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The MDS–UPDRS tracks motor and non–motor improvement due to subthalamic nucleus deep brain stimulation in Parkinson disease

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Abstract

Background—The Movement Disorders Society revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS) improves upon the original UPDRS by adding more non-motor items, making it a more robust tool to evaluate the severity of motor and non-motor symptoms of Parkinson disease. Previous studies on deep brain stimulation have not used the MDS-UPDRS.

Objective—To determine if the MDS-UPDRS could detect improvement in both motor and non-motor symptoms after bilateral subthalamic nucleus deep brain stimulation for Parkinson disease.

Methods—We compared scores on the entire MDS-UPDRS prior to surgery (baseline) and approximately six months following the initial programming visit in twenty subjects (12M/8F) with Parkinson disease undergoing bilateral subthalamic nucleus deep brain stimulation.

Results—STN DBS significantly improved the scores for every section of the MDS-UPDRS at the 6 month follow-up. Part I improved by 3.1 points (22%), Part II by 5.3 points (29%), Part III by 13.1 points (29%) with stimulation alone, and Part IV by 7.1 points (74%). Individual non-motor items in Part I that improved significantly were constipation, light-headedness, and fatigue.

Conclusions—Both motor and non-motor symptoms, as assessed by the MDS-UPDRS, improve with bilateral subthalamic nucleus stimulation six months after the stimulator is turned on. We recommend that the MDS-UPDRS be utilized in future deep brain stimulation studies because of the advantage of detecting change in non-motor symptoms.

Keywords

Parkinson disease; deep brain stimulation; subthalamic nucleus; motor symptoms; non-motor symptoms

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1. Introduction

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established surgical therapy for Parkinson disease (PD) [1]. It can control the main motor symptoms of PD (tremor, rigidity and bradykinesia) for many years as well as reduce motor fluctuations and dyskinesias [2, 3]. Though control of motor symptoms is the main goal of DBS, non-motor symptoms of the disease and their contribution to poor quality of life have been increasingly recognized in recent years [4–6]. The effect of STN DBS on certain individual non-motor aspects of PD, such as cognition and depression, have been well characterized, but effects of STN DBS on other non-motor symptoms have not been well studied.

The Unified Parkinson Disease Rating Scale (UPDRS), the most widely used scale for clinical ratings of Parkinson disease (PD), was expanded and revised by the Movement Disorders Society (MDS-UPDRS) in 2008 [7]. The MDS-UPDRS improves upon the original UPDRS by enhancing scale properties and including more non-motor items so that the breadth of PD manifestations is adequately captured. The entire scale has been validated and shows high internal consistency [7]. The MDS-UPDRS Part I, encompassing the non-motor experiences of daily living, has also been separately validated and is highly associated with a composite score of several validated scales of individual non-motor symptoms in PD [8].

Despite its advantages over the original UPDRS, the assessment of PD symptoms before and after bilateral STN DBS with the MDS-UPDRS has not been reported in the literature, so the responsiveness of the MDS-UPDRS regarding both motor and non-motor features to DBS treatment is unknown. The aim of this study was to determine if the MDS-UPDRS could detect improvement in both motor and non-motor symptoms after bilateral STN DBS.

2. Methods

2.1 Participants

Clinical data from all PD patients undergoing STN DBS surgery at the University of Michigan Surgical Therapies Improving Movement (STIM) program were prospectively entered into a database. Patients qualified for DBS if they had a diagnosis of PD and motor fluctuations not optimally managed by medications or a severe rest tremor despite high doses of levodopa treatment. None of the subjects had structural brain abnormalities on preoperative magnetic resonance imaging (MRI) or dementia on formal neuropsychological testing prior to surgery. Written informed consent was obtained from all subjects, and the study was approved by the Medical Institutional Review Board of the University of Michigan.

2.2 Clinical assessments

Information regarding age, disease duration, and medications were collected. Clinical assessments included the Movement Disorder Society revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS), Hoehn and Yahr stage, Montreal Cognitive Assessment (MoCA), and Parkinson Fatigue Scale (PFS), which were performed prior to surgery (baseline) and approximately six months following the initial programming visit. The MDS-UPDRS replaced the original UPDRS as part of our clinical assessment battery in 2009. Parts I (Non-Motor Experiences of Daily Living), II (Motor Experiences of Daily Living) and IV (Motor Complications) were collected at baseline and at follow-up based on symptoms experienced the week prior to assessment. Part III (Motor Examination) was administered first OFF (all PD medications were withheld overnight prior to testing) then ON medication (approximately 1 hour after taking PD medication) at the baseline visit.

During the follow-up evaluation, Part III was administered in the following order: 1) OFF medication/ON stimulation, 2) OFF medication/OFF stimulation, 3) ON medication/OFF stimulation, and 4) ON medication/ON stimulation. The ON and OFF stimulation states were practically defined as 1 hour after the stimulator was turned on or off.

2.3 DBS Procedure

The DBS procedure has been previously described [9]. Briefly, bilateral STN DBS surgery was performed in a staged fashion. During the first stage of surgery, two quadripolar DBS electrodes (Model 3389, Medtronic Inc., Minneapolis, MN) were implanted, one into each STN. Intraoperatively, microelectrode recording was used to map the borders of the STN. DBS leads were then placed under fluoroscopic visualization with the tip of the DBS lead located near the ventral border of the electrophysiological STN. Macroelectrode testing was performed by a movement disorders neurologist (KLC) intraoperatively in order to document symptom improvement and side effect thresholds. Surgical placement was confirmed and hemorrhage excluded immediately after surgery with a high definition head CT scan. The second stage was performed 2–4 weeks later, where the implantable pulse generator was connected to the leads with extension wires. Initial programming of the DBS system was conducted approximately 2–3 weeks after the second stage of surgery.

2.4 Statistics

Wilcoxon signed-rank tests were used to determine if the post-DBS assessments significantly differed from baseline assessments. A repeated measures ANOVA was used to assess whether a main effect of condition existed for Part III. Statistical analysis was performed with IBM SPSS Statistics for Windows (V. 20.0. Armonk, NY, IBM Corp). A p-value of less than 0.05 was considered significant.

3. Results

We identified twenty PD subjects (12M/8F) who underwent bilateral STN DBS and had completed the entire MDS-UPDRS at baseline and approximately six months (mean 191 days, range 161–252) following their initial programming visit. At baseline evaluation, mean age was 62.7 ± 7.8 years and mean disease duration was 10.7 ± 4.8 years. Seventeen subjects were at Hoehn and Yahr stage 2, 3 subjects at Hoehn and Yahr stage 3, and 1 at Hoehn and Yahr stage 5. Hoehn and Yahr stage did not change at follow-up. Neither MoCA score (mean 25.0 ± 3.1 at baseline vs. 24.9 ± 3.4 at follow-up) nor PFS score (mean 3.19 ± 0.92 at baseline vs. 3.12 ± 0.91 at follow-up) changed after STN DBS. Levodopa equivalent doses decreased from 1228.6 ± 569.5 mg/day at baseline to 665.0 ± 409.0 mg/day at follow-up.

All sections of the MDS-UPDRS significantly improved from baseline to follow-up. The Part I subscore improved by 3.1 points (22%) after bilateral STN DBS (Table 1). Individual items in this section that improved significantly were constipation, light-headedness, and fatigue. The MDS-UPDRS Part II subscore was reduced by 5.3 points (29%) at follow-up (Table 2), but turning in bed, tremor, and freezing, were the only individual items that significantly improved in this section.

Table 3 shows the mean Part III scores for all possible stimulation and medication conditions at baseline and follow-up. Two subjects were able to come off medications completely so their OFF medication/OFF stimulation and OFF medication/ON stimulation scores were considered equivalent to their ON medication/OFF stimulation and ON medication/ON stimulation scores, respectively, at the six month follow-up. There was a reduction of 13.1 points (29%) in the Part III score with stimulation and without medication

and a reduction of 20.3 points (45%) with both stimulation and medication six months after the initial programming. A repeated measures ANOVA revealed a significant main effect of testing condition (off or on stimulation/medication) on Part III MDS-UPDRS motor examination scores ($F_{(1,17)} = 121.9$; $p < 0.001$).

The Part IV subscore was significantly reduced by 7.1 points (74%) (Table 4). All of the items assessed in this section were improved at follow-up.

Because the fatigue item of the MDS-UPDRS Part I improved with STN DBS, but not the PFS score, a post-hoc analysis was performed. Using the Spearman rank correlation coefficient, we found a high correlation between baseline PFS score and the baseline fatigue item of the MDS-UPDRS Part I ($r = 0.75$, $p < 0.001$) but not between the 6 month PFS score and the 6 month MDS-UPDRS Part I fatigue score ($r = 0.43$, $p = 0.06$).

4. Discussion

A recent revision of the UPDRS, the MDS-UPDRS, has not been utilized in DBS studies previously, so it is unclear whether this scale could detect changes in motor and non-motor function following bilateral STN DBS. In the present study, we found that all 4 MDS-UPDRS subscale scores, encompassing both motor and non-motor symptoms, improved significantly from baseline evaluation to approximately 6 months after bilateral STN DBS. Our results suggest that the MDS-UPDRS is responsive to DBS treatment effects.

The Part III score, encompassing the motor examination, improved by 13.1 points (29%) with stimulation alone and by 20.3 points (45%) with both stimulation and medication at six months in our study. This reduction is consistent with the amount of improvement seen in the STN stimulation group at 6 months in the prospective, randomized VA Cooperative Study [10], which used the original UPDRS-III. We also found the MDS-UPDRS Part II subscore was reduced by 29% at six months. While the results for the original UPDRS-II in the VA Cooperative Study were not reported separately for STN and GPi stimulation, DBS reduced UPDRS-II in that study by 24% at six months compared to baseline. The items covered in MDS-UPDRS are similar to the original UPDRS for both Parts II and III [7, 11], so it is not surprising that our results are comparable. The new items in MDS-UPDRS-Part II compared to the original were “Doing hobbies and other activities” (item 2.8) and “Getting out of bed, a car or a deep chair” (item 2.11), but these individual items did not improve with DBS.

The MDS-UPDRS-Part IV, which assesses motor complications, is different from the original version [7, 11]. It adds 2 new items beyond the original UPDRS-IV: the “Functional impact of fluctuations” (item 4.4), which determines the degree to which motor fluctuations impact the daily life of someone with PD, and “Complexity of motor fluctuations” (item 4.5), which looks at the predictability of motor fluctuations in PD. Both of these items improved significantly at 6 months with STN DBS in our cohort, going from mild-moderate impact on performance of activities/social interaction and some off time, to minimal impact on activities and minimal off time.

The MDS revision of the original UPDRS completely overhauled Part I, which expanded from 4 items focusing on just mentation and mood to 13 items covering several non-motor aspects of PD [7]. In our study, the MDS-UPDRS-Part I subscore improved by 22.5% at the six month evaluation, suggesting that bilateral STN DBS improves non-motor symptoms as assessed by the MDS-UPDRS. Only a few studies have looked at the impact of DBS on non-motor symptoms in PD using a comprehensive non-motor symptom scale [12, 13]; most DBS studies have used validated scales for individual non-motor symptoms [14]. The comprehensive non-motor symptom scales used in these DBS studies include the Non-

Motor Symptom questionnaire (NMS-Q) [15] and the Non-Motor Symptom Scale (NMS-S) [16]. Both have recently been validated in the PD population [15, 16], but only the NMS-S rates the severity of non-motor symptoms [16]. The NMS-Q asks about the presence of various non-motor symptoms [15]. Hwynn et al. compared both scales from before surgery to approximately 1 year after DBS in 10 subjects, 9 of whom had STN implants [12]. The only significant improvements were in the frequency of sleep problems and severity of miscellaneous symptoms (pain, anosmia, weight change, and sweating) and cardiovascular/falls. Nazzaro et al. [13], reporting on 24 patients with bilateral STN DBS, found a reduction from 12 non-motor symptoms at baseline to a mean of 7 symptoms one year after DBS, with subjects reporting less autonomic symptoms in general after surgery. Individual items in the MDS-UPDRS-Part I that improved in our study included constipation and light-headedness, both autonomic symptoms, consistent with the findings from Nazzaro et. al, [13]. The improvement in light-headedness could easily be explained by post-operative reduction in dopaminergic medications, which are known to cause orthostasis. Constipation is less likely to be a medication effect, as it can be present even before the onset of motor symptoms [17].

Fatigue, as assessed with the MDS-UPDRS, significantly improved at the six month evaluation in our study, yet there was no change between baseline and six months on the PFS, a PD-specific fatigue scale [18]. Responsiveness of the PFS to change has not been previously evaluated, so it may be that the PFS is unable to detect improvement in fatigue severity with treatment [19]. We found that the PFS and MDS-UPDRS fatigue item scores were highly correlated at baseline but not at 6 months, which would support this argument. We previously looked at fatigue in an earlier cohort of DBS patients pre- and post-operatively using the PFS and found that fatigue severity did not change overall with STN stimulation [20]. However, some subjects in that study had dramatic improvements in their PFS score after DBS, so it may be that the PFS cannot detect small changes in fatigue while the MDS-UPDRS fatigue item can. In a study by Gallagher et al. validating the MDS-UPDRS Part I with individual non-motor scales, the fatigue item correlated highly ($r=0.61$) with the Fatigue Severity Scale, which has been proven to be responsive to change [21]. Studies involving more subjects who have completed the fatigue item on the MDS-UPDRS, the PFS, and the Fatigue Severity Scale will be needed to clarify this issue.

5. Conclusions

We found that both motor and non-motor symptoms as assessed by the MDS-UPDRS improve with bilateral STN DBS six months after the DBS is turned on. To our knowledge, previous DBS studies have not used the MDS-UPDRS at baseline and post-DBS to track clinical symptoms. Although our sample size was small, the amount of improvement in motor symptoms from STN DBS in our study was similar to the amount of improvement reported in a large randomized trial of DBS that used the original UPDRS [10]. The MDS-UPDRS has advantages over the original UPDRS in that it more comprehensively assesses non-motor symptoms, and our results suggest that the MDS-UPDRS can detect some of these changes. Because the MDS-UPDRS demonstrates quantitative motor improvement following an intervention considered to improve PD and can potentially detect non-motor changes, we recommend that the MDS-UPDRS be utilized in future DBS studies. Future studies will be needed to confirm our findings and to see if the improvement in non-motor symptoms as assessed by the MDS-UPDRS can be maintained long-term.

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Table 1

MDS-UPDRS Part I scores before and after bilateral STN DBS in 20 PD subjects

	Baseline	Post-DBS	Z	p
	(mean ± SD)	(mean ± SD)		
1.1. Cognitive impairment:	0.8 ± 1.2	0.7 ± 1.2	-0.1	0.890
1.2. Hallucinations and psychosis:	0 ± 0	0.1 ± 0.3	-1.4	0.160
1.3. Depressed mood:	0.9 ± 1.3	0.8 ± 1.2	-0.2	0.860
1.4. Anxious mood:	1.1 ± 1.1	0.7 ± 0.8	-1.4	0.160
1.5. Apathy:	0.5 ± 0.9	0.5 ± 0.8	-0.2	0.860
1.6. DDS:	0.4 ± 0.7	0.4 ± 0.7	-0.3	0.780
1.7. Sleep problems:	2.0 ± 1.1	1.5 ± 1.1	-1.3	0.198
1.8. Daytime sleepiness:	1.7 ± 0.8	1.4 ± 0.8	-1.3	0.198
1.9. Pain:	1.8 ± 1.2	1.4 ± 1.0	-1.2	0.247
1.10. Urinary problems:	0.7 ± 0.8	1.1 ± 1.2	-1.5	0.136
1.11. Constipation:	1.3 ± 1.1	0.8 ± 1.0	-2.2	0.030 *
1.12. Light headedness:	0.9 ± 0.8	0.4 ± 0.8	-2.0	0.046 *
1.13. Fatigue:	1.9 ± 1.3	1.2 ± 0.7	-2.3	0.021 *
Total	13.8 ± 6.3	10.7 ± 4.7	-2.0	0.048 *

*
p<0.05

Table 2

MDS-UPDRS Part 2 scores before and after bilateral STN DBS in 20 PD subjects

	Baseline	Post-DBS	Z	p
	(mean ± SD)	(mean ± SD)		
2.1. Speech:	1.5 ± 1.0	1.8 ± 1.0	-1.0	0.320
2.2. Saliva and drooling:	1.6 ± 1.2	1.5 ± 1.4	-0.7	0.470
2.3. Chewing and swallowing:	0.7 ± 0.7	0.5 ± 0.5	-1.5	0.130
2.4. Eating tasks:	1.1 ± 0.9	0.6 ± 0.8	-1.7	0.080
2.5. Dressing:	1.4 ± 0.8	1.2 ± 1.1	-0.7	0.490
2.6. Hygiene:	0.7 ± 0.6	0.4 ± 0.6	-1.7	0.080
2.7. Handwriting:	1.3 ± 1.0	1.7 ± 1.4	-1.2	0.220
2.8. Hobbies:	1.8 ± 1.2	1.2 ± 1.0	-1.8	0.070
2.9. Turning in bed:	1.2 ± 0.7	0.6 ± 0.6	-2.4	0.020 *
2.10. Tremor:	2.1 ± 1.4	0.6 ± 0.7	-3.5	0.001 *
2.11. Getting up:	1.7 ± 1.2	1.5 ± 1.1	-0.7	0.516
2.12. Walking and balance:	1.7 ± 1.3	1.5 ± 1.3	-0.8	0.450
2.13. Freezing:	1.3 ± 1.3	0.3 ± 0.6	-2.8	0.005 *
Total	18.4 ± 8.0	13.1 ± 16.6	-2.2	0.027 *

*
p<0.05

Table 3

MDS-UPDRS Part III before and after bilateral STN DBS in all conditions (n=20)

Baseline		Post-DBS			
(mean $\pm$ SD)		(mean $\pm$ SD)			
Off meds	On meds	Off meds/Off stim	Off meds/On stim	On meds/Off stim	On meds/On stim
45.6 $\pm$ 16.6	24.6 $\pm$ 13.4	54.4 $\pm$ 17.7	32.5 $\pm$ 14.8	38.2 $\pm$ 18.8	25.3 $\pm$ 12.5

Table 4

MDS-UPDRS Part IV before and after bilateral STN DBS in 20 PD subjects

	Baseline	Post-DBS	Z	p
	(mean ± SD)	(mean ± SD)		
4.1. Time with dyskinesias:	1.3 ± 1.1	0.5 ± 0.7 *	-2.6	0.010 *
4.2. Impact of dyskinesias:	1.0 ± 1.4	0.1 ± 0.2 *	-2.4	0.020 *
4.3. Off time:	1.5 ± 0.9	0.4 ± 0.6 *	-3.2	0.000 *
4.4. Impact of fluctuations:	2.5 ± 1.7	0.7 ± 1.1 *	-3.2	0.000 *
4.5. Complexity of fluctuations:	1.9 ± 1.2	0.6 ± 1.0 *	-3.1	0.000 *
4.6. Off-state dystonia:	1.5 ± 1.6	0.4 ± 0.5 *	-2.6	0.010 *
Total:	9.6 ± 4.4	2.5 ± 2.3 *	-3.8	0.000 *

*
p<0.05