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Long-Term Effects of Pallidal or Subthalamic Deep Brain Stimulation on Quality of Life in Parkinson's Disease

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Abstract: We assessed the effects of deep brain stimulation of the subthalamic nucleus (STN-DBS) or internal pallidum (GPi-DBS) on health-related quality of life (HrQoL) in patients with advanced Parkinson's disease participating in a previously reported multicenter trial. Sickness Impact Profile (SIP) questionnaires were available for analysis in a subgroup of n = 20/20 patients with GPi-DBS and n = 45/49 patients with STN-DBS at baseline, 6 and 36 months. The SIP provides a physical dimension and a psychosocial dimension sum score and 12 category scores: Alertness/Intellectual Behavior (AIB), Ambulation (A), Body Care and Movement (BCM), Communication (C), Eating (E), Emotional Behavior (EB), Home Management (HM), Mobility (M), Recreation and Pastimes (RP), Sleep and Rest (SR), Social Interaction (SI), and Work (W). Motor functioning was assessed by means of the Unified Parkinson's Disease Rating Scale and diaries. At 6 months significant improvements in off-period motor symptoms and activities of daily living were paralleled by significant reductions in the total, physical, and psychosocial SIP score in both treatment groups. At 3 years, sustained improvements were observed in the physical dimension score, BCM, E, M, RP after STN-DBS and M, SI after GPi-DBS. All other SIP subscores approached baseline values, but were still the same or better (except C) whereas motor

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functioning remained stable after 36 months. STN-DBS and GPi-DBS led to significant early improvements in HrQoL. Despite sustained motor improvements many of these initial benefits were lost after 3 years. This may reflect either progression of the disease or adaptive changes in the subjective perception of health-related wellbeing over time. © 2009 Movement Disorder Society

Key words: quality of life; Parkinson's disease/parkinsonism; deep brain stimulation; subthalamic nucleus; globus pallidus

The long-term medical management of Parkinson's disease is often complicated by levodopa-induced motor fluctuations and dyskinesias. Deep brain stimulation (DBS) of the internal globus pallidus (GPi) or subthalamic nucleus (STN) are effective surgical treatments in advanced PD improving all cardinal motor symptoms and treatment-related motor complications.[1,2] Because DBS is a non-curative therapy for a chronically progressive neurodegenerative disorder, it is important to prove, that these symptomatic benefits outlast potential adverse effects of the procedure and have a positive impact on disability and quality of life.

The concept of health-related quality of life (HrQoL) was developed to evaluate the multidimensional, physical, psychological, and social aspects of wellbeing in a person.[3] Measurements of HrQoL are now widely used to assess and compare the global impact of medical therapies on impairment, disability, and handicap. Quality of life in PD patients is influenced by several motor and nonmotor aspects of the disease, such as disease severity, depression, sleep problems, pain, motor fluctuations, and age.[4,5] Progression of PD is associated with a decline in quality of life, but the exact longitudinal course and the contributing factors are not well established. Although HrQoL assessments have been included in a number of clinical trials for Parkinson's disease, little is known about the long-term effects of treatments on HrQoL.

The first large multicentre study on DBS in STN or GPi, which focused on the symptomatic effects of surgery at 3 to 6 month follow-up[6] and in a subset of patients at 3 to 4 years,[7,8] included the sickness impact profile (SIP), a widely used generic measure of quality of life. The aim of the present report is to analyze this prospective assessment of HrQoL and to discuss factors influencing the outcome in this group of patients.

METHODS

Patients and Methods

The patients, who suffered from advanced PD, had been operated on with bilateral DBS in either the GPi or the STN between January 1996 and July 1998, and were followed for 3 to 4 years in a multicentre protocol.[7] The aim of the present study was to assess the impact of bilateral DBS on HrQoL in a large group of patients followed for a minimum of 3 years. The parent trial, which was designed to blindly assess the effect of neurostimulation at 3 months postoperatively, had been conducted at 18 centres and included 143 patients.[6] A subgroup of patients was included in the long-term assessment as outlined elsewhere.[7] We confined this supplementary quality of life analysis to the same 69 patients reported in the recently published long-term efficacy study.[7] Of these patients, SIP questionnaires were available for analysis in a subgroup of n = 20/20 patients with GPi-DBS and n = 45/49 patients with STN-DBS at baseline, 6 and 36 months. The characteristics of the patients are summarized in Table 1. The institutional review board of each participating centre approved the follow-up protocol and all patients gave written informed consent. The details of patient selection, surgical procedure, and outcome at 3 to 6 months and at 3 to 4 years have been published.[6,7] The surgical target (either STN or GPi) was not randomized but was left to the discretion of each team according to their experience and clinical appreciation.[6,7]

Outcome Measures

In addition to the outcome criteria described in the companion publications,[6,7] HrQoL was assessed by the SIP, a 136-item generic measure of HrQoL in 12 cate-

TABLE 1. *Demographical data of the study population*

	STN-group (n = 45)	GPi-group (n = 20)
Sex*	22F/23M	7F/13M
Mean age at implant (y)*	58.5 (9.8)	55.8 (9.4)
Mean duration of follow-up (y)*	3.8 (0.6)	3.9 (0.7)
Mean duration of disease since onset*	15.3 (6.3)	15.4 (6.2)
Mean duration of disease since definite diagnosis*	13.9 (6.0)	14.4 (5.7)

Values in parentheses are SD.

*Fishers Exact-test or Mann-Whitney *U*-test (two-sided) were used to compare the STN and GPi-group at baseline. No statistical difference between groups was found for these variables.

gories: Alertness/Intellectual Behavior (AIB), Ambulation (A), Body Care and Movement (BCM), Communication (C), Eating (E), Emotional Behavior (EB), Home Management (HM), Mobility (M), Recreation and Pastimes (RP), Sleep and Rest (SR), Social Interaction (SI), and Work (W). The SIP questionnaire was filled out by the patients during the study visits. No interview with the patient or the caregiver was performed to verify or complete the self-rating of the patients. Aggregate scores can be calculated for the total SIP, the physical dimension (sum of BCM, M, and A) and the psychosocial dimension (sum of SI, EB, AIB, and C). By convention, scores are presented as a percentage of maximal dysfunction, ranging from 0 to 100%.

Statistics

The Wilcoxon Rank Sum test was applied for comparison between the individual scores preoperatively and at the follow-up visits. Pure discrete counting variables were compared using chi-square tests. The level of significance was 5% and all *P*-values reported are two-sided. Because the statistical analysis did not address one global answer of significance by multiple variables, a Bonferroni correction was not applied. Descriptive statistics, counts (n), quartiles, mean and standard deviation, or frequencies are reported where appropriate. Effect sizes (Cohen's d) were calculated for comparisons between baseline and follow-up measures. Effect sizes of ≥0.2 are generally considered as small, ≥0.5 as medium, and ≥0.8 as large. Effect sizes can also be interpreted in terms of the percent of nonoverlap in the two distributions. An ES of 0.8 indicates a nonoverlap of 47.4%. The analysis was performed using SAS release 8.02.

Role of the Funding Source

The sponsor (Medtronic Europe) and the participating centres designed and approved the protocol. Medtronic monitored the study and the data were entered into a validated database. A statistician used by the company (MJ) performed the statistical analyses according to the requests of the investigators. Finally, data were made available to the authors who independent of the sponsor assessed the analysis, interpreted the results, and wrote the manuscript.

RESULTS

Symptomatic Efficacy

Since the present article focuses on quality of life, we refer to the clinical efficacy article for details on the symptomatic effects of DBS.[7] The results in the subgroup of patients available for quality of life analysis are summarized in Table 2. At 3 to 4 year follow-up, STN-DBS improved off-period motor symptoms [Unified Parkinson's Disease Rating Scale (UPDRS) part III] by 50% and GPi-DBS by 39% compared to baseline. Dopaminergic medication was reduced only in the STN-DBS group. Dyskinesias improved significantly in both groups. As a result, activities of daily living (UPRDS II) in the off-period improved by 45% with STN-DBS versus 28% with GPi-DBS and motor fluctuations were reduced according to patient diaries in both groups.[7]

HrQoL

Both patient groups exhibited marked impairment in all aspects of HrQoL at baseline. The SIP domains most prominently affected by Parkinson's disease were HM, BCM, RP, and C (see Table 3).

Six months of neurostimulation improved the total SIP score by 48% in the GPi- and 45% in the STN-group. The changes were more pronounced in the physical (GPi: −49%, STN: −53%) than in the psychosocial domain score (GPi: −40%, STN: −39%), but significant in both (Fig. 1). Most SIP subscores exhibited significant improvements except for A and RP after GPi-DBS, AB after STN-DBS, and C or W after either treatment (Table 3).

The initial improvements in HrQoL as assessed by the total, physical, and psychosocial SIP declined in both groups significantly between 6 months and 3 to 4 years after surgery (Table 3, Fig. 1). However, compared to baseline, the average total SIP was still improved by 21% in the STN-group and 18% in the GPi-group at 3 to 4 years. This change from baseline was significant for DBS-STN, but not for GPi-DBS, probably owing to the smaller sample size in this group (Table 3, Fig. 1). The following SIP domains had retained a significant improvement at 3 to 4 years as compared to baseline: M in both groups, SI in GPi-DBS and BCM, E, and RP in STN-DBS.

To further characterize the pattern of change in HrQoL, we evaluated the distribution of total SIP-scores in the short- and long-term after surgery. Before surgery, no patient had a total SIP score below 6, which is considered the normal range of the general adult population and only one patient in the GPi-group had a total SIP score below 9 indicating relatively mild impairment. Six months after surgery, the proportion of patients within the score range <9 was 30% for GPi-DBS and 29% for STN-DBS. At 3 to 4 years,

TABLE 2. *Effect of pallidal and subthalamic stimulation on UPDRS scores on and off medication*

			P Value		*P* Value		Effect size (Cohen's d)	
	Baseline	6 mo (Stim On)	6 mo versus baseline	3–4 yr (Stim On)	3–4 yr versus baseline	3–4 yr versus 6 mo	6 mo versus baseline	3–4 yr versus baseline
GPi-DBS								
Off medication								
Activities of daily living (range, 0–52)	26.8 ± 8.9	16.5 ± 9.1	<0.001	19.2 ± 10.0	<0.02	ns	1.14	0.80
Total motor score (range, 0–108)	51.7 ± 13.6	31.9 ± 11.2	<0.0001	31.7 ± 12.8	<0.0001	ns	1.60	1.52
Tremor (range, 0–28)	11.3 ± 3.0	2.7 ± 2.1	<0.0001	1.7 ± 1.3	<0.02	ns	3.37	4.47
Rigidity (range, 0–20)	10.9 ± 3.8	7.1 ± 3.2	<0.001	6.8 ± 3.3	<0.001	ns	1.09	1.15
Gait (range, 0–4)	2.5 ± 1.0	1.6 ± 1.1	<0.02	1.8 ± 1.3	<0.02	ns	0.86	0.61
Bradykinesia (range, 0–32)	18.3 ± 4.6	12.7 ± 5.9	<0.02	12.9 ± 6.0	<0.02	ns	1.07	1.02
Postural Stability (range, 0–4)	2.3 ± 1.1	1.4 ± 1.0	<0.02	1.7 ± 1.1	ns	ns	0.86	0.55
Speech (range, 0–4)	1.5 ± .08	1.4 ± 0.7	ns	1.5 ± 0.7	ns	ns	0.26	0.00
Dyskinesias (range, 0–4)	0.70 ± 1.15	0.16 ± 0.50	ns	0.53 ± 0.77	ns	ns	0.65	0.18
On medication								
Activities of daily living (range, 0–52)	12.0 ± 7.2	8.7 ± 7.7	ns	12.2 ± 10.0	ns	<0.02	0.44	−0.02
Total motor score (range, 0–108)	18.6 ± 10.3	15.3 ± 10.6	ns	17.7 ± 13.0	ns	<0.05	0.32	0.08
Tremor (range, 0–28)	1.9 ± 2.5	0.4 ± 0.9	<0.02	0.4 ± 1.0	ns	ns	0.88	0.86
Rigidity (range, 0–20)	2.8 ± 4.0	2.7 ± 3.5	ns	2.7 ± 3.2	ns	ns	0.03	0.03
Gait (range, 0–4)	1.2 ± 1.0	0.7 ± 0.8	ns	1.1 ± 1.2	ns	<0.05	0.56	0.09
Bradykinesia (range, 0–32)	7.2 ± 4.3	6.7 ± 5.7	ns	7.8 ± 6.3	ns	ns	0.10	−0.11
Postural Stability (range, 0–4)	1.3 ± 0.9	0.9 ± 0.9	ns	1.2 ± 1.3	ns	ns	0.44	0.09
Speech (range, 0–4)	0.9 ± 0.8	0.9 ± 0.9	ns	1.1 ± 1.0	ns	ns	0.00	−0.22
Dyskinesias (range, 0–4)	2.83 ± 1.18	0.80 ± 0.77	$P < 0.0001$	0.68 ± 0.75	<0.0001	ns	2.08	2.23
STN-DBS								
Off medication								
Activities of daily living (range, 0–52)	30.4 ± 7.8	13.9 ± 7.1	<0.0001	16.6 ± 8.7	<0.0001	<0.001	2.21	1.67
Total motor score (range, 0–108)	56.7 ± 15.6	24.8 ± 14.1	<0.0001	26.6 ± 14.0	<0.0001	<0.001	2.15	2.03
Tremor (range, 0–28)	13.2 ± 4.3	2.2 ± 2.3	<0.0001	1.3 ± 1.8	<0.0001	ns	3.33	3.90
Rigidity (range, 0–20)	10.9 ± 4.0	4.4 ± 3.0	<0.0001	4.2 ± 3.5	<0.0001	ns	1.86	1.79
Gait (range, 0–4)	3.0 ± 1.0	1.0 ± 1.0	<0.0001	1.7 ± 1.1	<0.0001	<0.04	2.00	1.24
Bradykinesia (range, 0–32)	19.9 ± 6.6	10.7 ± 7.1	<0.0001	10.4 ± 7.0	<0.0001	ns	1.34	1.40
Postural Stability (range, 0–4)	2.7 ± 1.0	1.1 ± 0.9	<0.0001	1.7 ± 1.1	<0.0001	<0.001	1.68	0.95
Speech (range, 0–4)	1.9 ± 1.0	1.3 ± 0.9	<0.01	1.7 ± 1.0	ns	<0.01	0.63	0.20
Dyskinesias (range, 0–4)	0.95 ± 1.11	0.39 ± 0.57	<0.01	0.26 ± 0.69	<0.001	not done	0.67	0.77
On medication								
Activities of daily living (range, 0–52)	10.4 ± 6.8	9.1 ± 6.0	ns	12.2 ± 8.1	ns	<0.01	0.20	−0.24
Total motor score (range, 0–108)	21.7 ± 9.4	17.1 ± 11.8	<0.05	18.2 ± 12.9	ns	<0.01	0.43	0.31
Tremor (range, 0–28)	2.3 ± 3.2	0.6 ± 1.0	<0.01	0.3 ± 0.7	<0.001	ns	0.81	1.03
Rigidity (range, 0–20)	4.3 ± 2.7	2.9 ± 2.7	<0.02	2.6 ± 2.9	<0.01	ns	0.52	0.61
Gait (range, 0–4)	0.9 ± 0.8	0.6 ± 0.8	ns	1.1 ± 1.1	ns	ns	0.38	−0.21
Bradykinesia (range, 0–32)	8.4 ± 4.3	7.7 ± 6.3	ns	7.0 ± 6.0	ns	ns	0.13	0.27
Postural Stability (range, 0–4)	1.3 ± 0.8	0.9 ± 0.9	<0.05	1.4 ± 1.1	ns	<0.0001	0.47	−0.11
Speech (range, 0–4)	1.1 ± 0.9	1.2 ± 1.0	ns	1.6 ± 0.9	<0.002	<0.01	−0.11	−0.56
Dyskinesias (range, 0–4)	2.01 ± 1.05	0.82 ± 0.78	<0.0001	0.84 ± 0.76	<0.0001	not done	1.30	1.29

ns, not significant.

TABLE 3. *Effect of pallidal and subthalamic stimulation on health-related quality of life as assessed by the sickness impact profile total score and subdomain scores*

	Baseline		6 mo		*P*-value	3–4 yr		*P*-value		Effect size (Cohens's d)	
	mean	SD	mean	SD	0–6 mo	mean	SD	0–36 mo	6–36 mo	0–6 mo	0–36 mo
GPi-DBS											
SIP total	33	13	17	11	0.0001	27	14	ns	0.0011	1.33	0.44
SIP physical	35	15	18	17	0.0005	27	18	ns	0.014	1.06	0.48
SIP psychosocial	35	16	21	17	0.0041	31	15	ns	0.0010	0.85	0.26
A ambulation	29	17	18	20	ns	27	20	ns	ns	0.59	0.11
AB alertness behavior	35	24	24	26	0.012	32	29	ns	ns	0.44	0.11
BCM body care	38	19	16	17	0.0007	28	20	ns	0.010	1.22	0.51
C communication	37	29	35	27	ns	51	32	ns	ns	0.07	−0.46
E eating	11	13	0	0	0.001	7	12	ns	ns	1.69	0.32
EB emotional behavior	31.0	24	15	21	0.0024	27	26	ns	ns	0.71	0.16
HM home management	46.0	27	28	26	0.0077	35	31	ns	ns	0.68	0.38
M mobility	35	16	22	19	0.0010	22	19	0.012	ns	0.74	0.74
RP recreation past time	38	21	29	24	ns	39	24	ns	ns	0.40	−0.04
SI social interaction	35	18	16	15	0.0008	24	18	0.029	ns	1.15	0.61
SR sleep rest	35	23	18	17	0.016	29	21	ns	ns	0.85	0.27
STN-DBS											
SIP total	33	13	18	12	<0.0001	26	14	0.039	<0.0001	1.20	0.52
SIP physical	38	16	18	14	<0.0001	28	18	0.014	<0.0001	1.33	0.59
SIP psychosocial	33	18	20	16	<0.0001	28	18	ns	0.0003	0.76	0.28
A ambulation	34	17	19	17	<0.0001	30	18	ns	0.027	0.88	0.23
AB alertness behavior	31	25	21	23	ns	30	31	ns	ns	0.42	0.04
BCM body care	41	20	18	15	<0.0001	29	22	0.023	0.014	1.31	0.57
C communication	39	33	29	27	ns	43	29	ns	0.063	0.33	−0.13
E eating	12	13	5	7	<0.0001	9	16	0.027	ns	0.70	0.21
EB emotional behavior	29	23	12	17	0.0001	22	22	ns	ns	0.85	0.31
HM home management	42	23	25	22	0.0001	35	25	ns	0.035	0.76	0.29
M mobility	35	20	18	19	<0.0001	25	23	0.0024	ns	0.87	0.47
RP recreation past time	45	25	26	28	<0.0001	29	23	0.011	ns	0.72	0.67
SI social interaction	33	18	18	19	<0.0001	24	18	ns	0.053	0.81	0.50
SR sleep rest	35	24	16	17	<0.0001	27	24	ns	ns	0.93	0.33

ns, not significant.

10% versus 19% of patients within the two groups remained within this range. In general, the total SIP score improved by at least one 10 point category from baseline to 6 months in 82% of GPi- and 75% of STN-stimulated patients. At 3 to 4 years, 55% versus 57% of the patients were still improved according to this definition, whereas 3 (15%) patients in the GPi-group and 10 patients (22%) in the STN-group had worsened by at least one category compared to baseline.

Predictors of Outcome in HrQoL

To analyze which baseline variables were associated with a better outcome in HrQoL, we tried to explain the physical and psychosocial SIP score at 6 months after surgery, using multiple linear regression analyses, with the following candidate regressors: age, duration of disease, UPDRS I, UPDRS part II in on and off, UPDRS part III in on and off, UPDRS part IV, and the physical and psychosocial SIP at baseline. Both patient groups were pooled to increase the power of this analysis. The best regression terms selected by a stepwise, backward and adjusted-$R2$ method were: Physical SIP (6 month) = $-0.19757 + 0.0037 * \text{age} + 0.0106 * \text{UPDRS II ON} + 0.0250 * \text{UPDRS IV}$ ($R2 = 54.1\%$) and Psychosocial SIP (6 month) = $-0.05947 + 0.32755 * \text{psychosocial SIP (baseline)} + 0.01159 * \text{UPDRS II} + 0.01368 * \text{UPDRS IV}$ ($R2 = 62.7\%$). In other words, younger age, less impairment in the activities of daily living in the on-state, and a lower UPDRS IV score at baseline predicted a lower physical SIP at 6 months after surgery. After 3 to 4 years, age remained the only significant predictor, which explained 22% of the variance. A lower psychosocial SIP before surgery was an additional predictor for better psychosocial functioning after surgery at 6 months and 3 to 4 years.

Impact of Adverse Effects on HrQoL After Surgery

The proportion of patients suffering from non-surgical and non-device related adverse events increased

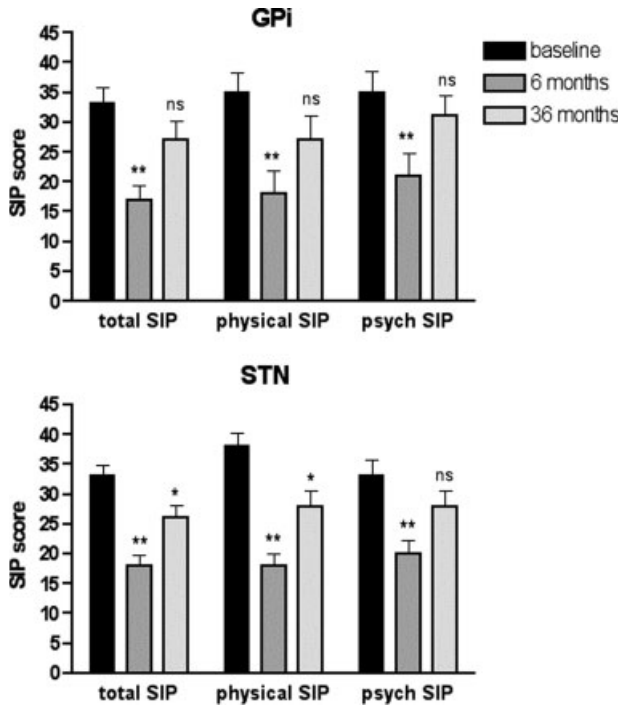

FIG. 1. Evolution of the total SIP, physical SIP, and psychosocial SIP score from baseline to 6 and 36 months after surgery. Bars denote the group mean and whiskers the standard error of the mean. $^{**}P < 0.01$, $^{*}P < 0.05$, ns: not significant compared to baseline (Wilcoxon Rank Sum test, two-tailed).

between the 6-month and 3- to 4-year visit. At the final visit, 53% of STN-DBS patients and 35% of GPi patients reported at least one (adverse effect) AE, although most of them were not deemed severe.[7,8] The most common AE included cognitive decline, dysarthrophonia, poor balance, gait disorders, and depression.[7] To analyze the impact of the most common types of AE onto HrQoL they were categorized into the following three groups: neuropsychiatric AE (memory decline, psychiatric disturbance, depression, apathy, mood disturbances, and hypersexuality), speech and swallowing AE (speech difficulties, dysphonia, dysarthria, and dysphagia), and gait and balance AE (disequilibrium, falls, and balance disturbance). The analysis had to be restricted to STN-DBS, because only a small proportion of GPi-patients exhibited any AE within the three categories defined above.[8]

At 3 to 4 years, total SIP ($P = 0.01$), psychosocial SIP ($P < 0.01$), and SIP subscore SI ($P = 0.03$) differed significantly between STN-DBS patients experiencing or not experiencing a neuropsychiatric AE. There was also a tendency for a higher physical SIP in patients suffering from a neuropsychiatric AE ($P = 0.09$). However, no significant group effects on the total SIP or subscores were found for patients with or without AE, affecting speech and swallowing or gait and balance.

DISCUSSION

Patients included into this first controlled, prospective, multicenter evaluation of GPi- or STN-DBS in Parkinson's disease suffered from a markedly impaired HrQoL at baseline, which becomes apparent when comparing the baseline total SIP scores to published score ranges of other clinical conditions. The general adult population has a total SIP score of about 5.[9,10] The average total SIP score for patients with a clinically relevant essential tremor was 6.3 $\pm$ 4.1 and 9.2 $\pm$ 0.3 in two previous studies.[10,11] A SIP score of 20 is found in patients with a poor outcome after stroke, who are unable to live independently and require assistance in their activities of daily living.[12] A score of greater than 30 indicates the need for almost complete care[9] and was found in a group of very frail elderly persons receiving home care.[13] Thus, an average total SIP score of 33 $\pm$ 13 at baseline in this study suggests, that a group of severely disabled patients was selected, most likely, because DBS was still considered an investigational therapy at study initiation and a last resort treatment. More remarkable are the pronounced early improvements in HrQoL in both treatment groups, which encompassed almost all domains with the exception of work and communication skills.

Our results are in line with several other open studies that found marked improvements in physical and psychosocial aspects of HrQoL after STN stimulation, using generic or Parkinson-specific scales.[14–19] A recent large short-term randomized controlled multicenter study compared HrQoL in a group of 156 patients with severe motor symptoms of Parkinson's disease, who were randomly assigned in pairs to receive either bilateral DBS of the STN in combination with medical treatment or best medical therapy alone.[20] At 6 months, an improvement of HrQoL (PDQ-39 score) by about 25% was only found in the surgically treated group, indicating that the symptomatic benefits of STN-DBS outlast the inherent surgical risks and lead to a more effective reduction of the burden of disease than optimal drug therapy. An extended observational period, however, is necessary to assess the stability of these results along the chronic course of PD.

The impact of pallidal DBS on HrQoL has been explored in only a few, small cohort studies. Straits-Tröster et al.[21] and Vingerhoets et al.[22] described significant benefits on the SIP at short-term after uni- or

bilateral GPi-DBS, which were within the range of this study. Durif et al. reported an annual follow-up of HrQoL measured by the disease-specific PDQ-39 questionnaire in six patients for up to 3 years after surgery. They showed that mobility, ADL, stigma, and communication categories were improved at the first year. However, in the long-term the improvement for the ADL category decreased from 30% at 1 year to 10% at the last assessment, and the other categories (mobility, stigma, and communication) returned to their baseline values.

Although the assignment to either STN- or GPi-DBS was not random and our study was not intended to compare the two therapies, the demographic baseline parameters of both treatment groups were quite comparable (see Table 1). Our observation of an almost identical early improvement of HrQoL in the STN- and GPi-group despite previously reported differences in the reduction of the off-period motor score or medication[6,7] suggests, that these outcome parameters are less relevant for subjective wellbeing, daily functioning, and social participation as assessed by the SIP scale.

Our study provides the longest follow-up of HrQoL so far in a relatively large number of GPi- or STN-DBS treated patients, who were followed in a prospective and controlled clinical trial. Despite a sustained improvement in off-period motor symptoms and activities of daily living, HrQoL declined and many of the initial improvements in subdomains of the SIP were no longer significant at 3 to 4 years after surgery, using group statistics. The analysis of the score distributions, however, indicated that the average decline was not a general phenomenon, but rather affected a subgroup of patients. At 3 to 4 years after surgery, 24% of patients treated by GPi-DBS and 40% of patients treated by STN-DBS had sustained their total SIP score category reached at 6 months after surgery. What might be factors associated with a more rapid decline in HrQoL in some patients as compared to others? Our multiregression analysis found that younger age, better functioning in ADL, less psychosocial impairment, and a lower motor complication score were associated with a better early outcome in HrQoL. This is consistent with the current view, that the role of surgery within the treatment algorithm of PD may need to be redefined,[23] because the goal of maintaining quality of life and preventing the psychosocial decline associated with PD may be better achieved in younger patients operated at an earlier stage of disease.[24,25]

The presence of neuropsychiatric adverse effects was associated with a significantly lower HrQoL in the STN-group at 3 to 4 years. This AE category included cognitive decline, apathy, or depression, which are the important determinants of functional status and quality of life in PD.[4,5,26] In general, non-motor symptoms of PD, such as mood disturbances, drive problems, pain, or sleep disorders, have an impact on HrQoL, which may equal or exceed the influence of motor impairment. Well-known motor problems after STN-DBS, such as poor gait, balance, or speech, had surprisingly little impact on HrQoL in this study. We therefore suspect that a progression in nonmotor domains of PD is primarily driving the decline in quality of life in the long-term after DBS surgery. This would be consistent with the pattern observed in two studies that evaluated the longitudinal course of HrQoL in medically treated PD patients.[27,28] Because our study did not include a control group and patients were not randomly assigned to the two treatment groups, we cannot reliably address whether stimulation was directly responsible for the appearance or persistence of neuropsychiatric or other nonmotor AEs. Nor can we address the impact of target site, medication changes, or disease progression on HrQoL. Another weakness of this study is the lack of a controlled evaluation of nonmotor symptoms. Future studies on HrQoL after DBS will need to address this issue using now available multidimensional rating scales for PD.

In this study, we used the generic SIP to assess HrQoL. A previous study used the generic SF-36 and the disease-specific PDQ-39 scale to assess long-term effects of STN-DBS on quality of life and found sustained gains after 18 months on several PDQ39 domains, but not on the SF-36.[29] Thus, reduced sensitivity of the generic measure SIP to the therapeutic effect on common impairments in PD may have contributed to some of the negative long-term results in this study. Moreover, the SIP has not been validated for longitudinal assessments of treatment effects. When patients are retrospectively evaluated after successful DBS, they tend to underestimate their preoperative level of disability, therefore obscuring the improvement in quality of life found prospectively.[30] This observation indicates that the subjective impression of impairment and disability may change over time. With improved motor functioning after surgery, patients may judge their own abilities based on the expectations that they did not have before surgery. Such a frame shift in the subjective perception of health related wellbeing over time might constitute another confounder of this long-term assessment.

Notwithstanding these limitations, we found sustained improvements in HrQoL at 3 to 4 years in a relatively large proportion of parkinsonian patients that

suffered from substantial disability at baseline despite best medical treatment. Future prospective studies are necessary to better delineate the factors associated with a more stable reduction of disability and improved HrQoL in the long-term. These studies need to include a control group to dissociate effects of treatment disease progression. Patient selection criteria for DBS, which are now primarily directed at predicting an optimal motor response after surgery, may need to be redefined and incorporate additional criteria in the future to better address the multidimensional aspects of HrQoL in PD.

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