

## Long-Term Results of a Multicenter Study on Subthalamic and Pallidal Stimulation in Parkinson's Disease

Elena Moro, MD, PhD,<sup>1\*</sup> Andres M. Lozano, MD, PhD,<sup>2</sup> Pierre Pollak, MD,<sup>3</sup>  
Yves Agid, MD,<sup>4</sup> Stig Rehncrona, MD,<sup>5</sup> Jens Volkmann, MD, PhD,<sup>6</sup> Jaime Kulisevsky, MD,<sup>7</sup>  
Jose A. Obeso, MD,<sup>8</sup> Alberto Albanese, MD, PhD,<sup>9,10</sup> Marwan I. Hariz, MD,<sup>11,12</sup>  
Niall P. Quinn, MD,<sup>11</sup> Jans D. Speelman, MD,<sup>13</sup> Alim L. Benabid, MD, PhD,<sup>3</sup>  
Valerie Fraix, MD,<sup>3</sup> Alexandre Mendes, MD,<sup>3</sup> Marie-Laure Welter, MD,<sup>4</sup>  
Jean-Luc Houeto, MD,<sup>4,14</sup> Philippe Cornu, MD,<sup>4</sup> Didier Dormont, MD,<sup>4</sup>  
Annalena L. Tornqvist, RN,<sup>5</sup> Ron Ekberg, MD,<sup>5</sup> Alfons Schnitzler, MD,<sup>15</sup>  
Lars Timmermann, MD,<sup>15,16</sup> Lars Wojtecki, MD,<sup>15</sup> Andres Gironell, MD,<sup>7</sup>  
Maria C. Rodriguez-Oroz, MD, PhD,<sup>8</sup> Jorge Guridi, MD,<sup>8</sup>  
Anna R. Bentivoglio, MD, PhD,<sup>10</sup> Maria F. Contarino, MD,<sup>10,13</sup>  
Luigi Romito, MD,<sup>9</sup> Massimo Scerrati, MD,<sup>10,17</sup> Marc Janssens, PhD,<sup>18</sup>  
and Anthony E. Lang, MD,<sup>1</sup>

<sup>1</sup>Toronto Western Hospital, Movement Disorders Center, University of Toronto and University Health Network, Toronto, Ontario, Canada

<sup>2</sup>Division of Neurosurgery, University of Toronto and University Health Network, Toronto, Ontario, Canada

<sup>3</sup>Service de Neurologie, CHU de Grenoble, Grenoble, France

<sup>4</sup>Hôpital de la Salpêtrière, Fédération de Neurologie, Paris, France

<sup>5</sup>Neurosurgery Service, Lund University Hospital, Lund, Sweden

<sup>6</sup>Neurologische Klinik der Christian-Albrecht-Universität, Kiel, Germany

<sup>7</sup>Department of Neurology, Sant Pau Hospital, Autonomous University of Barcelona, CIBERNED, Barcelona, Spain

<sup>8</sup>Department of Neurology and Neurosurgery, Clinica Universitaria and Medical School, University of Navarra, CIBERNED, Pamplona, Spain

<sup>9</sup>Istituto Nazionale Neurologico C. Besta and Università Cattolica, Milano, Italy

<sup>10</sup>Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Roma, Italy

<sup>11</sup>Institute of Neurology, Queen Square, London, UK

<sup>12</sup>Department of Neurosurgery, University Hospital of Northern Sweden, Umeå, Sweden

<sup>13</sup>Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands

<sup>14</sup>Service de Neurologie, CHU de Poitiers, University of Poitiers, Poitiers, France

<sup>15</sup>Department of Neurology and Institute of Clinical Neurosciences, Heinrich-Heine-Universität Duesseldorf, Duesseldorf, Germany

<sup>16</sup>Department of Neurology, University Hospital, Cologne, Germany

<sup>17</sup>Dipartimento di Neuroscienze, Sezione di Neurochirurgia, Università Politecnica delle Marche, Ancona, Italy

<sup>18</sup>Bakken Research Center, Maastricht, The Netherlands

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

\*Correspondence to: Dr. Elena Moro, Toronto Western Hospital, Movement Disorders Center, 399 Bathurst Street McL7-402, University of Toronto and University Health Network, Toronto, Ontario, M5T 2S8 Canada E-mail: elena.moro@uhn.on.ca

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**Abstract:** We report the 5 to 6 year follow-up of a multicenter study of bilateral subthalamic nucleus (STN) and globus pallidus internus (GPi) deep brain stimulation (DBS) in advanced Parkinson's disease (PD) patients. Thirty-five STN patients and 16 GPi patients were assessed at 5 to 6 years after DBS surgery. Primary outcome measure was the stimulation effect on the motor Unified Parkinson's Disease Rating Scale (UPDRS) assessed with a prospective cross-over double-blind assessment without medications (stimulation was randomly switched on or off). Secondary outcomes were motor UPDRS changes with unblinded assessments in off- and on-medication states with and without stimulation, activities of daily living (ADL), anti-PD medications, and dyskinesias. In double-blind assessment, both STN and GPi DBS were significantly effective in improving the motor UPDRS scores (STN,  $P < 0.0001$ , 45.4%; GPi,  $P = 0.008$ , 20.0%)

compared with off-stimulation, regardless of the sequence of stimulation. In open assessment, both STN- and GPi-DBS significantly improved the off-medication motor UPDRS when compared with before surgery (STN,  $P < 0.001$ , 50.5%; GPi,  $P = 0.002$ , 35.6%). Dyskinesias and ADL were significantly improved in both groups. Anti-PD medications were significantly reduced only in the STN group. Adverse events were more frequent in the STN group. These results confirm the long-term efficacy of STN and GPi DBS in advanced PD. Although the surgical targets were not randomized, there was a trend to a better outcome of motor signs in the STN-DBS patients and fewer adverse events in the GPi-DBS group. © 2010 Movement Disorder Society

**Key words:** deep brain stimulation; globus pallidus internus; Parkinson's disease; subthalamic nucleus

Significant improvements in quality of life and motor function have been obtained in the short-term and long-term with both subthalamic nucleus (STN) and globus pallidus internus (GPi) deep brain stimulation (DBS) in Parkinson's disease (PD).<sup>1-9</sup> In relatively short-term follow-up studies, trends to both less motor improvement and fewer complications have been observed with GPi-DBS,<sup>1,10,11</sup> findings which were supported by preliminary 12-month follow-up data from a randomized study of pallidal vs. STN stimulation<sup>12</sup> and by a comparison of the effects of bilateral STN- vs. bilateral GPi-DBS in patients operated on both targets.<sup>13</sup> In the long-term, a multicenter DBS study reported significant benefits with both targets at 4 years.<sup>2</sup> The only study with 5-year follow-up data in patients with GPi-DBS reported a progressive loss of initial benefit in 11 bilateral GPi-DBS patients, leading to subsequent successful bilateral STN-DBS implantation in 4 of them.<sup>14</sup> In contrast, the larger number of studies with STN-DBS suggests that these patients continue to obtain a significant benefit in the long-term.<sup>15-17</sup> These observations emphasize the importance of long-term follow-up studies for both targets.

This article reports 5- to 6-year follow-up data of the previously reported multicenter DBS trial<sup>1,2,18</sup> on STN- and GPi-DBS in advanced PD.

## PATIENTS AND METHODS

### Patients

The main aim of this study was to evaluate the effects of bilateral STN- and GPi-DBS in patients with advanced PD followed for a minimum of five and a maximum of 6 years. Of 160 patients with PD initially

recruited from 18 centers as part of a nonrandomized, multicenter study,<sup>1</sup> 134 patients were implanted with bilateral STN- or GPi-DBS between January 1996 and July 1998. Criteria of inclusion and exclusion, initial outcome at 3- and 6-month follow-up and the surgical procedure have previously been reported.<sup>1</sup> One hundred and five patients from eight surgical centers later agreed to participate in the extension (up to 5-6 years) of the initial study. The results of 69 patients with bilateral STN (49 patients) and GPi (20 patients) DBS at 3 to 4 year follow-up have also been reported earlier.<sup>2,18</sup>

Fifty-one patients (35 with STN-DBS and 16 with GPi-DBS) were available at the 5 to 6 year follow-up. The Figure 1 illustrates the steps of the trial and the reasons for the subsequent drop outs.

The study was approved by each local ethics boards and all patients gave written informed consent to the study extension.

### Study Design

The study was initially designed as an open, non-randomized, prospective multicenter clinical trial aimed at evaluating safety and effectiveness of bilateral STN and GPi stimulation in patients with advanced PD.<sup>1</sup> The study planned a randomized double-blind evaluation with cross-over on the second day of the 3-month follow-up visit and unblinded assessments at 1-, 6-, and 12-month follow-up. A subsequent extension of the study was performed to obtain data from the long-term (3-4 years and 5-6 years) and from a double-blind randomized crossover assessment at 5-6 years.

105 enrolled patients at baseline	
<b>68 STN</b>	<b>37 GPi</b>
4 died	2 died
1 unilateral	2 change of target
3 lost to F-U	10 from uni- to bilateral
2 consent withdrawn	1 consent withdrawn
4 other termination	2 other termination
4 from bilateral to unilateral	
1 explanted battery	

  

69 patients at 3-4 years evaluation <sup>2</sup>	
<b>49 bil STN at 3-4 year</b>	<b>20 bil GPi at 3-4 years</b>
10 died	1 change of target
2 consent withdrawn	1 lost to F-U
1 lost to F-U	2 other termination
1 other termination	

  

51 patients at 5-6 years evaluation	
<b>35 bil STN at 5-6 years</b>	<b>16 bil GPi at 5-6 years</b>
10 died	1 consent withdrawn
1 consent withdrawn	1 change of target
3 lost to F-U	1 from bi- to unilateral
	1 other termination

FIG. 1. The overall study profile.

As previously reported,<sup>1,2</sup> the patients were assessed before surgery in the *defined off* anti-PD medications (meds) condition (after 12-hour medication withdrawal) and in the *defined on* meds condition<sup>19</sup> after an acute levodopa (L-dopa) challenge. The same preoperative dose of L-dopa was used for all the postoperative assessments in on meds condition. At each postsurgery follow-up, patients were assessed using the previously reported four-condition schedule: off meds/off stimulation (stim) and on meds/off stim (after 60–120 minutes stim off), off meds/on stim and on meds/on stim (after 30–90 minutes stim on).<sup>2</sup>

In contrast with the 3 to 4 years assessment, the patients were also evaluated in a double-blind fashion with cross-over 1 or 2 days after the open 5 to 6 year follow-up assessment, using the same protocol used for the 3-month assessment.<sup>1</sup> After overnight discontinuation of both anti-PD medications and stimulation, patients were randomly assigned to have motor assessments with stimulation off for another 2 hours and after 2 hours after switching stimulation on (sequence A) or to the reverse sequence (first stimulation turned

on for 2 hours and then stimulation turned off for another 2 hours, sequence B).

Patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS)<sup>20</sup> and a dyskinesia rating scale.<sup>21,22</sup> Only the UPDRS part II (activities of daily living, ADL) and III (motor) and some UPDRS-III and IV subscores (see later) were analyzed in this study.

For the double-blind assessments, only the UPDRS motor score was analyzed. Anti-PD medications required before and after surgery were recorded and converted to L-dopa equivalent daily dose (LEDD).<sup>2</sup>

Adverse events (AEs) were defined and recorded as previously described.<sup>1,2,18</sup>

### Statistics

The primary outcome measure was the differences between the UPDRS motor scores in the off meds condition with and without stimulation in the double-blind crossover assessment. A mixed linear model was used to evaluate the effect of sequence, period, and stimulation. The analysis of the sequence effect and period effects assessed whether the stimulation intervention in the first assessment influenced the results acquired in the second.

Secondary outcome measurements included changes in the UPDRS part II and III scores in the stim on condition between preoperative (baseline) and postoperative follow-up at 3 to 4 and 5 to 6 years in off and on meds conditions. Some subscores of the motor UPDRS were analyzed separately: speech (item 18), tremor (items 20 and 21), rigidity (item 22), akinesia (items 23–26), postural stability (item 28), and gait (item 29). Other secondary outcomes were changes in dyskinesia scores (UPDRS-IV, items 32, 33, 34, and 35) and changes in the LEDD compared with before surgery and at the two latest follow-ups and changes of the parameters of stimulation between 3 to 4 and 5 to 6 years.

As normality could not be assumed in the relatively small STN and GPi groups of patients, nonparametric testing was used. The type 1 error limit was set to 0.025 to account for multiple comparisons.

Regression analysis was performed to assess possible preoperative factors predictive of benefit or failure in both STN and GPi patients. Stepwise model-selection multiple-regression method was used to predict motor scores on the basis of four independent variables: preoperative L-dopa response, surgical target, age, and disease duration at time of surgery.

Data are presented as both medians (and quartiles) and means (with Standard Errors). All *P*-values are

**TABLE 1.** Main baseline clinical characteristics of the patients with PD involved in the long-term study

	STN (n = 35)	GPi (n = 16)
Gender, M/F	17/18	11/5
Age at surgery (yr)	59.6 (54.1–64.9); 59.3 (1.6)	54.4 (48.8–63.9); 56.0 (2.1)
Duration of follow-up (yr)	5.2 (4.9–5.5); 5.3 (0.1)	5.5 (5.2–5.9); 5.6 (0.1)
Duration of PD since onset (yr)	13.5 (10.9–22.7); 15.3 (1.1)	13.2 (11.6–17.5); 15.1 (1.5)
Duration of PD since diagnosis (yr)	12.6 (10.0–16.7); 14.1 (1.0)	12.6 (10.1–17.5); 14.0 (1.3)
UPDRS-II		
Off medication	32.5 (24.5–36.0); 30.0 (1.3)	26.8 (21.0–33.5); 26.7 (2.3)
On medication	8.5 (5.0–14.0); 10.4 (1.1)	9.8 (6.5–18.5); 12.0 (1.6)
UPDRS-III		
Off medications	56.5 (42.0–69.0); 56.0 (2.7)	52.5 (44.8–61.0); 52.2 (3.5)
On medication	24.5 (13.3–31.3); 22.9 (1.8)	16.5 (11.0–20.0); 18.5 (2.8)
Hoehn & Yahr, off medications	5.0 (4.0–5.0); 4.4 (0.1)	4.0 (3.0–4.5); 3.9 (0.2)
Dyskinesias <sup>a</sup>		
Off dystonia	0.5 (0.0–2.0); 1.0 (0.2)	0.0 (0.0–0.5); 0.6 (0.3)
On dyskinesia	2.0 (1.0–3.0); 2.1 (0.2)	3.0 (2.0–4.0); 2.8 (0.3)
LEDD (mg)	1,475 (1,025–2,050); 1,709.3 (166.8)	1,275 (913–1,998); 1,417.8 (153.0)

<sup>a</sup>Using the Dyskinesia Scale from Langston<sup>21</sup> and Goetz.<sup>22</sup>

Data are presented as both median (values in parentheses are lower and upper quartiles) and mean (values in parenthesis are the standard errors). LEDD, levodopa equivalent daily dose.

two-tailed. The analysis was performed using SAS release 8.02.

## RESULTS

Evaluations were performed between March 2001 and September 2003. The median follow-up for all patients was 5.3 (5.0–5.7) years. The main clinical characteristics at time of surgery of the 51 patients with PD with 5 to 6 year follow-up are summarized in Table 1.

Fifty-four (51.4%) of the initial 105 patients were lost to follow-up at the 5 to 6 year period (Fig. 1). Details about patient drop out during the first 3 to 4 year follow-up have been published.<sup>2,18</sup> Compared with the 3 to 4 year evaluation, 18 more patients exited the study before the 5 to 6 year assessment (Fig. 1). Among these patients, 10 STN patients died (1 of a stroke, 1 after fracture, 8 for unknown reasons), 3 STN patients were lost to follow-up, 1 STN and 1 GPi patient withdrew their consent, 1 GPi patient with sub-optimal clinical benefit underwent bilateral STN-DBS, 1 bilateral GPi-DBS patient remained with unilateral stimulation, and 1 GPi patient had leads and batteries explanted and not replaced.

### Long-Term STN Stimulation

Data were available on the 5 to 6 year double-blinded evaluation in 31 of 35 patients and nonblinded assessments in all 35.

The electrical parameters of stimulation were unchanged compared with the 3 to 4 year follow-up.<sup>2</sup>

Fourteen patients (40%) had battery replacement (bilateral replacement in 11 patients and unilateral in 3 patients) between the two time points, with a mean battery lifetime of  $4.6 \pm 0.7$  years.

### Double-Blind Evaluation (Cross-Over)

Table 2 shows the main results of the assessments at 5 to 6 years compared with the 3-month follow-up. The UPDRS motor scores at 5 to 6 years remained significantly improved (45.4%;  $P < 0.0001$ ) comparing the on and the off stim conditions. There were no significant sequence effects or carry-over effects ( $P = 0.131$ ).

### Unblinded Evaluation

Table 3 and Supporting Information Table 1 show the main results of the unblinded assessments at 5 to 6 years.

In the off meds condition, the total UPDRS motor scores were significantly ( $P < 0.001$ ) improved by stimulation (50.5%) when compared with baseline. However, there was a significant decline in this benefit when compared with the 3 to 4 year follow-up scores (Table 3). Overall, stimulation at 5 to 6 years significantly improved the main off meds UPDRS-III subscores (tremor by 81.1%, rigidity by 59.1%, akinesia by 30.8%, postural stability by 66.6%, and gait by 33.3%), with the exception of speech (Supporting Information Table 1). Akinesia subscores improvement declined significantly when compared with the 3 to 4 year follow-up. The UPDRS-II total scores and early morning dystonia scores also significantly improved at

**TABLE 2.** UPDRS motor scores in double-blind randomization using sequence evaluations at 3-month and 5–6 year follow-up for STN and GPi patients (off medications)

	Motor scores			
	STN (31 patients)		GPi (15 patients)	
	3 months	5–6 years	3 months	5–6 years
Off stimulation	54.0 (40.0–63.0)	55.0 (43.0–66.0)	49.0 (36.0–60.0)	35.0 (30.5–67.0)
	51.5 (3.1)	52.7 (3.2)	48.7 (4.8)	43.9 (4.6)
On stimulation	21.0 (15.0–33.0)	30.0 (19.0–43.0)	27.0 (21.0–46.0)	28.0 (21.0–46.0)
	23.7 (2.2)	30.1 (2.5)	32.3 (3.9)	32.6 (4.6)
<i>P</i> -value	<0.0001	<0.0001	0.004	0.008

Data are presented as both median (values in parentheses are lower and upper quartiles) and mean (values in parenthesis are the standard errors). Using a mixed linear model, sequence, and period effects were not significant, thus the comparison was made between on and off stimulation. The 3-month data are presented on only those patients undergoing 5–6 years evaluation.

5 to 6 years (49.2%) compared with baseline, without any change with respect to the 3 to 4 year follow-up (Table 3). There was no significant worsening of the motor UPDRS scores over the years in off meds/off stim condition when compared with baseline (Table 3).

In the on meds condition, stimulation did not further improve the motor UPDRS scores at 5 to 6 years when compared with baseline and there was a significant decrease in the improvement achieved at 3 to 4 year follow-up (Table 3). Among the UPDRS motor subscores, only rigidity was significantly improved by 5 to 6 year stimulation (25.0%) when compared with baseline, whereas speech and gait showed a significant worsening (Supporting Information Table 1). No change was observed in the other subscores. Initial improvement in akinesia and gait scores declined significantly at 5 to 6 years when compared with the 3 to 4 year time point. There was a significant worsening of the total UPDRS-II scores when compared with both baseline and 3 to 4 year follow-up (Table 3). Dyskinesia scores (total, duration, and disability) were significantly improved at 5 to 6 years compared with baseline (by 83.3%, 75%, and 100%, respectively) and unchanged when compared with 3 to 4 years (Supporting Information Table 1). Although in the on meds and off stim condition the motor UPDRS scores significantly deteriorated over the years, stimulation added a significant benefit to the total on meds motor scores at 5 to 6 years (26.0%,  $P = 0.001$ ) (Table 3).

LEDD was significantly reduced at 5 to 6 years compared with baseline (29.7%) (Supporting Information Table 1).

Only the preoperative L-dopa response (i.e., the difference between on and off meds UPDRS motor scores during the acute L-dopa challenge) was positively correlated with the motor improvement at the 5 to 6 year follow-up ( $P = 0.0098$ ).

### Adverse Events

Three hardware-related AEs were observed: one lead was replaced in 2 patients and one battery plus extension was replaced in another. Table 4 shows the number and type of non-hardware-related AEs reported as unresolved at the last follow-up.

### Long-Term GPi Stimulation

Data related to the double-blind evaluations at 5 to 6 years were available for 15 of 16 patients and open assessments in all 16. The electrical parameters of stimulation and the electrode contacts of stimulation were unchanged at 5 to 6 years when compared with the 3 to 4 year follow-up<sup>2</sup> and 8 (50%) patients had battery replacement (7 bilateral and 1 unilateral replacements), with a mean battery lifetime of  $4.5 \pm 0.7$  years.

### Double-Blind Evaluation

Table 2 shows the main results of the UPDRS motor assessments at 5 to 6 years compared with the 3-month follow-up in the same group of patients. The UPDRS motor scores improvement between off and on stim conditions was significant (20.0%;  $P = 0.008$ ). There were no significant sequence effects or carry-over effects ( $P = 0.21$ ).

### Unblinded Evaluation

Table 3 and Supporting Information Table 2 show the main results of the unblinded assessments at 5 to 6 years.

In the off meds condition, the total UPDRS motor scores were significantly improved by stimulation at 5 to 6 years compared with baseline (35.6%). This improvement was stable when compared with the 3 to 4 year scores (Table 3). However, tremor and rigidity subscores were the only motor UPDRS items

**TABLE 3.** Main results of STN and GPi stimulation on the total scores of the UPDRS part II and III in off and on medication conditions (unblinded evaluations)

Target and condition	UPDRS-III total scores			P-value	
	Baseline	3–4-years	5–6 years	5–6 years vs. baseline	5–6 years vs. 3–4 years
STN (n = 35)					
Off medication					
UPDRS-II total	32.5 (24.8–36.0) 30.0 (1.3)	15.0 (12.0–24.0) 17.3 (1.6)	16.5 (14.5–23.5) 18.7 (1.4)	<0.001	0.061
UPDRS-III total					
Off stimulation	56.5 (42.0–69.0) 56.0 (2.7)	57.0 (47.0–65.0) 54.7 (2.9)	57.0 (42.0–69.0) 54.3 (3.0)	0.196	0.797
On stimulation		26.0 (16.0–31.0) 25.8 (2.7)	28.0 (22.0–42.0) 30.8 (2.9)	<0.001	<0.001
On medication					
UPDRS-II total	8.5 (5–14) 10.4 (1.2)	11.0 (6.0–16.0) 12.7 (1.6)	14.0 (10.0–19.0) 14.7 (1.3)	<0.001	0.001
UPDRS-III total					
Off stimulation	24.5 (13.3–31.3) 22.9 (2.0)	21.5 (11.5–43.0) 28.1 (3.8)	29.0 (17.5–48.0) 32.9 (3.8)	<0.001	0.003
On stimulation		15.0 (6.0–30.0) 18.6 (2.6)	23.0 (11.0–33.0) 24.6 (2.9)	0.261	<0.001
GPi (n = 16)					
Off medication					
UPDRS-II total	26.8 (21.0–33.5) 26.7 (2.3)	17.5 (13.0–21.5) 17.3 (2.1)	17.0 (10.0–31.0) 19.8 (2.8)	0.024	0.207
UPDRS-III total					
Off stimulation	52.5 (44.8–61.0) 52.2 (3.5)	44.0 (40.5–59.5) 48.4 (2.9)	47.0 (39.0–61.5) 48.8 (3.5)	0.792	0.772
On stimulation		29.5 (24.0–41.0) 31.2 (3.1)	33.0 (21.0–49.0) 33.9 (4.4)	0.002	0.382
On medication					
UPDRS-II total	9.8 (6.5–18.5) 12.0 (1.6)	10.0 (4.5–16.5) 10.9 (2.0)	12.0 (6.5–18.0) 14.5 (2.5)	0.165	0.002
UPDRS-III total					
Off stimulation	16.5 (11.0–20.0) 18.5 (2.8)	19.0 (9.0–33.0) 21.7 (3.9)	20.0 (16.0–32.0) 26.0 (3.9)	0.008	0.013
On stimulation		16.5 (7.5–27.0) 16.6 (3.0)	19.5 (15.0–25.0) 21.6 (3.2)	0.375	0.01

Data are presented as both median (values in parentheses are lower and upper quartiles) and mean (values in parenthesis are the standard errors). The *P*-values were calculated using the Wilcoxon signed rank test. Bonferroni correction was used to issue testing multiplicity. Type 1 error was set to 0.025.

significantly improved at 5 to 6 years (Supporting Information Table 2) (65.5% and 41.7%, respectively). The UPDRS-II total scores were significantly improved at 5 to 6 years (36.7%) and stable compared with the previous 3 to 4 year scores (Table 3). No difference was observed in early morning dystonia scores. There was no significant worsening of the motor UPDRS scores over the years in off meds/off stim conditions.

In the on meds condition, stimulation did not further improve the motor UPDRS at 5 to 6 years when compared with baseline and there was a significant worsening between the scores at the 3 to 4 and 5 to 6 year time points (Table 3). None of the UPDRS motor subscores showed further improvement with stimulation (Supporting Information Table 2), whereas speech showed a significant worsening at 5

to 6 years compared with baseline and the 3 to 4 year follow-up. Although there was no significant worsening of the total UPDRS-II scores at 5 to 6 years compared with baseline, the difference was significant when compared with the 3 to 4 year follow-up (Table 3). Dyskinesia scores were significantly improved at 5 to 6 year stimulation compared with baseline (total 75.0%, duration 75.0%, and disability 100%), with no loss of this sustained benefit compared with 3 to 4 years (Supplementary Table 2). There was a significant worsening of the motor UPDRS scores over the years in on meds/off stim conditions (Table 3) and no additional benefit was seen when stimulation was added.

LEDD was not significantly reduced at 5 to 6 years compared with baseline (Supporting Information Table 2).

**TABLE 4.** Unresolved AEs present at 5-year follow-up in both STN and GPi patients

	STN (n = 35)	GPi (n = 16)
No of patients with AEs	26	8
Total no of AEs	47	11
Cognitive decline	8	2
Depression/anxiety	7	2
Hypersexuality	1	2
Speech difficulties	10	2
Balance disturbances	5	1
Gait disorders	9	1
Motor fluctuations	3	
Sleep disorders	4	

Only the preoperative L-dopa response was positively correlated with the motor improvement at 5 to 6 year stimulation ( $P = 0.0098$ ).

#### Adverse Events

One hardware-related AE and a lead fracture that required surgery were observed. Table 4 shows the number and the type of non-hardware-related AEs reported as unresolved at 5 to 6 years.

#### DISCUSSION

These long-term follow-up results of bilateral DBS in patients with advanced PD confirm the effectiveness of both STN- and GPi-DBS in improving L-dopa-responsive PD signs, L-dopa-induced dyskinesias, and ADL up to 5.7 years after surgery and show that the preoperative response to L-dopa predicts long-term benefit with both targets.

Both the double-blind and the open label clinical assessments documented a significant treatment effect of bilateral STN-DBS on the motor scores in off meds conditions. All the UPDRS motor subscores (except speech), the off-meds ADL, the early morning dystonia, and dyskinesias were also markedly improved and LEDD was greatly reduced. Some of the clinical benefit of STN DBS declined between 3 to 4 and 5 to 6 year follow-up, as previously reported,<sup>2,15-17</sup> probably related to a combination of the natural progression of PD and the parallel reduction of the L-dopa response.

Bilateral GPi-DBS was also significantly effective in improving motor PD signs in both the blinded and unblinded assessments. In particular, tremor and rigidity were significantly improved by stimulation in off meds condition, as were off meds ADL and dyskinesia scores. LEDD was unchanged at 5 to 6 years compared

with before surgery. There was no significant difference in stimulation benefit between the 3- and 5-year follow-up. However, as previous reported,<sup>14</sup> one patient (Fig. 1), who lost the DBS motor benefit between the 3 to 4 and 5 to 6 year follow-up, subsequently underwent successful bilateral STN DBS surgery. Although the reasons for this loss of GPi-DBS benefit are unclear, one possible explanation may be a suboptimal placement of the electrode inside the pallidum, which is larger than the STN and has more functional segregation.<sup>14</sup>

Both STN- and GPi-DBS patients showed deterioration of the L-dopa response at 5 to 6 years, suggesting a relationship more with the progression of PD<sup>2,15,17</sup> rather than with the target of stimulation, stimulation parameters, or medication dose reduction.<sup>23</sup>

Although the lack of initial randomization between the two target sites prevents direct comparison and possibly represents the major limitation of the study, treatment-related AEs were proportionally more frequent in the STN patients compared with the GPi patients over the 5 to 6 year evaluation period. A recent separate article has specifically addressed the DBS associated AEs at 3 to 4 years in this same group of patients.<sup>18</sup> Most of these AEs were unresolved at the 5 to 6 year follow-up.

Although over the 6-year duration of the study about 50% of the patients were lost to follow-up for various reasons, this is not an uncommon problem in clinical trials with patients with PD.<sup>24</sup> Proportionally more patients died in the STN group than in the GPi group. Although the reason for the mortality differences is unclear, no difference in mortality rate between patients with PD with and without STN-DBS has been reported.<sup>25</sup>

In summary, both STN and GPi DBS have been shown to be effective in improving motor PD signs with sustained benefit at the 5 to 6 year follow-up. STN-DBS patients obtained relatively greater benefit as measured by the magnitude and quality of the motor benefit and improvement in ADL, whereas GPi-DBS patients experienced fewer AEs. However, it is important to emphasize that this study was not designed to enable comparison between STN- and GPi-DBS in patients with advanced PD.

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