.M.: 1C
T.F.: 1C
S.M.: 1C
Y.F.: 1C

N.M.: 1C
H.M.K.: 1C
S.O.: 1C, 3B
H.K.: 1B, 3B.

Acknowledgments

The authors thank the young neurosurgeons and neurologists at Osaka University Hospital for their clinical support and contribution to patient care. We are grateful for their dedication and expertise, which were instrumental in the successful completion of this study.

Disclosure

Ethical Compliance Statement: This study was approved by the Institutional Ethics Committee of Osaka University Hospital (approval no.: 20450-3). Informed consent was obtained from all participants after they were fully informed of the nature of the study, its potential risks, and benefits. The study was conducted in accordance with the principles of the Declaration of Helsinki. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: This work was supported by JST FOREST Program (grant number: JPMJFR205F, Japan) and by JSPS KAKENHI (grant number: JP23K08519, Japan). Naoki Tani and Haruhiko Kishima have received speaker fees from Medtronic Japan. The other authors declare that they have no conflicts of interest relevant to this work and have received no specific funding for this research.

Financial Disclosures for the Previous 12 Months: Satoru Oshino reports a grant from JSPS KAKENHI (24K12262). Koichi Hosomi reports a grant from JSPS KAKENHI (22K09206). Hui Ming Khoo reports a grant from JSPS KAKENHI (20K09368). Nobuhiko Mori reports a grant from JSPS KAKENHI (23K10559). The other authors declare that there are no additional disclosures to report for the past 12 months.

Use of AI in Publication and Research

The authors used Perplexity AI (Perplexity Labs) on October 8, 2024, to assist with the English translation of some portions of the manuscript. The authors reviewed, edited, and take full responsibility for the content and integrity of the entire manuscript.

Data Availability Statement

Drs Tani, Emura, and Kishima had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data that support the findings of this study are available from the corresponding author, Naoki Tani, upon reasonable request. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. (**A**) Median stimulation amplitudes for left and right sides at baseline (BL), 6 months (6 m), and 12 months (12 m). Significant differences were observed between BL and 12 m. (**B**) Levodopa-equivalent daily dose (LEDD) changes over time.

Figure S2. Boxplots of current level distributions for 14 participants at 6 and 12 months, showing inter-participant variability. The *x*-axis represents current amplitude (mA), and the *y*-axis represents the proportion of time at each current level per day.

Figure S3. Boxplots of daily time proportions for the top three used current levels at 6 and 12 months, with a significant increase in the second most-used level from 18% to 25%.

Table S1. cDBS, conventional deep brain stimulation; aDBS, adaptive deep brain stimulation; yes, using directional mode; no, using ring mode; ⋆, also using as sensing contact; #, changing stimulus contact at the aDBS initiation.

Table S2. cDBS, conventional deep brain stimulation; IPG, implantable pulse generator; quadrupole, Medtronic 3389 quadrupole leads, directional, Medtronic SenSight directional leads; n.s., not sensing.

Data S1. Supplementary methods. A detailed description of other methodologies that could not be detailed in the text, such as inclusion criteria and aDBS setup, is provided here.