

PAPER

Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease

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Aim: To assess the long-term cognitive and behavioural outcome after bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients affected by Parkinson's disease, with a 5-year follow-up after surgery.

Methods: 11 patients with Parkinson's disease treated by bilateral DBS of STN underwent cognitive and behavioural assessments before implantation, and 1 and 5 years after surgery. Postoperative cognitive assessments were carried out with stimulators turned on.

Results: A year after surgery, there was a marginally significant decline on a letter verbal fluency task ($p=0.045$) and a significant improvement on Mini-Mental State Examination ($p=0.009$). 5 years after surgery, a significant decline was observed on a letter verbal fluency task ($p=0.007$) and an abstract reasoning task ($p=0.009$), namely Raven's Progressive Matrices 1947. No significant postoperative change was observed on other cognitive variables. No patient developed dementia 5 years after surgery. A few days after the implantation, two patients developed transient manic symptoms with hypersexuality and one patient developed persistent apathy.

Conclusion: The decline of verbal fluency observed 5 years after implantation for DBS in STN did not have a clinically meaningful effect on daily living activities in our patients with Parkinson's disease. As no patient developed global cognitive deterioration in our sample, these findings suggest that DBS of STN is associated with a low cognitive and behavioural morbidity over a 5-year follow-up, when selection criteria for neurosurgery are strict.

Chronic bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective neurosurgical procedure for treatment of motor symptoms in patients with advanced Parkinson's disease, who cannot be satisfactorily treated with pharmacological treatments. The safety of this procedure has been investigated by several studies, which have assessed the effects of STN DBS on cognition and behaviour.^{1–3} Some investigations have also attempted to distinguish between the cognitive effects of surgical intervention and those of DBS of STN in itself.^{4–7}

All neuropsychological investigations in patients treated by STN DBS showed a postoperative decline of verbal fluency, whereas less consistent effects have been reported on other cognitive tasks in different studies. A postoperative decline of episodic verbal memory, which was detectable 3 months after surgery, has been reported in some investigations.^{6, 8}

Different effects of STN DBS on various frontal cognitive functions have been described. STN stimulation may impair response-inhibition performance on the interference task of the Stroop test, as compared with the off-stimulation condition.^{5, 7, 9} A positron emission tomography study showed that such impaired performance on the Stroop test in the on-stimulation condition is associated with decreased activation in both the right anterior cingulate cortex and the right ventral striatum.⁹ Conversely, short-term STN stimulation may improve performance on cognitive flexibility tasks, including random number generation⁷ and the Modified Wisconsin Card Sorting Test (MWCST).⁵

Various behavioural effects have been described in patients with Parkinson's disease treated by STN DBS. Some studies reported cases of depression¹⁰ or increased apathy,¹¹ whereas cases of mania were described in other studies^{12–14} and an improvement of depression¹ or apathy¹⁵ was also found.

The long-term cognitive and behavioural effects of bilateral STN DBS were investigated in 70 patients with Parkinson's disease followed up for 3 years.¹¹ In this study, a decline of verbal fluency, an improvement of depression and an increased apathy were observed 3 years after surgery. Some patients showed behavioural changes (aggressive behaviour, hypomania, depression and psychosis), which were mostly transient. Recently, the long-term outcome of bilateral DBS of STN was investigated in a multicentre study conducted in 49 patients with Parkinson's disease followed up for 3 or 4 years.¹⁶ This study showed that stimulation of the STN induced a significant improvement in Parkinsonian motor symptoms and activities of daily living 3–4 years after surgery. Among the adverse events, the authors reported memory decline or psychiatric disturbances (including hallucinations, delirium, depression, apathy and anxiety), which occurred in about 30% of the patients.

In two recent investigations, the long-term outcome of bilateral DBS of STN was investigated in patients with a 5-year follow-up.^{17, 18} In one study conducted on 49 patients with Parkinson's disease,¹⁷ cognitive performance was assessed by means of the Mattis Dementia Rating Scale (MDRS)¹⁹ and a frontal-lobe score.⁴ Five years after surgery, there was a marked improvement of both motor function, while off drugs, and activities of daily living, a statistical trend towards a decline on the MDRS (reflecting the appearance of progressive dementia in three patients between the third and the fifth postoperative years) and a significant decline in the average frontal-lobe

Abbreviations: DBS, deep brain stimulation; LEDD, levodopa-equivalent daily dose; MDRS, Mattis Dementia Rating Scale; MMSE, Mini-Mental State Examination; MWCST, Modified Wisconsin Card Sorting Test; RAVLT, Rey's Auditory Verbal Learning Test; RPM, Raven's Progressive Matrices; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale

score. Another study carried out on 37 patients with Parkinson's disease¹⁸ also assessed cognitive performance by means of MDRS¹⁹ and a frontal score.²⁰ Five years after the implantation, there was an improvement in Parkinsonian motor symptoms and activities of daily living and a reduction of levodopa-related motor complications and levodopa daily doses. However, a significant decline in cognitive performance was detected on the MDRS and the frontal score.

To our knowledge, no extensive neuropsychological data have been reported so far in patients with a follow-up >3 years. The aim of the present study was to assess the long-term cognitive and behavioural outcome after bilateral DBS of the STN in a series of patients followed up for 5 years after surgery.

METHODS

Patients

From our initial series of 26 patients with Parkinson's disease who underwent bilateral DBS of STN, 11 patients completed 5-year follow-up cognitive and behavioural assessments after implantation. All patients who were selected for implantation showed disabling motor fluctuations and on-state dyskinesias, according to previously described inclusion criteria.²¹ Severe psychiatric symptoms, moderate or severe cognitive impairment, as measured by scores <20 on the Mini-Mental State Examination (MMSE), and diagnosis of dementia were among the exclusion criteria.⁶ Table 1 shows the main demographic and clinical characteristics of patients with Parkinson's disease at the time of implantation.

Procedures

All patients received a bilateral stereotactic STN implant, according to previously described neurosurgical procedures.²¹ Patients underwent cognitive assessments while they were on drugs for Parkinson's disease, both preoperatively and postoperatively. Cognitive assessment was carried out by means of a neuropsychological test battery described previously,⁶ including the MMSE, tasks of verbal (digit span forward and backward) and spatial (Corsi's block-tapping test) short-term memory, tasks of episodic verbal memory (Rey's Auditory Verbal Learning Test (RAVLT)) and non-verbal abstract reasoning (Raven's Progressive Matrices (RPM) 1947), a letter verbal fluency task and a task assessing frontal-executive cognitive functions (MWCST). In addition, a clinical interview was conducted to detect the presence of behavioural abnormalities or psychiatric disorders. A preoperative assessment (baseline) was carried out during the 4 weeks preceding the bilateral implantation of electrodes. Postoperative assessments were carried out 12 and 60 months after implantation, with stimulators turned on.

Statistical analysis

To assess the outcome, the scores obtained on each postoperative assessment were compared with preoperative scores by means of the Wilcoxon's signed-rank test, given the small sample size and non-normally distributed data. Given the

explorative nature of our study, the standard non-corrected significance α level of $p < 0.05$ was used, to reduce the risk of a type II error. However, given the risk of type I error due to multiple comparisons, significant results should be considered cautiously when the α levels are only marginally < 0.05 .⁸ To evaluate postoperative changes among individual patients on cognitive variables, each individual postoperative raw score was transformed to a standard z score, using means and standard deviations (SD) of the sample at baseline. The criterion of an increase >1 SD was used to tally individual postoperative improvements, whereas the criterion of a decrease > -1 SD was used to tally individual postoperative declines.⁶

RESULTS

Group outcome

Five years after surgery, parkinsonian motor symptoms improved in all patients with Parkinson's disease. As compared with preoperative assessment (table 2), there was a significant improvement in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores ($p = 0.003$) and activities of daily living ($p = 0.003$) on 12-month and 60-month postoperative assessments without drugs for Parkinson's disease and a significant reduction in the total levodopa-equivalent daily dose (LEDD) on 12-month ($p = 0.006$) and 60-month ($p = 0.005$) postoperative assessments.

Table 3 shows the group outcome on cognitive variables.

One year after surgery, there was a marginally significant postoperative decline on the letter verbal fluency task (mean decline: -16.2% ; $p = 0.045$) and a significant postoperative improvement on the MMSE (mean improvement: $+8.9\%$; $p = 0.009$). Five years after surgery, there was a significant postoperative decline on the letter verbal fluency task (mean decline: -33.1% ; $p = 0.007$) and on RPM (mean decline: -10.1% ; $p = 0.009$). Moreover, there was a trend towards a postoperative decline on both the delayed recall of the RAVLT (mean decline -15.8% ; $p = 0.075$) and on Corsi's span backward (mean decline -17.4% ; $p = 0.091$), whereas no significant postoperative change was observed on other cognitive variables. When the raw scores obtained by each individual patient on the letter verbal fluency task at 5 years were adjusted for age and educational level,²² only 3 of 11 patients performed below the normal range. In these three patients, the scores on the verbal fluency task were 12.2, 10.6 and 10.2, respectively, with a cut-off score of 17.35. Interestingly, two of these three patients performed below the normal range on the verbal fluency task also before the implantation. Similarly, when the raw scores obtained by each individual on the RPM at 5 years were adjusted for age and educational level,²² only 2 of 11 patients performed slightly below the normal range (their scores were 18.3 and 18.0, respectively, with a cut-off score of 18.96). In one of these two patients, the score on RPM was below the normal range even on preoperative assessment. No patient developed dementia 5 years after surgery, according to the criteria of the *Diagnostic and statistical manual of mental disorders*, 4th edn.²³

Comparison between scores obtained on cognitive tasks 1 year versus 5 years after surgery showed a significant long-term decline on the letter verbal fluency task (mean decline -20.1% ; $p = 0.005$), the MMSE (mean decline -7.2% ; $p = 0.008$) and the Corsi's span backward (mean decline -19.1% ; $p = 0.028$).

Table 4 shows the individual outcome on cognitive variables on 1-year and 5-year postoperative assessments.

One year after surgery, on some cognitive variables (verbal fluency, digit span forward, perseverative errors on the MWCST) the percentage of patients who declined was clearly higher than the percentage of patients who improved, whereas on other tasks (MMSE, digit span backward) the percentage of

Table 1 Main demographical and clinical characteristics of patients with Parkinson's disease

Number of patients	11
Sex (M:F)	7:4
Age at implant (years; mean (SD))	57.5 (7.4)
Disease duration at implant (years; mean (SD))	15.5 (5.6)
Age at 5-year follow-up (years; mean (SD))	62.6 (7.5)
Educational level (years; mean (SD))	11.0 (5.1)

F, female; M, male.

Table 2 Motor scores, activities of daily living, levodopa-equivalent daily dose (LEDD) at baseline and at 1-year and 5-year follow-up, with stimulators turned on, on and off drugs

	Baseline off	Baseline on	1 year off	1 year on	5 years off	5 years on
UPDRS-III						
Mean (SD)	57.73 (10.65)	24.27 (8.68)	27.82 (15.33)	20.82 (12.11)	22.00 (10.31)	18.10 (11.39)
Variation v baseline (%)			-51.8	-14.2	-61.9	-25.4
p Value			0.003	0.374	0.003	0.284
UPDRS-II						
Mean (SD)	32.36 (5.41)	10.27(9.68)	8.73 (5.02)	5.91 (4.99)	8.82 (6.23)	7.09 (6.06)
Variation v baseline (%)			-73.0	-42.5	-72.8	-31.0
p Value			0.003	0.126	0.003	0.398
LEDD						
Mean (SD)	1406.55 (750.15)		427.66 (354.89)		489.80 (394.46)	
Variation v baseline (%)			-69.6		-65.2	
p Value			0.006		0.005	

UPDRS, Unified Parkinson's Disease Rating Scale.

patients who improved was substantially higher than the percentage of patients who declined. Five years after surgery, on the verbal fluency task there was a remarkably high percentage of patients who declined, although 46% of the patients remained stable. At 5 years, on tasks of abstract reasoning (RPM), episodic memory (delayed recall of RAVLT) and short-term memory (digit span forward and Corsi's span backward), the percentage of patients who declined was substantially higher than the percentage of those who improved. A marked individual variability was observed on digit span forward at 5 years. A minority of patients showed no postoperative change on this verbal short-term memory task, whereas most patients had either a postoperative improvement or decline.

Over a 5-year follow-up, 3 of 11 patients experienced adverse events. A few days after the implantation, two patients, who were previously described elsewhere,¹² developed transient manic symptoms with hypersexuality, which lasted for some months and then gradually disappeared spontaneously. Moreover, one patient developed persistent apathy. None of our patients committed suicide or expressed suicidal intentions.

DISCUSSION

To our knowledge, this is the first study that extensively reports the long-term cognitive effects in patients with Parkinson's disease 5 years after lead implantation in the STN.

The results of neuropsychological assessment in our 11 patients treated by STN DBS with 5 years of follow-up show a significant decline in the letter verbal fluency task and in the

abstract reasoning task (RPM). However, when the raw scores obtained by each patient 5 years after surgery were adjusted for age and educational level, only 3 of 11 patients performed below the range of normal subjects on the verbal fluency task, whereas on RPM only 2 of 11 patients performed slightly below the normal range. Interestingly, most of the patients who performed below the normal range on the verbal fluency task and RPM 5 years after surgery did perform below the normal range on these two tasks preoperatively also. One year after surgery, we observed a marginal decline in the letter verbal fluency task and a significant postoperative improvement on the MMSE, which could most likely reflect a practice effect.⁶ The analysis of postoperative cognitive changes in individual patients 5 years after surgery showed some degree of inter-individual variability in cognitive outcome. Although on the verbal fluency task 56% of patients declined, 46% of the patients remained stable. At 5 years, the percentage of patients who declined on tasks of abstract reasoning, episodic memory and short-term memory was substantially higher than the percentage of those who improved.

Our observation of a decline in verbal fluency 5 years after implantation for STN DBS is in agreement with previous studies reporting a decreased verbal fluency in patients with a 1-year⁴⁻⁶ or a 3-year follow-up.¹¹ The only two studies published so far reporting a 5-year follow-up after bilateral DBS of STN¹⁷⁻¹⁸ were mainly focused on the long-term outcome of Parkinsonian motor symptoms. In both investigations, a significant decline in cognitive performance was detected on the MDRS and on neuropsychological measures sensitive to

Table 3 Results obtained on cognitive variables in the overall group of 11 patients at baseline, 1-year and 5-year follow-up

Variable	Score range	Baseline Mean (SD)	1 year Mean (SD)	Comparison 1 year v baseline % (p Value)	5 years Mean (SD)	Comparison 5 years v baseline % (p Value)	Comparison 5 years v 1 year % (p Value)
MMSE*	0-30	26.5 (3.0)	28.9 (1.2)	+8.9% (0.009)	26.8 (2.0)	+1.0 (0.760)	-7.2 (0.008)
Raven Progressive Matrices 1947*	0-36	28.5 (5.2)	28.2 (6.0)	-1 (0.541)	25.5 (6.2)	-10.2 (0.009)	-9.4 (0.050)
Rey immediate recall*	0-75	40.5 (12.9)	39.8 (13.1)	-1.6 (0.959)	37.8 (12.6)	-6.5 (0.721)	-5.0 (0.477)
Rey delayed recall*	0-15	9.2 (4.0)	8.6 (4.8)	-5.9 (0.418)	7.7 (3.7)	-15.8 (0.075)	-10.5(0.214)
Digit span forward*		5.5 (1.1)	5.4 (0.8)	-3.3 (0.584)	5.1 (1.1)	-8.2 (0.176)	-5.1 (0.311)
Digit span backward*		3.7 (1.0)	4.2 (1.5)	+12.2 (0.161)	3.7 (1.7)	0.0 (0.933)	-10.9(0.176)
Corsi's span forward*		4.8 (1.1)	4.9 (0.8)	+1.9 (0.715)	4.6 (1.1)	-3.8 (0.554)	-5.6 (0.273)
Corsi's span backward*		4.2 (1.3)	4.3 (1.1)	+2.2 (0.787)	3.5 (1.0)	-17.4 (0.091)	-19.1(0.028)
Letter verbal fluency*		33.0 (12.6)	27.6 (9.4)	-16.2 (0.045)	22.1 (9.5)	-33.1 (0.007)	-20.1(0.005)
MWCST: correct criteria*0-6		4.3 (1.9)	4.5 (1.8)	+4.9 (0.201)	4.2 (1.9)	-3.5 (0.715)	-8.0 (0.612)
MWCST: total errors†	0-48	12.6 (12.1)	10.8 (11.9)	-13.8 (0.327)	14.2 (9.7)	+13.0 (0.779)	+31.1 (0.062)
MWCST: perseverative errors†	0-48	5.0 (6.3)	4.6 (6.5)	-7.3 (0.499)	4.5 (4.9)	-9.1 (0.554)	-2 (1.000)

Significant data are in bold face. * +, improvement; -, decline; lower score = worse performance. † -, improvement; +, decline; lower score = better clinical condition. MMSE, Mini-Mental State Examination; MWCST, Modified Wisconsin Card Sorting Test.

Table 4 Individual postoperative changes on cognitive variables at 1-year and 5-year follow-up

Variable	Improvement		No change		Decline	
	1 year (%)	5 years (%)	1 year (%)	5 years (%)	1 year (%)	5 years (%)
MMSE*	45	9	55	82	0	9
Raven Progressive Matrices 1947*	18	0	64	73	18	27
Rey immediate recall*	18	9	64	73	18	18
Rey delayed recall*	27	9	46	55	27	36
Digit span forward*	0	18	82	46	18	36
Digit span backward*	27	18	73	55	0	27
Corsi's span forward*	18	18	73	55	9	27
Corsi's span backward*	9	0	82	82	9	18
Letter verbal fluency*	0	0	82	46	18	54
MWCST: correct criteria*	0	11	89	67	11	22
MWCST: total errors†	33	0	45	78	22	22
MWCST: perseverative errors†	0	0	78	89	22	11

MMSE, Mini-Mental State Examination; MWCST, Modified Wisconsin Card Sorting Test.

*An increase >1 SD indicates improvement, whereas a decrease >-1 SD indicates decline. †An increase >1 SD indicates decline, whereas a decrease >-1 SD indicates improvement.

frontal-lobe dysfunction (frontal-lobe scores) 5 years after implantation, but no information about performance on verbal fluency tasks was available, as no extensive neuropsychological data have been reported in such studies.

In our sample, behavioural adverse events included transient mania with hypersexuality in two patients, which appeared a few days after surgery, did not require treatment and might be due to the synergistic effects of the implantation (surgical procedure or STN stimulation) with other factors such as dopaminergic treatment or individual predisposition.¹²

At 5 years, the postoperative decline of verbal fluency did not seem to have a clinically meaningful effect on daily living activities in our patients with Parkinson's disease. As the decline in verbal fluency observed after implantation for STN DBS seems to begin immediately after surgery, it has been speculated that such decline could be due to surgical microlesions possibly involving cortical-basal ganglionic circuits, which might play a critical role in word retrieval processes,²⁴ rather than due to STN stimulation in itself.²⁵ Alternatively, it has been suggested that STN stimulation might give rise to a decreased activation of inferior frontal, insular and temporal cortex in the left cerebral hemisphere, resulting in a decreased verbal fluency.²⁶ Poor performance on verbal fluency tasks is frequently observed in patients with Parkinson's disease who are not treated by neurosurgery²⁷ and in those treated by pallidotomy, particularly after left-sided pallidotomy.^{24, 28} These findings should be taken into account in studies reporting a verbal fluency decline in patients treated by chronic stimulation of STN.

A limitation of our study is the lack of a control group of patients with Parkinson's disease who did not undergo neurosurgical intervention, as cognitive decline may occur over time in patients with the disease, owing to the disease progression. Several other studies on DBS in Parkinson's disease have the same limitation, owing to the difficulties in the recruitment of a control group of patients with Parkinson's disease who are not treated by neurosurgical procedures, which should be ideally matched at baseline to the group of patients who undergo DBS of STN with regard to several variables (age, educational level, disease duration, severity of motor impairment and overall cognitive status). Moreover, longitudinal studies focused on an extensive neuropsychological assessment are lacking in patients with Parkinson's disease, even in patients who do not undergo neurosurgical procedures. Such longitudinal studies are also needed, to compare the long-term cognitive outcome in patients with Parkinson's disease who are not treated by neurosurgery with those of patients who undergo STN DBS.

In conclusion, our findings suggest that DBS of STN in patients with Parkinson's disease may be associated with low cognitive and behavioural morbidity over a 5-year follow-up and can therefore be considered relatively safe as to the long-term outcome, when appropriate criteria are used to select candidates for neurosurgery. Further studies are needed to elucidate the mechanisms underlying the postoperative decline of verbal fluency observed in patients with Parkinson's disease treated by DBS of STN, which is already detectable in these patients early after STN DBS and becomes more evident in late postoperative stages.

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