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The clinical impact of precise electrode positioning in STN DBS on three-year outcomes

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ABSTRACT

Few studies have analyzed the clinical impact of subthalamic nucleus (STN) deep brain stimulation (DBS) as a function of the positioning of the inserted electrode. We investigated retrospectively the three-year outcomes in Parkinson's disease (PD) patients following bilateral STN DBS in terms of the electrode positions. Forty-one advanced PD patients were followed up for over three years following bilateral STN DBS. Patients were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging, Schwab and England Activities of Daily Living (ADL), and the Short Form-36 Health Survey (SF-36) before surgery and one, two, and three years after surgery. The patients were divided into two groups according to the electrode position based on the fused preoperative MRI and postoperative CT images: group I included patients who had both electrodes in the STN (n = 30) while group II included patients who had one of the electrodes in the STN (n = 11). The UPDRS, the Hoehn & Yahr staging, the Schwab and England ADL, and the SF-36 scores showed significant improvements with decreased L-dopa equivalent daily doses (LEDDs) in both groups as well as in the group as a whole for up to three years following bilateral STN DBS. However, the off-medication UPDRS total and motor (part III) scores significantly deteriorated with increased LEDDs for patients in group II three years after STN DBS compared to that of the group I patients. We conclude that more accurate electrode positioning in the STN leads to better long-term outcomes in advanced PD patients following DBS.

1. Introduction

Since the introduction of deep brain stimulation (DBS) by Benabid and colleagues in 1987, it has become the preferred surgical treatment for patients with various movement disorders including Parkinson's disease [1–5]. Patients with advanced Parkinson's disease (PD) who have received subthalamic nucleus (STN) deep brain stimulation (DBS) have shown significant improvements in symptoms such as motor fluctuation and dyskinesia which facilitate a reduction in their dosage of levo-dopa. These significant improvements in motor function have been documented for both short-term and long-term periods [2,3,7–14].

We have previously compared the short-term clinical outcomes of advanced PD patients following bilateral STN DBS using estimations of the electrode position which were estimated by fused images of the pre- and post-operative MRIs that had been taken six months after surgery [6]. However, no studies have assessed the long-term impact of precise electrode positioning on clinical outcomes in advanced PD patients following bilateral STN DBS. The aim of this retrospective study was to compare the long-term clinical outcomes of advanced PD patients for up to three years following bilateral STN DBS in terms of the positioning of their electrodes, which was estimated from the fused images of the preoperative MRI and postoperative CTs that were taken more than one month after the surgery using the mutual information technique [15].

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2. Methods

2.1. Population

Seventy-six patients with advanced PD were treated with STN DBS between March 2005 and October 2006 at the Movement Disorder Center of Seoul National University Hospital. Among these patients, 41 had been treated with bilateral STN DBS and were followed up for more than three years; thus, they were enrolled in this study. The indications for bilateral STN DBS have been previously described elsewhere [6]. Patients with severe cognitive impairment, ongoing psychiatric problems, an unsatisfactory general condition for surgery, or an inability to comply with the study protocol were excluded. The Institutional Review Board of SNUH approved this study (IRB Number: H-1011-022-338).

2.2. Clinical evaluation

The patients were evaluated with the Unified Parkinson Disease Rating Scale (UPDRS), the Hoehn and Yahr (H&Y) Staging, the Schwab and England Activities of Daily Living (SEADL), the Short Form-36 Health Survey (SF-36), and neuropsychological tests. These detailed items are described elsewhere [6]. Evaluations were performed before surgery and 12, 24, and 36 months after surgery. All neurological evaluations were performed by neurologists. Patients were assessed under two conditions on stimulation and on or off medication: when the patients were off their medication, i.e., they had taken no medication for 8 to 12 h; and when the patients were on medication, i.e., they had experienced maximal clinical benefits 1 to 3 h after the usual morning dose of dopaminergic treatment. The levo-dopa equivalent daily dose (LEDD) was computed as previously described [16]. Neuropsychological tests such as the MMSE, BDI, Grooved Pegboard Test, Stroop and Fluency tests, Trail Making Test, Korean Boston Naming Test, Wisconsin Card Sorting Test, and Rey-Kim Memory Battery were performed before and at 6, 12, and 36 months after STN DBS. Table 1 presents the clinical information of the 42 patients with advanced PD who had undergone bilateral STN DBS.

2.3. Surgical procedure

A stereotactic Leksell®-G frame (Elekta Instruments AB, Stockholm, Sweden) was mounted on the head of each patient while they were under local anesthesia. Brain images were acquired using a 1.5-T Signa system (General Electric Medical System, Milwaukee, WI, USA). The STNs were localized through a combination of direct visualization by MRI, microelectrode recording (MER), and a stimulation technique as previously described [3,17,18]. A multi-channel parallel probe (four or five channels, so called "Ben Gun") was used for MER and test stimulation. Quadripolar chronic electrodes (DBS 3389, Medtronic, Minneapolis, MN) were introduced under local anesthesia, and the implantable pulse generators (IPG) were subcutaneously implanted immediately thereafter under general anesthesia at the same day.

Table 1
Baseline characteristics of the 41 patients with advanced Parkinson's disease.

		Total (n = 41)	Group I (n = 30)	Group II (n = 11)	*p*-Value[1] (2-group difference)
Gender (number of patients)	Male	19	14	5	0.592
	Female	22	16	6	
Age (years)	Mean ± S.D.	61.9 ± 7.9	62.8 ± 7.8	59.3 ± 8.2	0.208
	Range	43–76	43–76	45–71	
Symptom duration (years)	Mean ± S.D.	13.7 ± 4.1	13.9 ± 4.4	13.1 ± 2.8	0.591
	Range	5–26	5–26	7–17	

[1] For gender (discrete scale), the *p*-value was estimated by Chi-square test; For other variables (continuous scale), the *p*-value was estimated by independent t-test.

Electrical stimulation was started one day after surgery as previously described [6]. The stimulation parameters and medications were progressively adjusted using the N'vision® programmer (Medtronic, Minneapolis, MN).

2.4. Adjustment after STN DBS

An examination for the effectiveness and side effects of the four electrode contacts was performed for all the patients with the N'vision® programmer (Medtronic, Minneapolis, MN) to select the best contacts and settings of the electrodes for chronic stimulation. After turning on the stimulation at the lowest setting of 1.0 V, the medication and stimulation parameters were optimized to achieve the best motor functions.

2.5. Image fusion of preoperative MRI and postoperative CT imaging

3-D spiral stereotactic CT scans (64-channel Brilliance CT, Philips, Eindhoven, Netherlands) with 1-mm-thick slices were taken more than one month (mostly six months) after bilateral STN DBS as previously described [6,19]. By fusing the CT and MRI images, the positions of the electrodes were plotted on the human brain atlas of Schaltenbrand and Wahren as previously described [6,19]. Briefly, the lateral distance from the midline and the antero-posterior distance from the mid-commissural line to each electrode were measured in the reformatted axial images which were aligned with the anterior (AC)–posterior commissural (PC) line. The lateral angle of the electrode trajectory from the midline, the antero-posterior angle of the electrode trajectory from the line perpendicular to the AC–PC line, and the depth of each electrode were also measured in the reformatted coronal and sagittal images, respectively.

Based on the plotted position of the electrode in the axial view which is 3.5 mm below the AC–PC line in the human brain atlas of Schaltenbrand and Wahren, the electrode positions in 41 patients were categorized into two groups as follows: (1) group I included patients in which both electrodes were in the STN (n = 30) and (2) group II included patients in which only one of the electrodes was in the STN (n = 11) (Fig. 1). The average Euclidean coordinates for the X-, Y-, and Z-coordinates of the left electrodes for patients in group I were 12.67 ± 1.39 mm laterally from the midline, 1.65 ± 1.48 mm posteriorly to the mid-commissural line between the AC and PC, and 3.88 ± 1.44 below the horizontal AC–PC plane. The average Euclidean coordinates for the X-, Y-, and Z-coordinates of the right electrodes for patients in group I were 11.90 ± 1.30 mm laterally from the midline, 2.01 ± 1.54 mm posteriorly to the mid-commissural line between the AC and PC, and 4.01 ± 0.91 below the horizontal AC–PC plane. The average Euclidean coordinates for the X-, Y-, and Z-coordinates of the left electrodes for patients in group II were 12.91 ± 1.39 mm laterally from the midline, 2.35 ± 2.09 mm posteriorly to the mid-commissural line between the AC and PC, and 3.82 ± 0.93 below the horizontal AC–PC plane. The average Euclidean coordinates for the X-, Y-, and Z-coordinates of the right electrodes for patients in group II were 10.52 ± 1.37 mm laterally from the midline, 3.22 ± 1.23 mm posteriorly to the mid-commissural line between the AC and PC, and 3.27 ± 1.63 below the horizontal AC–PC plane. Table 1 presents the clinical information on the patients in these two groups.

2.6. Statistical analysis

From the statistical analyses, the primary outcomes were the total scores and part III scores of the UPDRS; the H&Y staging; the SEADL; the dyskinesia disability scale, which is based on the subscores of part IV of the UPDRS; the LEDD; the SF-36 scores, and the neuropsychological tests. The secondary outcomes included the subscores of part III of the UPDRS. These variables are presented as the means ± standard deviation. Repeated measured ANOVAs were performed to

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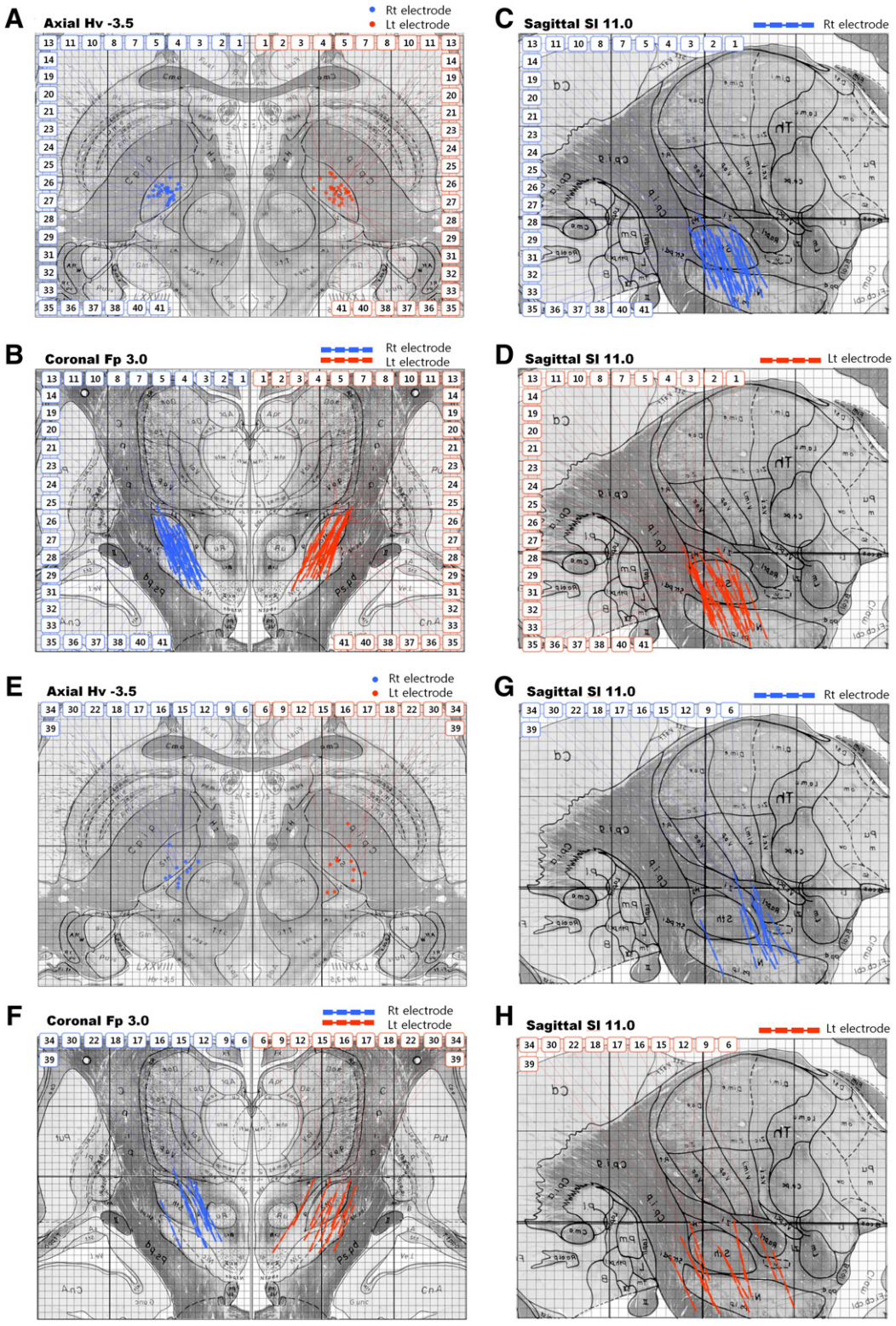

Fig. 1. Based on the plotted electrode position on the axial view which is 3.5 mm below the AC–PC line in the human brain atlas of Schaltenbrand and Wahren, the electrode positions of the 41 investigated patients were categorized into two groups: (1) group I (panels A–D), in which both electrodes were in the STN (n = 30) and (2) group II (panels E–H), in which only one of the electrodes was in the STN (n = 11).

examine the within-factor effect of the three repetitions, which were measured at baseline before surgery and at 12, 24, and 36 months after surgery, and the between-factor effect of the two groups (groups I and II) classified by the position of the electrodes in the STN for the average clinical outcome scores.

To assess the baseline characteristics of the 41 patients with advanced PD, independent t-tests and Chi-square or Fisher's exact tests were done to determine the differences between the two groups in the distributions of the continuous variables and discrete variables. P-values of less than 0.05 were considered statistically significant. All

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statistical analyses were done with SAS, version 9.1 (SAS institute, Cary, NC).

3. Results

As seen in Table 1, there was no significant difference in the preoperative clinical status of the patients in group I and group II.

The clinical outcomes of the 41 advanced PD patients were compared in terms of the preoperative status and postoperative status at 12, 24, and 36 months after bilateral STN DBS (Table 2). Significant improvements in the off-time scores of the total UPDRS, UPDRS III, H&Y, SEADL, and dyskinesia disability and decreased LEDDs were observed for up to three years after surgery in groups I and II and in the entire cohort of patients. Moreover, LEDDs significantly decreased for up to three years after surgery in patients from groups I and II and in the entire cohort of patients (Fig. 2).

Interestingly, the improvements in symptoms for the off-time scores of the total UPDRS, UPDRS III, H&Y, SEADL, and dyskinesia disability had deteriorated by the time 36 months had passed after the surgery in the group II patients compared to that of the group I patients. LEDDs had increased after 36 months in the group II patients compared to that of the group I patients (Fig. 2).

Most scores in the eight sub-scales of the SF-36 scores significantly improved at 12 and 24 months after surgery in the group I patients while scores did not significantly improve for most patients in group II (Table 3); however, improvements in symptoms in the eight sub-scales of the SF-36 were less prominent in the group I patients at 36 months after the surgery compared to their scores at 12 and 24 months after surgery.

Despite minor detrimental long-term impacts on frontal lobe function and mood, bilateral STN DBS in patients with advanced PD did not lead to a significant global deterioration in cognitive function for up to three years after surgery regardless of the positions of the electrodes; however, the MMSE and BDI showed a general decline in group II 36 months after the surgery. The Grooved Pegboard Test on the right was improved in group I patients at 12 and 36 months after STN DBS. In terms of frontal lobe function, Stroop and fluency tests were both found to be abnormal. The Stroop-a (color dot) test showed a decline in group II at 36 months after STN DBS. No significant differences in the pre- to postoperative test scores were observed for the Trail Making Test (TMT), Korean Boston Naming Test (K-BNT), Wisconsin Card Sorting Test (WCST), and Rey-Kim Memory Battery.

Monopolar stimulation was done for all but two patients in group 1. The average stimulation parameters for the group 1 patients were an amplitude of 2.6 V (±0.55 V), a pulse width of 66.5 μs (±13.6 μs), and a frequency of 126.9 Hz (±25.7 Hz). The average stimulation parameters for the group 2 patients were an amplitude of 2.8 V (±0.55 V, p-value = 0.04), a pulse width of 63.8 μs (±10.1 μs), and a frequency of 130.6 Hz (±3.06 Hz).

Adverse effects related to stimulation such as dizziness, dysarthria, double vision, cold sweating, contraction of extremities, aggravation of pre-existing symptoms, and dyskinesia were all reversible and there was no difference between groups 1 and 2. However, dysarthria seemed to be worse in the group 1patients than in the group 2 patients.

4. Discussion

Many reports have assessed the clinical outcome and prognostic factors of advanced PD patients after STN DBS. Some studies have shown a correlation between clinical improvement after surgery and localization of the electrodes determined by fused brain CT/MRI or MRI/MRI images that were taken in the perioperative period [1,12,13,16,20–26]; however, few reports have analyzed the clinical outcomes of STN DBS focusing on the positions of the inserted electrodes that were estimated at the stabilized period long after STN DBS [6,14,27]. An Immediate postoperative CT or MRI can make it difficult to precisely localize the electrode centers in relation to the STN because of brain shift from CSF leakage during the immediate

Table 2
The clinical outcome of 41 patients with advanced Parkinson's disease after bilateral subthalamic nucleus stimulation.

		Total subjects				Subjects according to each group (group I, n = 30; group II, n = 11)				
	Mx	Baseline	12 months[1]	24 months[1]	36 months[1]	Group	Baseline	12 months[1]	24 months[1]	36 months[1]
Total UPDRS	*On*	31.4 ± 17.7	26.5 ± 12.4	28.8 ± 12.8	34.9 ± 17.4	I	30.1 ± 15.5	26.4 ± 13.2	28.3 ± 12.7	32.2 ± 17.6
						II	35.0 ± 23.4	26.8 ± 10.4	29.7 ± 13.4	40.9 ± 16.2
	Off	**63.8 ± 19.5**	**37.7 ± 15.1**$^{\#}$	**39.4 ± 16.4**$^{\#}$	**44.9 ± 19.7**$^{\#}$	I	64.2 ± 20.1	36.9 ± 16.7	38.8 ± 18.2	**40.8 ± 20.1**$^{\#\#}$
						II	62.5 ± 18.4	39.9 ± 10.0	41.2 ± 10.1	**55.5 ± 14.8**$^{\#\#}$
UPDRS III	*On*	19.2 ± 12.4	15.0 ± 8.8	14.2 ± 7.5	19.5 ± 9.9	I	17.3 ± 10.2	15.0 ± 8.8	14.5 ± 8.0	17.9 ± 9.8
						II	24.6 ± 16.7	17.2 ± 6.2	13.7 ± 6.6	23.2 ± 9.8
	Off	**37.3 ± 13.7**	**19.2 ± 9.1**$^{\#}$	**18.8 ± 9.9**$^{\#}$	**21.8 ± 10.5**$^{\#}$	I	37.4 ± 13.5	18.6 ± 9.6	18.6 ± 10.6	**19.7 ± 10.3**$^{\#\#}$
						II	37.3 ± 14.9	20.6 ± 8.0	19.6 ± 7.7	**27.3 ± 9.4**$^{\#\#}$
Hoehn & Yahr Stage	*On*	2.3 ± 0.7	2.2 ± 0.7	2.4 ± 0.5	2.7 ± 0.7	I	2.2 ± 0.6	2.2 ± 0.7	2.5 ± 0.5	2.7 ± 0.6
						II	2.4 ± 0.8	2.2 ± 0.4	2.3 ± 0.5	2.8 ± 1.0
	Off	**3.1 ± 1.0**	**2.4 ± 0.5**$^{\#}$	**2.4 ± 0.5**$^{\#}$	**2.7 ± 0.7**$^{\#}$	I	3.2 ± 1.0	2.4 ± 0.5	2.4 ± 0.6	2.6 ± 0.5
						II	3.0 ± 0.7	2.5 ± 0.5	2.5 ± 0.4	2.9 ± 0.9
Schwab & England ADL	*On*	80.0 ± 14.6	85.8 ± 10.1	85.0 ± 9.3	80.8 ± 12.6	I	79.8 ± 13.9	85.9 ± 11.2	85.8 ± 9.7	**84.2 ± 11.4**$^{\#\#}$
						II	80.5 ± 17.1	85.5 ± 6.9	83.0 ± 8.2	**72.9 ± 12.7**$^{\#\#}$
	Off	**52.3 ± 20.8**	**77.3 ± 14.8**$^{\#}$	**75.1 ± 11.2**$^{\#}$	**70.7 ± 15.2**$^{\#}$	I	53.1 ± 20.4	78.3 ± 16.0	75.5 ± 12.4	**73.7 ± 14.7**$^{\#\#}$
						II	50.0 ± 22.8	74.5 ± 11.3	74.0 ± 7.0	**62.7 ± 14.2**$^{\#\#}$
Dyskinesia disability		1.9 ± 1.4	**0.6 ± 1.2**$^{\#}$	**0.5 ± 1.0**$^{\#}$	**0.7 ± 1.2**$^{\#}$	I	1.9 ± 1.3	0.7 ± 1.3	0.4 ± 0.9	0.5 ± 1.1
						II	2.1 ± 1.8	0.5 ± 0.9	0.9 ± 1.3	1.2 ± 1.5
LEDD (mg/day)		**896.8 ± 423.7**	**270.0 ± 260.2**$^{\#}$	**245.6 ± 232.6**$^{\#}$	**275.6 ± 299.8**$^{\#}$	I	833.4 ± 423.7	259.1 ± 281.0	230.3 ± 255.3	**200.9 ± 233.7**$^{\#\#}$
						II	1075.7 ± 530.3	300.7 ± 198.3	288.9 ± 153.5	**479.5 ± 72.5**$^{\#\#}$
SF-36 Physical health		132.1 ± 68.1	**195.1 ± 75.8***	**187.2 ± 71.6***	**170.6 ± 70.0***	I	123.6 ± 53.6	207.9 ± 74.5	200.6 ± 72.0	183.5 ± 73.5
						II	144.7 ± 85.2	175.6 ± 75.5	166.3 ± 67.6	150.9 ± 60.9
SF-36 Mental health		153.8 ± 77.2	**203.7 ± 87.3***	**200.5 ± 77.0***	177.2 ± 81.5	I	150.3 ± 72.7	224.4 ± 85.8	211.5 ± 76.7	182.6 ± 85.2
						II	158.8 ± 85.2	172.1 ± 81.9	183.3 ± 76.5	169.0 ± 77.0

All data was expressed as a mean ± standard deviation.
Values in BOLD: p-value <0.05 for between follow-ups and baselines ($^{\#}$) and for between two groups ($^{\#\#}$): group I (both electrodes were in the STN) and group II (both electrodes were not in the STN).
Abbreviations: ADL; Activities of Daily Life, LEDD; Levo-dopa Equivalent Daily Dose, UPDRS; Unified Parkinson's Disease Rating Scale.
* P<0.05.

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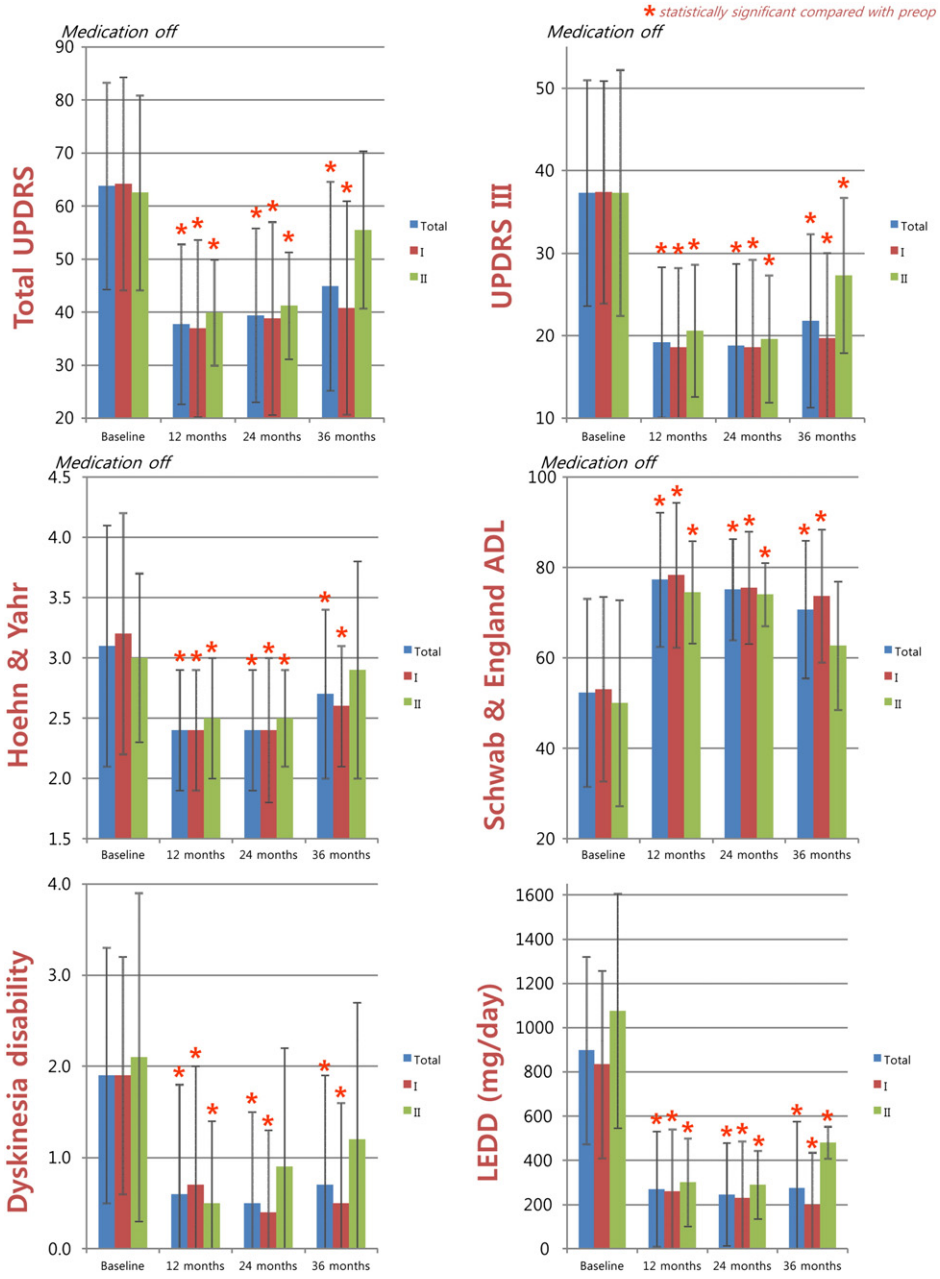

Fig. 2. Medication-off baseline scores compared with medication-off, stimulation-on scores of 41 patients before surgery and 12, 24, and 36 months after surgery. Significant improvements in the total UPDRS, UPDRS III, H&Y, SEADL, and dyskinesia disability and decreased LEDDs were observed up to three years after surgery in groups I and II and in the entire cohort of patients. Symptom improvements in the total UPDRS, UPDRS III, Hoehn and Yahr, Schwab and England ADL, and dyskinesia disability deteriorated 36 months after surgery in group II patients. LEDDs increased 36 months after surgery in group II patients in comparison to those in group I patients. Abbreviations: ADL, Activities of Daily Living; LEDD, L-dopa Equivalent Daily Dose; UPDRS, Unified Parkinson Disease Rating Scale; UPDRS III, Unified Parkinson Disease Rating Scale part III; Total, total patients; I, patients in group I; II, patients in group II. * means significant difference of p-value less than 0.05 in comparison to the preoperative status.

postoperative period, or electrode artifacts that are caused by electrode-induced magnetic inhomogeneity [6,23,28–30]. We previously compared the clinical outcomes of 56 patients with advanced PD at 3 and 6 months after bilateral STN DBS with electrode positions that were estimated from fused pre- and post-operative MRI images [6]. Regarding the long-term outcome after bilateral STN DBS, many studies have shown stable improvement in the UDPRS scores after STN DBS [4,7,14,31–33] which were observed to diminish over time due to disease progression [7,10,14,18,34,35]. Benabid et al. have reviewed the literature and found that improvements in the UDPRS III scores due to STN DBS were reasonably stable over time, decreasing from 66% improvement at one year to 54% at five years after surgery [36].

Unfortunately, there is little in the literature regarding the long-term outcomes of patients with different electrode positions that have been measured in a stable period following bilateral STN stimulation. In this study, we report the three-year clinical outcomes of advanced PD patients for up to 36 months after bilateral STN DBS as a function of the electrode position, which was estimated using fused preoperative MRI and postoperative CT images that were taken more than one month after surgery. We used postoperative CT images that were taken more than one month after surgery since we found in a previous study that at least one month is needed for stabilization of the brain following CSF leakage during surgery [15,37]. In this study, we found that 11 patients out of 42 patients had one of their DBS electrodes outside the margin of the STN and there were significant

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Table 3
SF-36 physical and mental health scores by the SF-36 health survey of 41 patients with advanced Parkinson's disease after bilateral subthalamic nucleus stimulation.

	Total subjects				Subjects according to each group (group I, n = 30; group II, n = 11)				
	Baseline	12 months	24 months	36 months	Group	Baseline	12 months	24 months	36 months
Physical health components									
Physical functioning	34.5 ± 21.1	**45.6 ± 21.1***	**43.7 ± 21.1***	37.1 ± 21.8	I	35.0 ± 19.1	47.9 ± 20.6	48.8 ± 21.9	**43.8 ± 22.4****
					II	33.7 ± 24.4	42.1 ± 21.9	35.8 ± 17.6	**26.8 ± 16.5****
Role-physical	14.9 ± 23.7	**28.6 ± 36.5***	**24.5 ± 31.4***	19.3 ± 28.8	I	8.9 ± 18.3	33.6 ± 39.7	26.8 ± 34.6	21.6 ± 32.5
					II	23.7 ± 28.2	21.1 ± 30.3	20.8 ± 26.1	15.8 ± 22.4
Bodily pain	40.7 ± 27.9	**67.6 ± 21.5***	**67.3 ± 22.0***	**63.4 ± 22.4***	I	41.5 ± 25.0#	71.1 ± 18.2	69.3 ± 20.6	67.5 ± 19.5
					II	39.6 ± 32.4	62.2 ± 25.4	64.2 ± 24.3	57.1 ± 25.6
General health	42.0 ± 19.8	**52.2 ± 17.1***	**51.8 ± 19.0***	**50.9 ± 20.8***	I	38.1 ± 17.4	55.2 ± 16.1	55.8 ± 15.6	50.7 ± 20.2
					II	47.7 ± 22.1	50.2 ± 18.6	45.4 ± 22.3	51.2 ± 22.4
Mental health components									
Vitality	38.8 ± 20.9	**49.5 ± 22.3***	**50.4 ± 17.0***	45.5 ± 17.8	I	39.6 ± 21.6	53.8 ± 21.4	52.9 ± 16.4	45.7 ± 19.4
					II	37.6 ± 20.4	42.9 ± 22.6	46.7 ± 17.6	45.3 ± 15.7
Social functioning	44.6 ± 28.4	**61.6 ± 23.0***	**57.9 ± 24.2***	49.9 ± 23.9	I	50.4 ± 25.7	67.6 ± 22.4	61.7 ± 25.2	52.9 ± 25.1
					II	36.1 ± 30.6	52.4 ± 21.3	52.1 ± 22.1	45.4 ± 21.7
Role-emotion	19.1 ± 32.4	32.6 ± 41.5	33.3 ± 39.8	22.9 ± 39.6	I	9.5 ± 23.8	40.2 ± 43.1	34.5 ± 42.0	24.1 ± 41.7
					II	33.3 ± 38.5	21.1 ± 37.2	31.5 ± 37.0	21.1 ± 37.2
Mental health	51.1 ± 21.2	**60.0 ± 18.2***	58.8 ± 17.2	58.8 ± 17.2	I	50.7 ± 21.8	62.8 ± 18.4	62.4 ± 15.1	59.9 ± 15.0
					II	51.8 ± 20.8	55.8 ± 17.6	53.1 ± 19.1	57.3 ± 20.5

All data was expressed as a mean ± standard deviation. *, P<0.05.
Values in BOLD: p-value <0.05 for between follow-ups and baselines (*) and for between two groups (**): group I (both electrodes were in the STN) and group II (both electrodes were not in the STN).

differences in the clinical outcomes of the investigated patients, which is in contrast to the results of our previous study that compared short-term clinical outcomes for up to six months after STN DBS. We do not know the exact reasons why eleven patients had one of their DBS electrodes off target. MER and intraoperative test stimulation were carried out to optimize clinical effect and improve the accuracy of electrode locations. Although test stimulation could be helpful concerning electrode position, in some cases, it is difficult to confirm the off-the target location of the electrode because of the microlesion effect resulting from MER. Furthermore, the clinical effect and side effect from the second test stimulation were masked by the lasting effect and side effect from the first test stimulation. Possible brain shift due to CSF leakage, mechanical error in the stereotactic device from the microdrive adaptor to the stereotactic device for MER, man-made error in handling the stereotactic device, and possible electrode bending during the surgery could make it difficult to precisely localize the center of the electrodes in our series. We do think these things also could happen to any neurosurgeon doing STN DBS and similar occurrences cannot be noticed unless postoperative electrode positions are thoroughly investigated with the fusion image of preoperative MRI and postoperative CT taken during a stable period after surgery as in this study. In our previous analysis, we assessed the short-term clinical outcome at six months after STN DBS and found little difference in the clinical outcome except in the off-medication speech sub-scores in patients whose electrodes were positioned either correctly or incorrectly in their respective STNs after bilateral STN DBS [6]. We had thought there was a significant target volume in the region of the STN that provides an equivalent clinical efficacy, described by McClelland et al. [38]. However, in this study, we found significant differences in the long-term outcomes of motor symptoms after three years in advanced PD patients following bilateral STN DBS depending on whether both DBS electrodes were positioned in the STN. We also found that there was a significant decline in the MMSE and BDI scores in group II at 36 months after surgery, even though there was no significant global deterioration in cognitive function for the entire group for up to three years after surgery. The position of the electrodes was confirmed to significantly influence the long-term clinical outcomes of advanced PD patients, which was not observed in the short-term period after bilateral STN DBS. Thus, we suggest that accurate electrode positioning in the STN and documentation thereof are more important in the assessment of long-term outcomes in advanced PD patients than in the assessment of short-term outcomes after STN DBS.

These differences in long-term outcome are influenced by the position of the electrodes. Some experiments with non-human primates have suggested that DBS has a positive impact in PD animal models [39]. Others have suggested that slow disease progression continues in patients with advanced PD over time despite effective STN DBS [7,10,14,18,34,35,40]; however, based on our observations, we think that it is necessary to dichotomize advanced PD patients who have been treated with bilateral STN DBS depending on whether the electrodes of the patients were positioned in their respective STNs following bilateral STN DBS to properly assess the neuro-protective effects of DBS against slow progressive deterioration. We observed a difference in the three-year clinical outcomes between patients whose electrodes were correctly positioned in their respective STNs and those whose electrodes were not.

Previously, we reported on the two-year clinical outcomes of intentional unilateral STN DBS in eight patients with high asymmetric Parkinson's disease [41]. We found that unilateral STN DBS does not provide sufficient benefit in highly asymmetric PD over time. The ipsilateral motor symptoms progressively worsened over time in most patients and reversed asymmetry became difficult to manage, which led to compromised medication. At 24 months, all of the patients had considered a second-side surgery. From this point of view, the long-term clinical outcomes of the eleven patients who had one of their DBS electrodes outside the margin of the STN could be considered similar to the long-term efficacy of the intentional unilateral STN DBS in selected PD patients who had highly asymmetrical symptoms of Parkinson's disease.

This study has several limitations. First, this retrospective analysis had a small number of patients from a single institution. We need further prospective and randomized clinical studies with larger numbers of patients from multiple centers to confirm the results discussed herein. Second, we did not estimate the three-dimensional view of the electrode position in relation to STN to assess the potential differences in long-term clinical outcome in advanced PD patients after bilateral STN DBS. We must develop tools that are more sophisticated in order to completely understand the three-dimensional relationship of each electrode in STN. Third, we did not characterize the long-term clinical outcome as a function of the electrode position 5 to 10 years after STN DBS. We do not know the long-term outcomes of patients

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whose electrodes are not located in their respective STNs. In addition, we do not know the long-term outcomes of patients whose electrodes were not originally positioned in their respective STNs but were later correctly repositioned into their STNs. Further, long-term clinical studies are required to clarify these issues.

5. Conclusion

We investigated the three-year clinical outcomes of advanced PD patients after bilateral STN DBS to investigate whether there were significant differences in the clinical outcomes of patients as a function of electrode positioning. The positions of electrodes were estimated with fused preoperative MRI and postoperative CT images that were taken during a stable period after surgery. We found that there were significant differences in the three-year clinical outcomes of advanced PD patients following bilateral STN DBS as a function of electrode positioning. It has been suggested that the electrode location following STN DBS influences the long-term clinical outcome; a better electrode positioning leads to better long-term outcomes in advanced PD patients following STN DBS.

Hence, electrode positioning in the STN and documentation thereof should be considered when adjusting long-term management plans and assessing the long-term effects of DBS on disease progression in advanced PD patients following STN DBS.

Conflicts of interest

The authors do not report any conflicts of interest.

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