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Long-term comparison of subthalamic nucleus stimulation between patients with young-onset and late-onset Parkinson's disease

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ABSTRACT

Objectives: The aim of this study was to compare the long-term effectiveness of subthalamic nucleus deep brain stimulation (STN-DBS) between patients with young-onset Parkinson's disease (YOPD) and late-onset Parkinson's disease (LOPD).

Materials and Methods: Twenty-one YOPD patients with a mean age at onset of 32.8 ± 6.9 years and another 69 LOPD patients with a mean age at onset of 53.2 ± 6.9 years undergoing STN-DBS were followed. The mean durations of follow-up for those who were followed for more than 3 years were 57.22 ± 14.54 months in the YOPD group and 46.77 ± 13.84 months in the late onset group.

Results: Motor disabilities and activities of daily living in patients with LOPD and YOPD significantly improved after the operation. However, YOPD patients showed significantly less improvement in Unified Parkinson's Disease Rating Scale Part II ($p = 0.001$) and Part III ($p = 0.031$), rigidity ($p = 0.033$), and axial ($p = 0.046$) scores than late onset patients more than 3 years after surgery. YOPD patients had higher scores for rigidity ($p = 0.007$) and bradykinesia ($p = 0.044$) than LOPD patients at the final post-surgery follow-up. Late onset PD patients had more postoperative hypophonia, whereas EOPD patients displayed more stimulation dyskinesia. The effects of STN-DBS on psychiatric complications and cerebral bleeding were similar in both groups.

Conclusion: YOPD patients and LOPD patients had similar benefits and risks from medication-related complications with STN-DBS. The YOPD group had relatively less improvement from acute deep brain stimulation than the LOPD group during long-term follow-up, which could possibly be explained by different disease evolutions and underlying pathophysiology in these two groups.

1. Introduction

Young-onset Parkinson's disease (YOPD) is arbitrarily defined as an onset of symptoms between ages 21 and 40 years [1]. Although these patients seem to experience motor symptoms similar to those of patients with late-onset Parkinson's disease (LOPD), earlier motor fluctuation and dyskinesia with slower progression of motor features have been noted chronologically. In addition to its great impact on the everyday, occupational, and social functioning of patients, YOPD is also characterized by several neuropsychological features [2,3]. Researchers have discussed the similar frequency of psychiatric diseases in patients with YOPD and LOPD, and suggested that psychosocial issues deserve more attention in YOPD patients [4,5].

The long-term effectiveness of subthalamic nucleus deep brain stimulation (STN-DBS) has been reported in patients with PD [6]. Differences in the evolution of disease between different patient groups may influence the impact of STN-DBS on quality of life, even though these patient groups may all display similar responses to levodopa treatment preoperatively [7]. Although previous studies have recommended STN-DBS over internal *globus pallidus* deep brain stimulation (GPi-DBS) for YOPD patients, comparison of the long-term results of STN-DBS between patients with YOPD and LOPD has not been addressed [8].

Conflict of interest: none.

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The neuroprotective effect of STN-DBS in PD is still under debate. While positron emission tomography studies have revealed progressive degeneration of dopaminergic neurons upon STN modulation, animal studies demonstrated a neuroprotective effect from STN modulation [9,10]. Levodopa responsiveness deteriorates during long-term follow-up, which may be a result of disease progression or of a direct stimulation effect [11]. It is uncertain whether STN-DBS is neuroprotective for YOPD patients and this effect needs to be confirmed.

To illustrate the long-term benefits and impact of STN-DBS for YOPD patients, we compared DBS effectiveness and adverse effects between patients with YOPD and LOPD. Short-term and long-term follow-up of disease progression and evolution relative to preoperative characteristics was carried out.

2. Materials and methods

2.1. Patients

A total of 90 consecutive parkinsonian patients underwent bilateral STN-DBS performed by the operative team at Department of Neurosurgery Tzu Chi General Hospital, Taiwan, between February 2003 and May 2010. The diagnosis of PD conformed to the diagnostic criteria of the United Kingdom PD Society Brain Bank. There were 21 patients in the YOPD group (disease onset between ages 21 and 40 years) and the other 69 patients had typical PD (LOPD) group. The inclusion criteria were as follows: (1) good levodopa response on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (>30%); (2) drug-related complications (e.g., dyskinesia, and "on-off phenomenon") even under optimal antiparkinsonian medication adjustment; (3) no structural lesions on brain magnetic resonance imaging (MRI); and (4) absence of dementia. All patients participating in this study signed informed consents for STN-DBS surgery and the procedures involved in the study. The evaluation procedures in the study were carried out with the ethical approval of our institutional review board (Tzu Chi General Hospital, Hualien, Taiwan).

2.2. Surgical procedure

A Leksell G frame was used for the stereotactic procedure. Images for targeting were obtained from a 1.5-Tesla MRI unit (General Electric, Milwaukee, WI, USA). The standard settings included T1-weighted axial images (TR: 26 ms, TE: 6.9 ms, matrix size: 256 x 192, thickness: 0.7 mm) and T2-weighted axial images (TR: 4800 ms, TE: 95 ms, matrix size: 256 x 192, thickness: 2.0 mm). Each of these sequences was performed in contiguous slices. The images were transferred to a database (Digital Image Communications in Medicine) through the picture archiving and communication system on a neuronavigation workstation (BrainLab VectorVision, Westchester, IL, USA). T1 images were used for the identification and measurement of the anterior commissure and posterior commissure length in both groups. The tentative surgical target coordinates for the tip of the permanent implantable electrode were set at the central lowest border of the STN, the intersection point between the line of the anterior border and 2 mm lateral of the red nucleus on T2 images. The quadripolar DBS electrodes (Model 3389; Medtronic, Englewood, CO, USA) were implanted after microelectrode recording and test stimulation procedures. After 1 week, the electrode cables were connected to an implantable pulse generator (Kinetra; Medtronic, Minneapolis, MN, USA). The same surgical team performed all of the surgical procedures, which have been described in detail in our previous study [12]. An acute stimulation test was performed 1 week after surgery to select the optimal stimulation contact and parameters for chronic stimulation.

2.3. Clinical evaluation

Mentation, behavior and mood, activities of daily living, motor examination, and levodopa-related motor complications (UPDRS Parts I, II, III, and IV) were evaluated 1 month prior to surgery and 3, 12, 24, 36, 48, 60, and 72 months after surgery. We included patients with different durations of follow-up in order to collect all the data up to more than 3 years of follow-up. The preoperative characteristics did not show significant differences between groups except for age at disease onset and UPDRS Part IV scores. The "medication (MED) off" status for the motor examination was evaluated at least 12 hours after the withdrawal of dopaminergic medication as defined by the Core Assessment Program for Surgical Interventional Therapy in Parkinson's Disease [13]. The magnitude of levodopa response in "MED on" was assessed after administration of a dose of levodopa/benserazide (Roche Products, Basel, Switzerland) equivalent to the usual morning and effective dose of dopaminergic treatment. The bradykinesia scores included Items 23–26 and 31 of UPDRS Part III. The axial score evaluation included speech, rising from a chair, gait, and postural instability (Items 18 and 27–30 of UPDRS Part III). All patients were evaluated postoperatively in 4 conditions: (1) "stimulation (DBS) off" and "MED off", after the DBS was switched off for at least 2 hours and with no dopaminergic treatment for 12 hours; (2) "DBS on" and "MED off", after stimulation was switched on for at least 2 hours; (3) "DBS off" and "MED on"; and (4) "DBS on" and "MED on". We also followed Schwab and England Activities of Daily Living Scale (SEADL) and mini-mental state examination (MMSE) between groups.

The dosage of antiparkinsonian medication was expressed as the levodopa equivalent daily dosage (LEDD) with the sum of the dose of regular levodopa-benserazide (or levodopa-carbidopa), plus 0.75 times the dose of controlled-release levodopa benserazide (or levodopa-carbidopa), plus 10 times the dose of bromocriptine, plus 25 times the dose of ropinirole. In patients taking entacapone, the sum of regular levodopa and 0.75 times the dose of controlled-release levodopa was multiplied by a factor of 1.25 [14].

2.4. Statistical analysis

For preoperative characteristics, means of normally distributed variables were compared using the independent-samples *t* test and nonnormally distributed variables were assessed with Mann-Whitney tests. To analyze the data from the preoperative period to 3, 6, 12, 24, and >36 months after surgery, comparisons of the acute DBS effect (in "MED off") on UPDRS scores, baseline UPDRS scores (in "DBS off"/"MED off") Hoehn and Yahr (H&Y) staging, and the LEDD between groups (YOPD vs LOPD) were conducted with the independent-samples *t* test. Repeated measures of analyses of variance were performed for serial follow-up of stimulation parameters and MMSE between groups.

Adverse effects were compared using the Wilcoxon matched-pairs signed rank sum test. A p value of <0.05 was considered significant. Statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA).

3. Results

There were 21 YOPD patients with a mean age at disease onset of 32.8 ± 6.9 years and 69 LOPD patients with a mean age at onset of 53.2 ± 6.9 years. YOPD patients had similar levels of levodopa responsiveness in UPDRS Parts I, II, and III scores compared with patients with LOPD. However, YOPD patients exhibited more severe

drug-related dyskinesia in Part IV. There were no differences in disease severity in "MED off" H&Y stage, SEADL scores and LEDD (Table 1).

Similar to previous long-term studies, the UPDRS Parts II, III, and IV all improved significantly in both groups postoperatively (Fig. 1). The intergroup comparison showed significant differences at more than 3 years follow-up, when YOPD patients showed a reduced response to DBS in Part II ($p = 0.001$) and Part III ($p = 0.031$). Further analysis of cardinal motor symptoms (tremor, rigidity, bradykinesia, and axial scores) demonstrated that the effect of DBS on rigidity and axial scores in YOPD patients was significantly less than in LOPD patients ($p = 0.033$ and $p = 0.046$, respectively).

In terms of disease progression and evolution, both groups were analyzed from preoperative "MED off" to postoperative "DBS off"/"MED off" status. There were no significant differences from UPDRS Parts I, II, and III scores to H&Y staging with the exception of an increased deterioration in rigidity scores ($p = 0.007$) and bradykinesia ($p = 0.044$) in YOPD patients during the 3-year follow-up. The within-group analysis did not show any significant difference in disease progression (Fig. 2).

The LEDD significantly decreased after the operation and remained stable up to the 3-year follow-up in both groups (YOPD vs. LOPD; 54.9% vs. 52.24% at 3 months, 53.83% vs. 51.85% at 1 year, 60.78% vs. 42.28% at 2 years, 34.62% vs. 41.81% at >3 years follow-up). Nevertheless, intergroup differences showed a trend at the 2-year follow-up ($p = 0.085$), with a lower LEDD in the YOPD group than the LOPD group. The stimulation parameters also did not show a significant difference between groups (Table 2). Following serial cognitive function evaluation with the MMSE, it was determined that STN-DBS did not cause memory decline in either group (Table 3).

In terms of complications, the LOPD group showed significantly more stimulation-related hypophonia, whereas the YOPD patients displayed more stimulation dyskinesia. There were no differences in postoperative psychiatric morbidity, such as depression or hypomania, between groups. Both groups showed similar risks in relation to debilitating intracerebral hemorrhage, malpositioned leads and infection (Table 4).

4. Discussion

Our study confirms the long-term effectiveness and safety of STN-DBS for YOPD patients. Although patients with YOPD did not differ significantly from those with LOPD in respect to disease severity and levodopa responsiveness, they showed fewer benefits on the UPDRS Parts II and III during long-term follow-up. The

Table 1
Preoperative clinical characteristics of young-onset (YOPD) and late-onset Parkinson's disease (LOPD) patients.

Sex, no. of patients	YOPD ($n = 21$)		LOPD ($n = 69$)		p value
Male/Female	17.0/4.0		42.0/27.0		0.0919
Disease onset age (y)	32.8 ± 6.9		53.2 ± 6.9		<0.0001**
Age at STN-DBS (y)	44.6 ± 10.1		62.9 ± 7.1		<0.0001**
Duration of the disease (y)	11.9 ± 7.3		9.5 ± 4.3		0.0679
Number of patients and mean duration of follow-up (mo)					
	Number	Duration		Number	Duration
3 mo	1	3		3	3.33 ± 0.58
6 mo	2	7 ± 1.41		7	6.86 ± 1.07
12 mo	1	12		17	13.47 ± 2.43
24 mo	8	25.63 ± 4.00		11	25.36 ± 3.14
>36 mo	9	57.22 ± 14.54		26	46.77 ± 13.84
Lost from follow-up	0		5		
UPDRS Part I "off"	3.9 ± 3.2		4.6 ± 2.5	0.2782	
UPDRS Part I "on"	2.9 ± 3.4		3.6 ± 2.3	0.2355	
UPDRS Part I improvement, %	32.2 ± 36.4		20.6 ± 26.7	0.1857	
UPDRS Part II "off"	22.0 ± 9.5		20.8 ± 9.3	0.5947	
UPDRS Part II "on"	10.6 ± 7.5		12.5 ± 8.1	0.3342	
UPDRS Part II improvement, %	49.9 ± 22.9		39.1 ± 27.0	0.1031	
UPDRS Part III "off"	49.6 ± 12.5		45.8 ± 15.5	0.3006	
UPDRS Part III "on"	26.3 ± 12.5		27.4 ± 13.2	0.7414	
UPDRS Part III improvement, %	48.2 ± 16.1		40.9 ± 17.2	0.0842	
Tremor "off"	7.0 ± 4.6		6.0 ± 5.4	0.4033	
Tremor "on"	1.5 ± 2.5		2.1 ± 3.5	0.4598	
Tremor improvement, %	66.5 ± 49.2		58.1 ± 40.9	0.4331	
Rigidity "off"	11.6 ± 4.3		9.6 ± 3.9	0.0590	
Rigidity "on"	6.0 ± 3.4		5.4 ± 3.6	0.5144	
Rigidity improvement, %	48.0 ± 21.3		47.4 ± 25.5	0.9206	
Posture & Gait "off"	4.4 ± 1.8		4.1 ± 1.7	0.4552	
Posture & Gait "on"	2.4 ± 1.7		2.6 ± 1.4	0.7115	
Posture & Gait improvement, %	46.2 ± 29.9		36.7 ± 26.0	0.1603	
Axial "off"	9.5 ± 4.0		9.4 ± 4.0	0.9253	
Axial "on"	5.6 ± 3.6		6.3 ± 3.0	0.4125	
Axial improvement, %	41.1 ± 26.6		31.8 ± 19.6	0.0854	
UPDRS Part IV	7.2 ± 3.7		5.0 ± 3.8	0.0180*	
Hoehn & Yahr stage "off"	3.6 ± 0.9		3.3 ± 0.8	0.0757	
Hoehn & Yahr stage "on"	2.5 ± 0.7		2.7 ± 0.7	0.2610	
SEADL score "off"	70.5 ± 30.1		73.5 ± 25.1	0.6486	
SEADL score "on"	86.7 ± 21.8		87.2 ± 19.4	0.9189	
LEDD, mg/day	789.7 ± 355.9		785.0 ± 374.4	0.9600	

Values are expressed as means ± standard deviation.
* $p < 0.05$, ** $p < 0.01$.
LEDD: levodopa equivalent daily dosage; SEADL: Schwab and England Activities of Daily Living Scale; STN-DBS: subthalamic deep brain stimulation, UPDRS: Unified Parkinson disease Rating Scale.

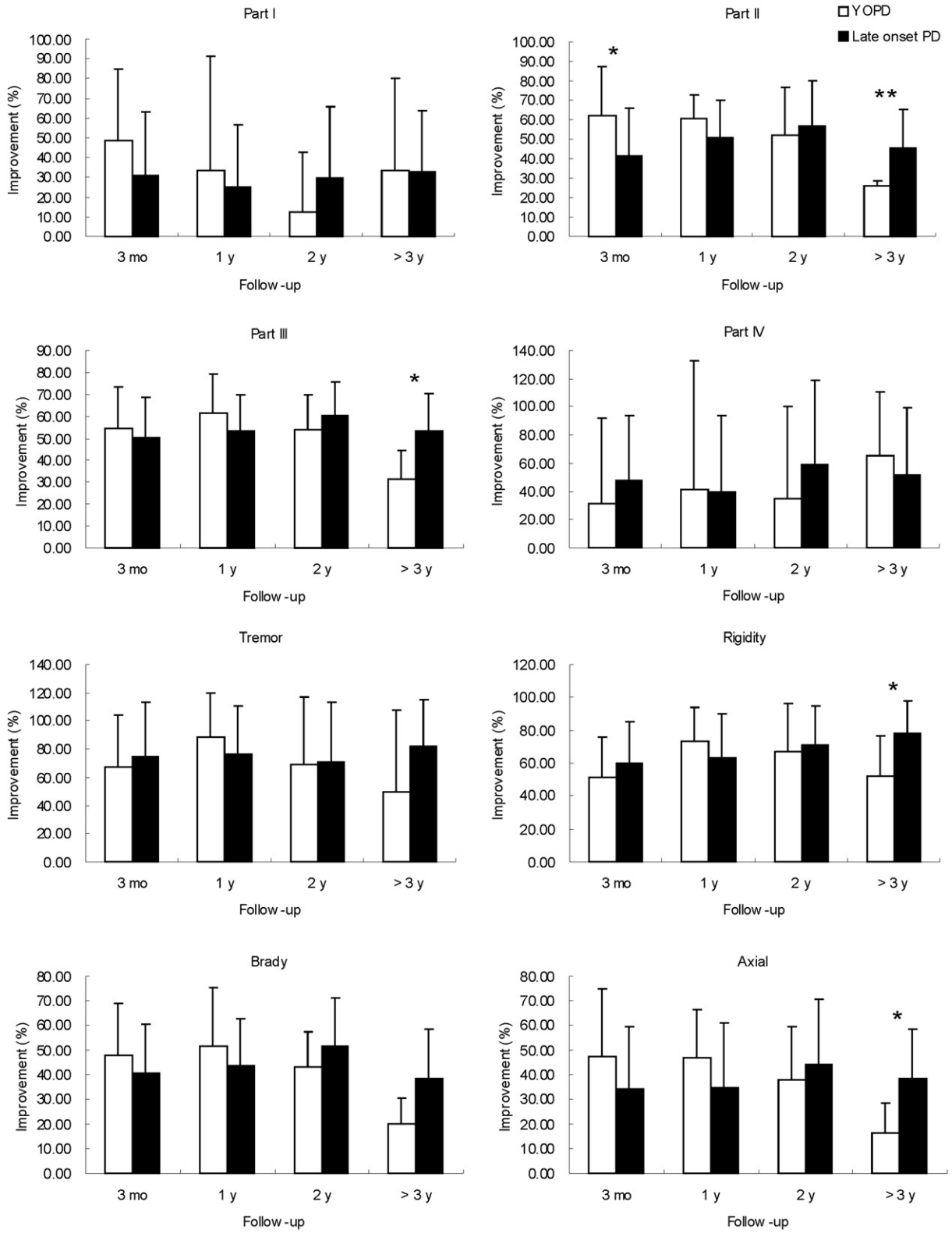

Fig. 1. The effect of acute deep brain stimulation (DBS) on the Unified Parkinson Disease Rating Scale (UPDRS; Parts I, II, III, and IV), tremor, rigidity, bradykinesia and axial scores between patients with young onset Parkinson's disease (YOPD; open bars) and late-onset Parkinson's Disease (PDPD; black bars) 3 months, 1 year, 2 years and >3 years post-operatively. The YOPD group had significantly reduced benefits on the UPDRS Parts II and III, rigidity, and axial scores from DBS compared with the LOPD group at >3 years follow-up (* $p < 0.05$, ** $p < 0.01$). Data are presented as means ± standard deviation.

LEDD also showed remarkable reduction in both groups post-surgery and there were similar trends in stimulation parameters during follow-up.

Because of the inclusion criteria for STN-DBS, the preoperative characteristics between YOPD and LOPD patients did not show significant differences in disease severity except for the time of

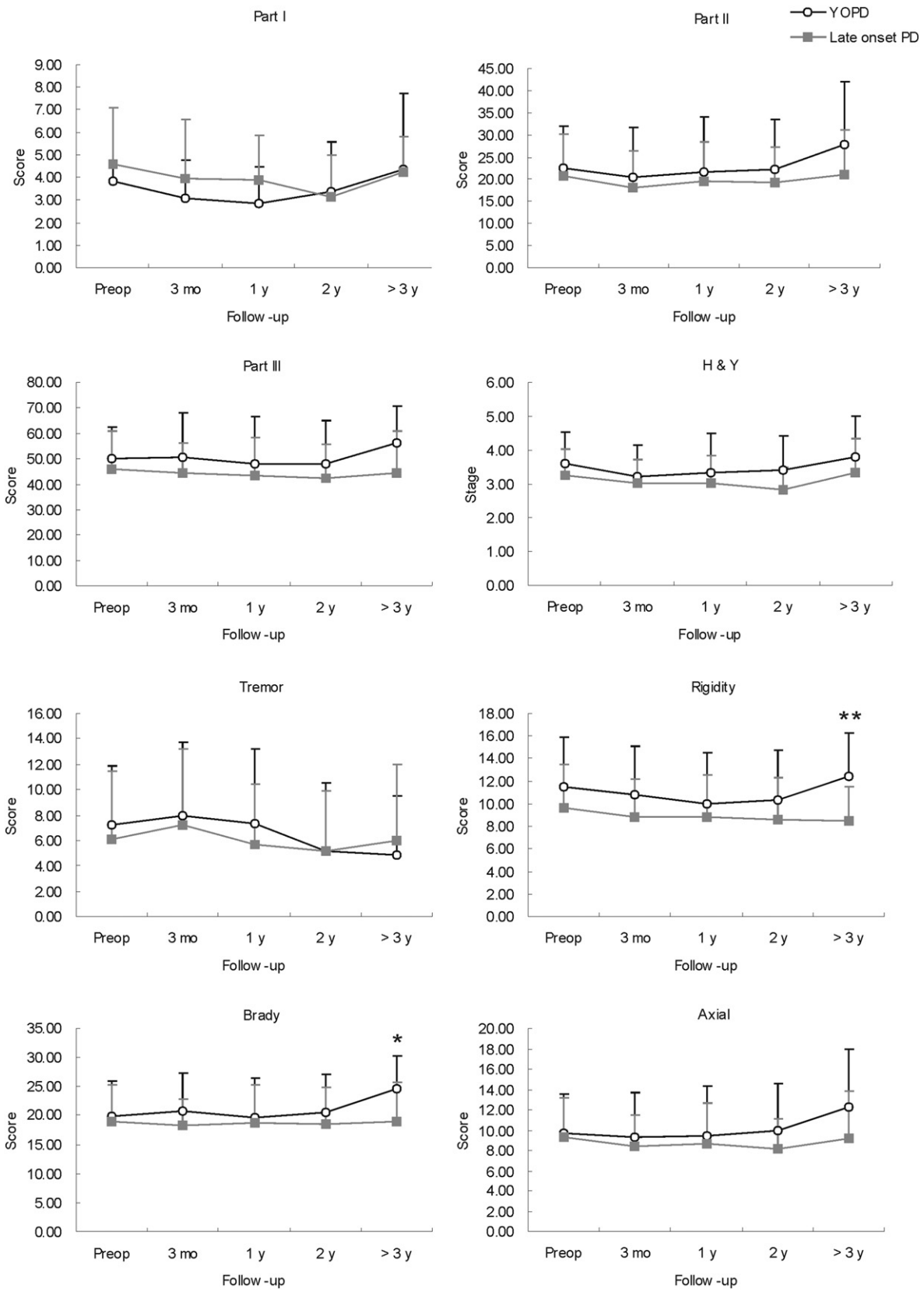

Fig. 2. Time course evolution of baseline scores on the Unified Parkinson Disease Rating Scale (UPDRS; Parts I, II, and III), Hoehn and Yahr staging (H&Y), tremor, rigidity, bradykinesia, and axial scores between patients with young onset Parkinson's disease (YOPD; open circles) and late-onset Parkinson's disease (LOPD; black squares) from preoperative medication off to stimulation off and medication off 3 months, 1 year, 2 years and >3 years postoperatively. The YOPD group had significantly* higher scores in rigidity and bradykinesia than LOPD patients at more than 3 years follow-up (* $p < 0.05$, ** $p < 0.01$).

Table 2
Stimulation parameters in young-onset (YOPD) and late-onset Parkinson's disease (LOPD) patients.

	3 months		6 months		12 months		24 months		*p*	
	Right side	Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side	Lt side
Voltage (V)										
YOPD	2.7 ± 0.7	2.9 ± 0.5	3.0 ± 0.6	3.2 ± 0.5	3.2 ± 0.6	3.3 ± 0.4	3.4 ± 0.5	3.4 ± 0.7	0.2975	0.8874
LOPD	2.9 ± 0.4	2.9 ± 0.6	3.1 ± 0.4	2.9 ± 0.7	3.4 ± 0.5	3.1 ± 0.8	3.3 ± 0.4	3.2 ± 0.4		
Frequency (Hz)										
YOPD	145 ± 19	143 ± 18	148 ± 21	146 ± 21	150 ± 24	150 ± 23	147 ± 18	150 ± 18	0.9632	0.9648
LOPD	145 ± 16	141 ± 26	148 ± 17	148 ± 17	149 ± 17	148 ± 17	150 ± 20	149 ± 20		
Pulse width (μS)										
YOPD	62 ± 7	60 ± 0	64 ± 11	64 ± 11	66 ± 13	66 ± 12	62 ± 8	69 ± 14	0.5219	0.3521
LOPD	61 ± 5	61 ± 5	62 ± 7	61 ± 5	63 ± 9	61 ± 6	64 ± 11	64 ± 11		

disease onset and higher Part IV scores in the YOPD group. The levodopa responsiveness was also similar between groups. These results are consistent with previous reports showing that YOPD patients develop earlier and have more severe levodopa-induced dyskinesia and motor fluctuation [15] than LOPD patients.

Young-onset parkinsonism occurs in 3% to 5% of all patients with parkinsonism but this is as high as 10% in Japan [1]. Of the 90 patients undergoing STN-DBS surgery, 23% had YOPD. These patients had a higher incidence of medication-related complications, which explains the necessity for STN-DBS in Asian populations such as in Taiwan. In one study, nearly all YOPD patients developed levodopa-related fluctuation and dyskinesia after a mean disease duration of 10 years or more [16]. Furthermore, the higher male predominance of 4:1 in our YOPD group undergoing STN-DBS might also explain the ethnic variability [7,8].

STN-DBS induced significant improvements in UPDRS Part III by 54.77% in YOPD patients and 50.16% in LOPD patients at the 3-month follow-up. These results were similar to previously reported short-term benefits from STN-DBS in YOPD patients [8].

In the activities of daily life (UPDRS part II scores), the YOPD group showed an even greater improvement with STN-DBS (61.85%) vs. a 41.26% improvement in the late-onset PD patients. Therefore, the magnitude of the preoperative levodopa response could also predict the short-term benefits of STN-DBS in YOPD patients [11]. During long-term follow-up, the effectiveness of STN-DBS seemed to decline in YOPD patients, such that UPDRS Part II showed only a 25.95% improvement in YOPD patients, which was less than the 45.37% improvement observed in LOPD patients; UPDRS Part III only improved 31.46% in YOPD patients, compared with 53.27% observed in LOPD patients. Phenotypic homogeneity has clustered YOPD as a specific manifestation of PD [17]. Our study echoed this observation after a long-term follow-up, which indirectly indicates that the specific phenotype and entity of YOPD are different from that of general idiopathic parkinsonism.

Most previous studies have reported slower disease progression in YOPD with medical treatment than in LOPD [18]. The annual progression and evolution after STN-DBS in our study showed different trends of disease evolution between YOPD and LOPD patients. The YOPD group showed significantly higher scores in rigidity and bradykinesia than the late onset group at the 3-year follow-up. This might at least partially explain the more rapid deterioration of acute STN-DBS effects in YOPD patients and also indicates the development of underlying neuropathological changes after neuromodulation that depends on the patient's age at disease onset [19]. Comparing preoperative "MED off" to postoperative "DBS off"/"MED off", motor function did not worsen in LOPD, indirectly supporting the neuroprotective effect of STN-DBS [20,21]. Although motor disability was similar in the 2 groups before surgery, YOPD patients displayed a trend towards longer disease duration before surgery in our study, which was probably because of slower progression. Future study should clarify whether this group of patients would benefit from STN-DBS in earlier stages of the disease [22].

The LEDD was significantly reduced and remained constant in both groups. This could explain the improvement in motor function in addition to the STN-DBS effects [23]. At the 2-year follow-up, the LEDD in the YOPD group seemed to be less than in the LOPD group. Four out of 13 patients were free from anti-parkinsonian medication after surgery. This might be due to the more restricted nigrostriatal dopaminergic deficit in YOPD patients and may account for the delayed onset of impairment of cognition, suggesting the possibility of DBS fully substituting for medication [16,24].

Hypophonia occurred more often in LOPD patients than YOPD patients, possibly because the LOPD group was older than the YOPD group. However, stimulation-related impairment of speech should be considered during long-term follow-up [25,26]. The YOPD group developed more stimulation-related dyskinesia. Although the provocation of dyskinesia with stimulation either during surgery or the early postoperative programming period predicts the long-term benefits from STN-DBS, the motor improvement might be offset by disabling dyskinesia [27,28]. The interaction between subthalamic and pallidal activity is suggested to play a major role in the pathogenesis of dyskinesia. The amelioration of stimulation-related dyskinesia through proximal contact (stimulating subthalamic fibers) in previous reports and our YOPD patients suggests possible beneficial effects from GPi-DBS [28–30]. Previous studies have shown the superiority of STN-DBS over GPi-DBS for YOPD patients after 6 months, but a recent large, randomized trial showed similar improvement after either pallidal or subthalamic stimulation for 24 months [8,31]. Given the early development of medication-related complications, lower medication requirements and concerns regarding stimulation-related psychiatric effects, GPi-DBS might be a good alternative for YOPD patients.

In this report, YOPD patients did not show significantly more psychiatric complications, such as depression and hypomania, than

Table 3
Cognitive evaluation with mini-mental state exam between young-onset (YOPD) and late-onset Parkinson's disease (LOPD).

	Pre-operative	3 months	6 months	12 months	24 months	>36 months	*p*
YOPD	28.2 ± 1.9	28.0 ± 1.3	28.7 ± 1.7	27.3 ± 2.3	26.9 ± 3.8	27.4 ± 2.8	0.7064
LOPD	26.0 ± 4.7	27.7 ± 2.7	25.6 ± 6.2	27.4 ± 2.9	24.2 ± 5.5	26.5 ± 3.8	

Table 4
Adverse effects with subthalamic nucleus deep brain stimulation in young-onset (YOPD) and late-onset Parkinson's disease (LOPD) patients.

	YOPD ($n = 21$)		LOPD ($n = 69$)		p
	n	%	n	%	
Adverse effects related to stimulation					
Hypophonia	1	4.8	17	24.6	0.0470*
Eyelid apraxia	0	0.0	2	2.9	0.4358
Increased libido	3	14.3	2	2.9	0.0470*
Sialorrhea	2	9.5	11	15.9	0.4694
Decreased memory	1	4.8	12	17.4	0.1528
Dystonia	1	4.8	0	0.0	0.0696
Dyskinesias	8	38.1	7	10.1	0.0020**
Dysarthria	2	9.5	13	18.8	0.3213
General neurological and surgical complications					
Depression	0	0.0	5	7.2	0.2087
Hypomania	2	9.5	8	11.6	0.7943
Perioperative confusion	1	4.8	7	10.1	0.4535
Weight gain	7	33.3	20	29.0	0.7073
Seizures	1	4.8	0	0.0	0.0696
Intracerebral hemorrhage	0	0.0	3	4.3	0.3366
Malpositioned leads	1	4.8	3	4.3	0.9366
Infections of the hardware	0	0.0	1	1.4	0.5840
Required removal of the system	0	0.0	1	1.4	0.5840
Battery failure	1	4.8	1	1.4	0.3729
IPG migration	0	0.0	1	1.4	0.5840
Wire revision	1	4.8	5	7.2	0.6934

* $p < 0.05$, ** $p < 0.01$.

LOPD patients after STN-DBS. However, two patients without prior psychiatric history in the YOPD group developed dopamine dysregulation syndrome and impulse control disorder after STN-DBS, which have been reported in previous studies with contradictory results [32,33]. Chronic dopamine stimulation in PD has been associated with dyskinesia and increased impulsivity, which provides further evidence that the basal ganglia is an organized circuit for the selection and facilitation of motor and nonmotor effects, which is especially true for YOPD [34,35]. Cerebral bleeding, which is probably the most devastating morbidity and an inevitable risk in DBS surgery, would have a lifelong impact on YOPD patients [36]. Fortunately, this did not occur in our YOPD group, but this issue still needs to be clarified and the importance of associated factors such as age should be assessed [37].

Our study showed the long-term benefits of STN-DBS for both YOPD and LOPD patients. Except for more stimulation-related dyskinesia, YOPD patients did not have significant differences in adverse effects from LOPD patients. However, the possibility that patients with advanced YOPD receive fewer benefits from STN-DBS than LOPD patients during long-term follow-up, as shown in our study, deserves attention. A well-designed study with more patients might shed light on the disease evolution for this specific group of patients after surgery.

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