Stereotactic pallidotomy in Parkinson's disease

de Bie, R.M.A.

Publication date
2002

Chapter 4

Unilateral pallidotomy in Parkinson's disease: a controlled study of cognitive and behavioural effects

Ben Schmand, Rob M.A. de Bie,
Martha Koning-Haanstra, Jofie S. de Smet,
Johannes D. Speelman, and
Adriaan H. van Zomeren on behalf of
the Netherlands Pallidotomy Study (NEPAS) group

Neurology 2000; 54: 1058-1064

Summary

Objective To investigate whether unilateral pallidotomy affects cognitive and behavioural functioning.

Methods At baseline and after 6 months we assessed neuropsychological functioning in 35 patients with advanced Parkinson's disease. After baseline examination, patients were randomised to pallidotomy within 1 month (six left-sided, 13 right-sided) or to pallidotomy after follow-up assessment, 6 months later (n=16, control group). We performed neuropsychological tests of language, visuospatial function, memory, attention, and executive functions. Self-ratings and proxy ratings of memory problems and dysexecutive symptoms were also collected.

Results No significant differences over time were found between pallidotomy and control groups, with the exception of a decrease of verbal fluency in the left-sided pallidotomy group.

Conclusions Unilateral pallidotomy is relatively safe with respect to cognition and behaviour. Left-sided pallidotomy may lead to minor deterioration in verbal fluency. The sample size of this study is too small, however, to rule out the possibility of infrequent but clinically important side effects.

Introduction

Patients with advanced Parkinson's disease frequently have levodopa-induced dyskinesias and rapid, seemingly unpredictable oscillations in their motor state despite optimal pharmacological treatment. Pallidotomy is a further treatment option in such cases. In the last decade, several cohort studies investigating the efficacy of posteroventral pallidotomy in advanced Parkinson's disease have been published.[1] The safety of the procedure with respect to cognition and behaviour has only recently been studied with appropriate neuropsychological tests. Little or no cognitive or behavioural effects have been reported.[2-12]

Most of these were open studies without a control group. This is a methodological flaw because it does not control for practice effects of neuropsychological testing, which may lead to better performance at follow-up. Absence of test score decline in a treated group, therefore, does not necessarily imply that there are no harmful effects. Only two studies have used control groups. However, these were self-selected groups, introducing possible bias such as a shorter disease duration in the control patients.[7,9] In many studies, follow-up examinations were not scheduled at fixed intervals; this renders the results difficult to interpret.[2,5,10,11] Finally, few studies appropriately distinguished between left and right pallidotomy in the statistical analysis of the psychological test results.[3,6,10-12] Failure of the remaining studies to do so may have attenuated the capacity to detect lateralised cognitive changes.

We studied the efficacy and possible side effects of unilateral pallidotomy in a randomised controlled trial. The results concerning motor symptoms have been described elsewhere.[13] In this article we report on cognitive and behavioural effects of the intervention.

Methods

Subjects Patients were recruited in the three participating centres by neurologists specialised in movement disorders. Inclusion criteria were idiopathic Parkinson's disease and at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia despite optimal pharmacological treatment. Exclusion criteria were Hoehn and Yahr stage[14] 5 at the best moment of the day, a score of 24 or less on the mini mental state examination,[15] psychosis, and contraindications for stereotactic neurosurgery.[16]

Patients were given written information about the study and gave their informed consent. The study protocol was approved by the institutional review boards of the participating centres.

Randomisation After inclusion, scoring of demographic and disease variables, and baseline neuropsychological assessment, patients were randomised to pallidotomy within 1 month (pallidotomy group) or to pallidotomy after follow-up assessment, 6 months later (control group).

Surgical procedure Patients did not receive antiparkinson drugs on the day of surgery until the end of the procedure. The Leksell stereotactic frame (Elekta; Stockholm, Sweden) was applied under local anaesthesia or under propofol sedation. A burr hole with a diameter of 10 mm was made 2-3 cm lateral from the midline just anterior to the coronal suture. For target localisation, a positive contrast ventriculography was made. The target coordinates were 2 mm anterior to the midcommissural point, 5 mm below the intercommissural line and 22 mm lateral to the midline of the third ventricle. Microelectrode recording was not performed. Electrical monopolar test stimulation was carried out using an electrode with a 2.1 x 4.0 mm bare tip with low-frequency (2 Hz) and high-frequency (100 to 130 Hz) stimulation (pulse width 0.1 ms) in 2 mm steps starting 8 mm above the target. Aim of the stimulation was to determine the proximity of the internal capsule and the optic tract. If necessary, the target structure was adjusted. Depending on the results of the stimulation, radiofrequency thermolesions were made using the same electrode at 80°C for 60 s at each 2 mm step directly after stimulation.

Assessments Neuropsychological examination was completed while patients were at their optimal status. The examination was suspended whenever a patient indicated that he went into 'off', or whenever dyskinesias were interfering with test administration. Duration of the test administration was 3 to 4 h including a break. The tests were administered by a board certified neuropsychologist or a test technician supervised by the neuropsychologist. With a few exceptions patients were tested by the same person at baseline and at follow-up.
In the days before the neuropsychological examination both the patient and a close relative or other proxy completed questionnaires on memory complaints and dysexecutive symptoms. Follow-up assessment was done at 6 months from baseline.

Neuropsychological tests We selected a battery of widely used tests so that any score declines would be interpretable in terms of clinical relevance. The following tests were used.

- Dutch adult reading test (DART).[17] Fifty words with irregular spelling are read aloud. The number of correctly read words is transformed into an estimate of verbal intelligence. The DART is the Dutch counterpart of the national adult reading test (NART).[18] This test gives an estimate of premorbid intelligence as

it is relatively insensitive to cognitive deterioration due to neurological disorders. It was used at baseline to describe the sample.

- Boston naming test (BNT).[19] Sixty line drawings of objects and animals of varying degrees of familiarity are named. This is a test of naming ability. Score is raw number correct.
- Category fluency.[20] Naming animals and occupations, for 1 min each. Score is raw number correct in 2 min.
- Controlled oral word association test (COWAT).[21] During 1 minute the subject must say as many words as he or she can think of that begin with a given letter. Three trials with different letters were done. At follow-up a parallel version was used. Score is raw number correct in 3 min.
- Similarities subtest of the Wechsler adult intelligence scale (WAIS).[22] The subject indicates what two objects or concepts have in common. This is a test of verbal concept formation or verbal abstraction. Raw scores are transformed into age-corrected T-scores.
- Block design subtest of the WAIS.[22] The subject constructs geometric patterns using coloured blocks. This is a test of visuoconstructive ability. Raw scores are transformed into age-corrected T-scores.
- Judgement of line orientation (JOLO).[23] The subject matches the direction of two angled line segments with two lines in a fan-shaped arrangement of 11 lines. This is a test of the ability to estimate angular relationships. Raw scores are corrected for age and sex. Parallel forms were used at follow-up.
- Bells test.[24] On a sheet of paper the subject detects and circles little bells among other silhouetted objects as quickly as possible. The distribution of the bells looks random but is divided in seven columns, five bells per column. Score is the raw number of circled bells in the leftmost two columns and in the rightmost two columns. This is a test of visual hemi-inattention.
- Auditory verbal learning test (AVLT).[25] The subject memorises a series of 15 words in five learning trials. Following a 20-min delay, the subject is asked to recall the word list, followed by a recognition trial in which the subject is presented with the 15 target words and 15 foils. Raw scores are used. Parallel forms were used at follow-up.
- Logical memory of the Rivermead behavioural memory test.[26] A 21-item news message is read to the subject, who repeats as many items as he or she can remember. After a 15-minute interval he or she is asked to recall the message again. Score is the number of items recalled. Parallel forms were used at follow-up.
- Recognition memory test faces.[27] Photographs of 50 male faces are shown, must be recognised out of 50 pairs of faces immediately after presentation. Raw scores of correctly recognised photographs are used.
- Stroop colour word test.[28] This test measures perceptual interference, response

inhibition, and selective attention by having the subject read words, name colours, and name the colour of ink of the words when the words are printed in a nonmatching coloured ink. In this study a fourth condition was used in which 20 percent of the words were in rectangular boxes. The instruction was the same as for the third condition, except that the subject now had to read the boxed words instead of naming their colour (Stroop-Bohnen).[29] Score is time to completion in seconds.

- Trail making test part A and part B.[30] The task is to connect numbers (part A), and to connect numbers alternating with letters (part B) on a sheet of paper. This is a test of visual scanning, visuomotor and conceptual tracking, mental flexibility, and motor speed. Score is time to completion in seconds.
- Modified Wisconsin card sorting test (MWCST).[31] This test uses a deck of cards on which different numbers of different forms in different colours are shown. The task is to sort the cards according to one of three possible sorting rules (colour, number, or form). These rules are not told to the subject; he or she must identify the sorting rules. After each sort feedback is given on whether it was correct. Once a sorting rule has been found (six correct sorts on a row), the subject is asked to change to a different rule. Of particular interest are perseverative errors of the kind where the subject keeps sorting according to a previously correct rule or to a rule, which he was told to be wrong in the immediately preceding sort. The MWCST is a test of concept formation and set shifting. Scores are the raw numbers of errors, perseverations and sort shifts ('categories').

Mood and behaviour rating scales The DEX Questionnaire of the behavioural assessment of the dysexecutive syndrome[32] and the memory assessment clinic rating scales (MAC)[33,34] were completed by the patient and a proxy. The DEX is a 20-item questionnaire for rating dysexecutive symptoms, such as apathy, distractibility, lack of social awareness, and planning problems. The MAC scales measure a wide range of everyday memory abilities and amnestic symptoms. MAC scales contain an ability subscale (21 items), which was used in this study. Subjects indicate how well they remember specific types of information such as "the name of a person just introduced to you" or "where you have put objects (such as keys) in the home or office." High scores indicate good memory abilities. The reliabilities of the DEX and MAC scales proved to be excellent in this study; their internal consistencies ranged from 0.87 to 0.94.

During the test session an abbreviated version of the profile of mood states (POMS)[35] was filled out by the patient. This is a list of 32 adjectives clustered in five subscales (depression, anger, fatigue, vigour and tension) by which subjects describe their mood during the week preceding the assessment. The reliabilities of these subscales ranged from 0.75 to 0.93.

Statistical analyses All analyses were conducted according to the intention-to-treat principle. For domains of lateralised cognitive functions (i.e., language, visuospatial and memory functions) the side of pallidotomy was taken into consideration. Therefore, three subgroups were distinguished in these function domains: control, left pallidotomy and right pallidotomy. For the analysis of functions that are not readily lateralisable the control group was compared with the total pallidotomy group. In view of the small and unequal subgroup sizes, nonparametric tests were used (Kruskal-Wallis one-way ANOVA and Mann-Whitney *U* test) to compare change over time in the two or three subgroups. Change scores were calculated as the score at follow-up minus the score at baseline. p-Values of less than 0.05 (two-tailed) were accepted as significant. We did not correct the level of significance to reduce the probability of type I error due to multiple comparisons because we were mainly interested in detecting adverse effects of the surgical intervention. Under this circumstance, type II error (failing to detect an effect when it actually exists) is more serious than type I error (considering an effect to be real when it actually is not).[36]

Three percent of the test scores were missing, primarily due to prolonged off phase. All analyses were repeated after imputation of these missing data. At baseline a missing value was replaced by the worst value observed when a patient had attempted a test but was unable to do it. In other cases the missing value was estimated on the basis of its main correlate (e.g., a missing score of trailmaking B was estimated using the score obtained at trailmaking A). Missing values at follow-up were either replaced by the worst value observed when the patient had attempted to do the test or else by the baseline value. Missing values of the DEX and MAC Questionnaires were due to administrative errors and were not imputed.

Table 1. Demographic and disease characteristics of the patient sample at baseline

	Control group (n=16)	Left pallidotomy group (n=6)	Right pallidotomy group (n=13)
Sex (male/female)	9/7	2/4	6/7
Age years	61.1 (7.8)	63.0 (5.3)	59.2 (7.1)
Education years	10.9 (2.0)	10.0 (2.3)	11.5 (3.4)
DART-IQ	100.8 (16.9)	102.5 (17.3)	102.8 (13.6)
Disease duration years	16.3 (4.8)	15.5 (4.7)	16.6 (5.1)
Hoehn and Yahr stage			
On-period median (range)	2.5 (1-4)	2.8 (2-4)	2.5 (2-4)
Off-period median (range)	4.0 (2-5)	4.0 (3-5)	4.0 (2-5)
Medication LEU	920 (320)	754 (269)	934 (458)
Anticholinergics, number of patients	2	2	4
Benzodiazepines, number of patients	7	1	5

Data are mean (SD) unless otherwise stated; LEU=levodopa equivalent units;[13] DART=Dutch adult reading test.

Results

Thirty-seven patients were included in the study. One patient from the control group died of a myocardial infarction during the follow-up interval. Another control patient was lost to follow-up because of hip surgery with complications. Of the remaining patients, 16 were in the control group, six underwent left pallidotomy and 13 right pallidotomy.

The demographic and disease characteristics of the three subgroups are listed in table 1. The subgroups were similar with respect to gender, age, educational level, and premorbid verbal intelligence. There was one left-handed patient in each of the three groups. Disease characteristics in terms of duration of disease,

Table 2. Scores on tests of lateralised cognitive functions at baseline and change scores at follow-up

	Control group (n=15-16)	Left pallidotomy group (n=6)	Right pallidotomy group (n=12-13)	p		
				A	B	C
Boston naming test	52.1 (6.0)	50.3 (8.7)	51.5 (7.2)			
Change score	-0.1 (3.7)	1.2 (2.8)	-0.3 (3.5)	0.38	0.99	0.23
Category fluency	36.6 (12.5)	39.2 (11.1)	36.3 (10.9)			
Change score	-0.8 (5.6)	-8.7 (5.5)	-3.1 (8.9)	0.04	0.006	0.91
COWAT letter fluency	32.6 (13.5)	34.2 (16.6)	30.7 (13.1)			
Change score	1.3 (4.6)	-8.0 (9.5)	2.6 (3.9)	0.01	0.02	0.14
WAIS Similarities (T)	57.1 (16.7)	53.7 (15.5)	57.2 (15.1)			
Change score (T)	3.0 (8.3)	1.3 (6.8)	0.8 (7.6)	0.92	0.91	0.72
WAIS Block Design (T)	48.4 (14.4)	39.8 (6.3)	47.8 (12.2)			
Change score (T)	-5.8 (8.0)	-1.7 (7.7)	-4.2 (11.1)	0.49	0.27	0.41
JOLO corrected score	20.8 (8.5)	25.0 (5.2)	22.8 (6.2)			
Change score	0.2 (5.7)	-0.5 (6.2)	-1.5 (5.7)	0.76	0.91	0.50
Bells test columns left	9.1 (1.9)	8.8 (0.8)	8.5 (1.3)			
Change score	0.5 (1.7)	0.3 (1.0)	-0.8 (2.3)	0.37	0.73	0.19
Bells test columns right	8.8 (1.5)	9.0 (1.3)	8.6 (1.3)			
Change score	-0.5 (2.3)	0.2 (1.0)	-0.5 (1.9)	0.91	0.91	0.72
Bells test (s)	143.3 (59.2)	105.5 (19.5)	150.3 (61.5)			
Change score (s)	-14.1 (39.7)	36.0 (35.9)	-12.5 (60.2)	0.05	0.02	0.56
AVLT total score	37.4 (12.4)	37.2 (11.7)	34.1 (9.3)			
Change score	-0.3 (9.0)	0.5 (4.5)	0.9 (7.1)	0.84	0.99	0.62
AVLT delayed recall	6.9 (3.6)	8.8 (3.1)	6.3 (2.8)			
Change score	0.3 (2.7)	-1.5 (2.5)	0.6 (2.2)	0.27	0.26	0.68
AVLT recognition	27.2 (2.7)	27.8 (1.9)	27.8 (2.7)			
Change score	-0.7 (2.7)	0.0 (1.1)	-0.6 (3.0)	0.76	0.64	0.78
Logical memory immediate	8.7 (4.2)	7.1 (1.6)	7.8 (2.9)			
Change score	-0.3 (3.4)	0.7 (3.7)	0.6 (4.1)	0.71	0.59	0.48
Logical memory delayed	8.1 (4.8)	6.5 (1.5)	6.9 (2.7)			
Change score	-0.5 (3.7)	0.5 (2.4)	0.0 (3.5)	0.79	0.54	0.75
Face recognition	38.9 (6.2)	38.0 (7.6)	30.9 (8.0)			
Change score	-2.1 (4.8)	0.0 (3.7)	-1.8 (3.7)	0.50	0.23	0.77

Values are mean (SD); a negative change scores signifies decline in performance except for speeded test variables; the number of patients varies owing to missing values on some of the test variables; A=Kruskal-Wallis test; B=Mann-Whitney *U* test control *vs* left pallidotomy group; C=Mann-Whitney *U* test control *vs* right pallidotomy group; COWAT=controlled oral word association test; WAIS=Wechsler adult intelligence scale; T=age-corrected T-score; JOLO=judgement of line orientation, age and sex corrected scores; AVLT=auditory verbal learning test.

Table 3. Scores on tests of nonlateralised cognitive functions at baseline and change scores at follow-up

	Control group (n=13-15)	Pallidotomy group (n=14-18)	p*
Stroop word (s)	54 (27)	55 (13)	
Change score (s)	-6 (23)	-1 (14)	0.88
Stroop colour (s)	66 (21)	66 (10)	
Change score (s)	-7 (17)	-2 (10)	0.59
Stroop colour-word (s)	115 (32)	124 (34)	
Change score (s)	1 (37)	5 (26)	0.49
Stroop-Bohnen (s)	148 (55)	157 (51)	
Change score (s)	6 (14)	-15 (37)	0.46
Trailmaking A (s)	47 (17)	62 (36)	
Change score (s)	1 (14)	-1 (25)	0.98
Trailmaking B (s)	136 (78)	138 (65)	
Change score (s)	4 (75)	-3 (43)	0.92
MWCST errors	15.4 (9.8)	14.6 (7.4)	
Change score	-0.9 (7.6)	0.6 (6.5)	0.63
MWCST perseverations	5.6 (4.3)	4.9 (4.0)	
Change score	-0.5 (3.1)	-0.1 (4.0)	0.98
MWCST categories	3.9 (2.3)	4.0 (1.6)	
Change score	0.2 (2.2)	-0.9 (1.6)	0.50

Values are mean (SD); a positive change scores signifies decline in performance (except for the modified Wisconsin card sorting test [MWCST] categories); owing to missing values, Stroop and Trailmaking are based on n=13+14; MWCST is based on n=14+18; * Mann-Whitney *U* test.

Table 4. Scores on questionnaires of dysexecutive symptoms (DEX) and memory abilities (MAC) at baseline and change scores at follow-up

	Control group (n=13-16)	Pallidotomy group (n=16-19)	p*
DEX Questionnaire self rating	20.9 (13.8)	21.8 (8.7)	
Change score	-1.4 (9.0)	-1.3 (8.3)	0.90
DEX Questionnaire proxy rating	18.6 (14.6)	20.4 (11.2)	
Change score	1.6 (7.3)	4.2 (11.5)	0.71
MAC Questionnaire self rating	74.3 (12.1)	70.9 (9.0)	
Change score	-0.6 (8.1)	-0.3 (9.9)	0.94
MAC Questionnaire proxy rating	77.9 (11.6)	78.4 (12.5)	
Change score	-5.5 (8.6)	-3.3 (10.1)	0.50
POMS Depression	8.4 (6.4)	8.2 (7.0)	
Change score	1.0 (5.2)	-0.2 (9.7)	0.36
POMS Anger	5.3 (4.9)	3.8 (3.8)	
Change score	0.7 (5.4)	-0.2 (6.6)	0.84
POMS Fatigue	10.1 (7.3)	11.8 (8.1)	
Change score	-0.3 (6.3)	-3.3 (7.8)	0.16
POMS Vigor	11.8 (3.1)	10.9 (4.0)	
Change score	0.1 (5.0)	-0.5 (5.0)	0.86
POMS Tension	8.8 (4.4)	8.6 (4.8)	
Change score	0.3 (6.0)	-1.6 (6.0)	0.38

Values are mean (SD); higher DEX scores means more dysexecutive symptoms; higher MAC scores mean better memory ability; a negative change score signifies improvement except for MAC; the number of patients varies owing to missing values on some of the test variables; * Mann-Whitney *U* test.

Hoehn and Yahr score in on and off phase, and medication expressed in levodopa equivalent units were the same across the three groups. Medication was not changed during the follow-up interval.

The main effects of surgery on motor symptoms were the following.[13] During off phase, the motor performance of pallidotomy patients increased with a median of 31 percent, whereas control patients slightly worsened. The pallidotomy patients became less dependent on caregivers with respect to activities of daily living when in the off phase. In the on phase, dyskinesias improved overall (i.e., left and right) with 50 percent in pallidotomy patients compared to no change in controls.

The neuropsychological test scores in the subgroups are shown in tables 2 and 3; the results of the behaviour and mood ratings are presented in table 4. The tables provide the mean score at baseline and the mean change score at follow-up for each test (data as observed, i.e., without imputation). For lateralised function domains (language, visuospatial, and memory functions, table 2), the distinction between left and right pallidotomy was maintained. For the remaining cognitive domains (attention and executive functions, table 3) and for the behaviour and mood ratings both pallidotomy groups were combined.

Category fluency and letter fluency showed significant group differences in change scores (table 2). For both types of fluency the left-sided pallidotomy subgroup scored significantly lower at follow-up than the control group. The speed of performance on the bells test slowed down in the left pallidotomy patients. However, they had been relatively quick at baseline and worked somewhat more accurately at follow-up. We therefore do not see this as a meaningful group difference. In the remaining cognitive tests no significant subgroup differences in score changes were found (tables 2 and 3). There were no significant differences on the behaviour rating scales, although there seems to be a consistent trend toward mood improvement in the pallidotomy group (table 4).

When these analyses were repeated after imputation of missing data, the pattern of results was the same. Two patients' (control group) scores were at a level, which is usually found in demented patients (although they had passed the MMSE criteria at inclusion). Another patient (right pallidotomy) was psychotic during the intervention and remained confused during the follow-up interval (for details, see de Bie et al.[13]). Removal of these three patients from the analyses did not change the pattern of results. Analyses of the nonlateralised functions maintaining the three subgroups' division also yielded the same pattern of results. There were no significant correlations (at $p<0.01$ two-tailed) of the demographic and disease characteristics with the change scores on the neuropsychological tests. We found no significant practice effects in the control group. Block design was the only test showing a significant retest effect, but this was a decline in performance.

Discussion

The main finding of this study was an isolated effect on verbal fluency in patients who underwent left-sided pallidotomy. We could not detect any effects of lesioning the right globus pallidus. Neither did we find effects in the other cognitive and behavioural domains. Patients' proxies did not report changes in cognitive or behavioural symptoms.

Detrimental effects of left-sided pallidotomy on verbal fluency have been reported before.[3-6,10-12] This decrease in verbal fluency is likely the most robust adverse effect of left-sided pallidotomy on cognitive functioning. It has also been found after pallidal stimulation,[37,38] although not consistently.[39] The finding of a decreased fluency in itself is not surprising, because symptoms of aphasia after subcortical lesions in the dominant hemisphere are not uncommon.[40] The fact that it is fluency that is affected, and not picture naming or verbal abstraction (as evidenced by the absence of score changes on the Boston naming test and the similarities subtest of the Wechsler adult intelligence scale), is perhaps due to the speeded character of the fluency task and to its high psychometric reliability. These characteristics render it a very sensitive task. Thus, speed of word generation is reduced, but quality of verbal functioning is not affected. Perhaps this explains why we did not find a parallel increase in reported symptoms on the self and proxy ratings. Even a specific MAC subscale aiming at semantic memory did not show a decrease of semantic ability in the left-sided pallidotomy group (data not shown). Thus, although statistically significant, the decrease of fluency probably has little impact on the patients' daily lives.

Several studies found an effect on other cognitive functions. Baron et al.[2] found a decline of verbal memory after 1 year, but not at intermediate assessments. The lack of a control group precludes the conclusion that this was an effect of the intervention per se and not, for example, of disease progression. Two other studies found a decline in verbal memory 3 to 6 months after left-sided pallidotomy. In one of these studies the verbal memory of right-sided pallidotomy patients also declined.[3] More in accordance with what one would expect, this was not the case in the other study.[10] Both studies reported right hemisphere dysfunction in visuospatial abilities and nonverbal memory after right pallidotomy. These abnormalities resolved after one year.[10] The same two studies also found decline in executive functioning regardless of the side of lesion, which again precludes drawing etiological conclusions. The decline may be an effect of surgery but also of disease progression. In defence of these studies, one might say that the follow-up duration of a year or less is too short to show much cognitive decline as a result of disease progression. This consideration, in combination with our own finding of absence of significant practice effects in untreated patients, gives more credence to the results of these earlier studies.

In all studies conducted until now, including our own, sample sizes were small

(maximum n=42). Neuropsychological assessments were performed as secondary analyses; the primary analyses concerned the effect of surgery on motor symptoms. In these primary analyses no distinction was made between left and right pallidotomy. However, in the analysis of neuropsychological test results the left-right distinction is essential, so that larger samples are needed. Still greater numbers of patients are necessary for the detection of clinically important but infrequent side effects.

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