Neuropsychological effects of subthalamic nucleus stimulation in Parkinson's disease

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Citation for published version (APA):

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Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD
A comparison of neuropsychological effects

Journal of Neurology 2005;252:176-182
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EM, Speelman, JD
Abstract

Objective: To compare the cognitive and behavioural effects of unilateral pallidotomy and bilateral subthalamic nucleus (STN) stimulation.

Methods: After baseline examination 34 patients were randomly assigned to unilateral pallidotomy (4 left-sided, 10 right-sided) or bilateral STN stimulation (n=20). At baseline and six and twelve months after surgery we administered neuropsychological tests of language, memory, visuospatial function, mental speed and executive functions. Also a depression rating scale, and self and proxy ratings of memory and dysexecutive symptoms were administered.

Results: Six months after surgery, the STN group and the pallidotomy group differed significantly in change from baseline in number of errors on two tests of executive functioning. After 12 months the STN group reported less positive affect compared to baseline than the pallidotomy group. One patient in the STN group showed an overall cognitive deterioration due to complications.

Conclusions: Although we need larger groups to draw firm conclusions, our results suggest that bilateral STN stimulation has slightly more negative effects on executive functioning than unilateral pallidotomy.
Introduction

In a prospective, randomised, observer blind, multicenter study our group established that bilateral subthalamic nucleus stimulation (STN) is a more effective surgical treatment than pallidotomy to reduce parkinsonian symptoms in patients with advanced PD. The safety of pallidotomy concerning neuropsychological aspects has been documented in several studies. The only consistent finding of these studies is a decrease in verbal fluency following left sided surgery. Studies into the neuropsychological effects of bilateral STN stimulation show inconsistent results. The only controlled study from Morrison et al. reported mildly adversely affected attention and verbal fluency. Other studies were not controlled. Ardouin and Pillon et al. and Alegret et al. found hardly any negative effect on cognition, while Saint Cyr et al. did find a decrease of performance in memory, mental speed and fluency. Dujardin et al found that STN stimulation can induce overall cognitive decline or behaviour changes in some patients. To establish if pallidotomy and bilateral STN stimulation are equally safe with respect to cognition, mood and behaviour, comparison studies are needed. Only one study compared the neuropsychological effects of bilateral STN stimulation and unilateral pallidotomy. This study found that bilateral STN stimulation causes a selective decrease in verbal fluency. This study was controlled but not randomised. Two other studies comparing bilateral pallidal and STN stimulation, did not show differences on cognitive measures at all. These two studies are respectively a pilot study and a retrospective study, which studied two bilateral interventions.

The present study is part of the prospective, randomised, observer blind, multicenter study mentioned above. We describe the neuropsychological effects of unilateral pallidotomy and bilateral STN stimulation.

Methods

Patients

Patients were recruited from the four participating Dutch hospitals experienced in pallidotomy and STN stimulation for PD between April 2000 and May 2001. Eligible patients had idiopathic Parkinson’s disease with an unequivocal reduction
in off phase symptoms on levodopa, and at least one of the following symptoms despite optimal pharmacological treatment: severe response fluctuations, dyskinesias, dystonia or bradykinesia. Exclusion criteria were: predominantly unilateral symptoms without severe response fluctuations, severe brain atrophy on CT or MRI scans, Hoehn and Yahr stage 4 or 5 in the best on phase, Dementia Rating Scale score of less than 120, psychosis or depression at inclusion, previous stereotactic operation, or a physical condition making stereotactic surgery hazardous. All patients gave their written informed consent. The medical ethics committees of the participating hospitals approved the study.

**Randomisation**

After inclusion, scoring of demographic and disease variables, and baseline neuropsychological assessment, patients were allocated randomly to unilateral pallidotomy (pallidotomy group) or to bilateral STN stimulation (STN group) by a computer program. A minimisation procedure was done according to severity of Parkinson’s disease (Hoehn and Yahr ≤ 3 versus Hoehn and Yahr stage 4 or 5 in the off phase) and ‘treatment centre’.

**Surgical procedure**

Within one month after randomisation, patients underwent stereotactic surgery as previously described, using ventriculography, MRI, or CT scan to determine the position of the target structure. Semi-microelectrode recording was used in one patient. After macroelectrode test-stimulation either a radiofrequency thermolesion was made or a four contact electrode (model DBS-3389, Medtronic, Minneapolis) was implanted. The electrodes were connected to the implantable pulse generator (Itrel II, Soletra, or Kinetra, Medtronic, Minneapolis) under general anaesthesia. We did not systematically perform MRI postoperatively, because this is not allowed in the Netherlands.

Assessments Neuropsychological examination was completed in the morning, while patients were at their optimal status. The examination was suspended whenever a patient indicated that he or she went into ‘off’. A board-certified neuropsychologist or a supervised test technician administered the tests. Follow-up assessment was done six and twelve months after surgery.
Neuropsychological effects of pallidotomy versus STN DBS

Neuropsychological tests
We selected a battery of tests to evaluate cognitive functions often affected in Parkinson’s disease. To minimise practice effects we used alternate forms where available in a balanced order across patients. The following tests were administered.

- Dementia Rating Scale (DRS) \(^{18}\). The DRS is a measure of general cognitive status. The scale consists of five subscales: attention, verbal and motor initiation and perseveration, visuospatial construction, conceptualisation, and memory. The score is the sum of the scores of the 5 subscales. Maximum score is 144.
- Category fluency \(^{17}\). Naming animals and occupations for 1 minute each. Score is raw number correct in 2 minutes.
- Controlled Oral Word Association Test (COWAT) \(^{29}\). 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 an alternate version was used. Score is raw number correct in 3 minutes.
- Alternating fluency \(^{4}\); this is a test of verbal set shifting. Naming items alternating between two different categories (body parts/cities or clothing/countries) during two minutes, and subsequently alternating between two different letters during two minutes. Score is raw number correct in 4 minutes. Parallel forms were used at follow-up.
- Dutch Adult Reading Test (DART). \(^{34}\) The DART is the Dutch counterpart of the National Adult Reading Test (NART) [22]. This test gives an estimate of premorbid intelligence, as it is relatively insensitive to cognitive deterioration due to neurological disorders. Fifty words with irregular spelling are read aloud. The number of correctly read words is transformed into an estimate of verbal intelligence.
- Paced Auditory Serial Addition Task (PASAT), speed 3.2 seconds per digit. \(^{11}\) This is a test of working memory as well as a test of information processing speed. Every 3.2 seconds a digit ranging from 1 to 6 is presented on audiotape. The subject has to add the currently presented digit to the previous digit and provide the answer aloud. This procedure includes one practice list of 11 digits followed by one trial of 61 digits. Score is number of correct additions. Maximum score is 60.
- Auditory Verbal Learning Test (AVLT). \(^{28}\) The subject memorises a series of 15 words in five learning trials. Following a 20-minute 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. Alternate forms were used at follow up.

- Groningen Intelligence Test: Visuospatial reasoning, a subtest of a Dutch Intelligence Test.\textsuperscript{17} Visuospatial puzzles of increasing complexity have to be solved. Score is number of correctly solved items. Maximum score is 20.

- Stroop Color Word Test.\textsuperscript{36} This test measures perceptual interference, response inhibition, and selective attention by having the subject read words, name colours, and the colour of ink of the words when the words are printed in a non-matching coloured ink. Scores are time to complete 100 items, and number of errors that are not self-corrected.

- Odd Man Out Test (OMO)\textsuperscript{7} This test measures the ability to maintain a mental set. Subjects are required to identify a rule by which one of a set of letters or figures is different from the others. This classification rule has to be followed on a series of cards. Feedback is given after every card. In a second series of identical cards a different rule has to be identified and followed with continuous feedback. These two series with the two rules are alternated four times. Score is total number of errors on 8 trials. Alternate forms were used at follow-up.

- Trail Making Test parts A and B\textsuperscript{27} This is a test of visual scanning, visuomotor and conceptual tracking, mental flexibility, and motor speed. The task is to connect numbers (part A), and to connect numbers alternating with letters (part B) on a sheet of paper. Scores are time to completion in seconds, and number of errors on part B. For both tasks a practice item is given in advance.

- Boston Naming test (BNT)\textsuperscript{13} This is a test of naming ability. We used an abbreviated version. Thirty line drawings of objects and animals have to be named. Scores of the original version were estimated by extrapolation.

**Mood and behaviour rating scales**

The DEX Questionnaire of the Behavioural Assessment of the Dysexecutive Syndrome\textsuperscript{40} and the Memory Assessment Clinic ratings (MAC)\textsuperscript{3} 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. High scores indicate executive dysfunction. The MAC scales measure a wide range of everyday memory abilities and amnesic symptoms.
In this study we used only the ability subscale (21 items). High scores indicate good memory abilities.

During the test session a combined version of the abbreviated Profile of Mood States (POMS) and the Positive And Negative Affect Scale (PANAS) was filled out by the patient. This is a list of 60 adjectives by which subjects describe their mood during the week preceding the assessment. For the POMS the adjectives are clustered in five subscales (depression, anger, fatigue, vigour, and tension), and for the PANAS the adjectives cluster into positive and negative affect. The Montgomery & Åsberg Depression scale (MADRS) was also administered. This is a 10-item depression rating-scale. High scores indicate depression.

**Statistical analyses**

All analyses were conducted according to the intention-to-treat principle. From patients who were lost at follow-up, the missing data were imputed by the last observation carried forward. This means that the individual test scores of the last available neuropsychological examination were used to replace the missing data. The STN group was compared with the pallidotomy group on all measures for both follow-up times. In view of the small and unequal subgroup sizes, nonparametric tests were used (Mann-Whitney $U$ test).

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 statistically significant. We did not correct the level of significance to reduce the probability of type I error due to multiple comparisons because we are mainly interested in detecting adverse effects of the surgical intervention. Under this circumstance, type II error (failure to detect an effect when it actually exists) is more serious than type I error (considering an effect to be real when it is actually not).

**Results**

Thirty-four patients were included in the study. Twenty patients were allocated to the STN group and 14 to the pallidotomy group of which 10 were treated on the right side and four on the left side. The difference in size of the groups was due to the minimisation procedure. The course of the follow-up is depicted in figure 1.
The demographic and disease characteristics of the groups are listed in table 1. The group did not differ significantly \((p=0.72)\) in the interval in months between baseline and follow-up at 6 months (STN group mean 6.7 (sd 0.5); pallidotomy 6.8 (sd 0.7); neither for the interval between baseline and follow-up at 12 months ((STN group mean 13.0 (sd 0.8); pallidotomy 12.9 (sd 0.7) \(p=0.45\)). The groups were comparable with respect to gender, age, educational level, and premorbid verbal intelligence. Disease characteristics in terms of duration of disease, Hoehn and Yahr score in “on” and “off” phase, and medication expressed in levodopa equivalent units (LED) were not significantly different for both groups at baseline (Table 1).
Neuropsychological effects of pallidotomy versus STN DBS

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

<table>
<thead>
<tr>
<th></th>
<th>Pallidotomy</th>
<th>STN</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Gender</td>
<td>5 / 9</td>
<td>6 / 14</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>62.1 (8.1)</td>
<td>59.2 (8.6)</td>
</tr>
<tr>
<td>Education, y, mean (SD)</td>
<td>10.2 (3.1)</td>
<td>10.7 (1.9)</td>
</tr>
<tr>
<td>DART-IQ, mean (SD)</td>
<td>100.2 (15.9)</td>
<td>99.6 (14.1)</td>
</tr>
<tr>
<td>Disease duration, y, median (range)</td>
<td>11 (7-20)</td>
<td>12 (3-50)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr “on” median (range)</td>
<td>2.5 (1.0-3.0)</td>
<td>2.5 (1.0-5.0)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr “off” median (range)</td>
<td>4.0 (2.5-5.0)</td>
<td>4.0 (3.0-5.0)</td>
</tr>
<tr>
<td>Medication in LEU pre-op, median (range)</td>
<td>1260 (340-2614)</td>
<td>935 (406-3000)</td>
</tr>
<tr>
<td>Medication in LEU post-op, median (range)</td>
<td>1110 (410-2904)</td>
<td>625 (210-1225)</td>
</tr>
</tbody>
</table>

LEU = levodopa equivalent units; DART = Dutch Adult Reading Test

The cognitive test scores of the groups are shown in Table 2. The table provides the mean scores at baseline and the mean change at follow-up. The STN and pallidotomy group did not differ at baseline in cognitive status except for number of errors on Trailmaking test part B. The pallidotomy group made significantly more errors than the STN group on this test (p=0.03). There were no significant differences at baseline on mood or behavioural questionnaires.

### Table 2: Cognitive test scores at baseline and change scores at 6 and 12 months follow-up for STN and pallidotomy groups

<table>
<thead>
<tr>
<th>Test</th>
<th>Pallidotomy</th>
<th>STN</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia Rating Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>change after 6 months</td>
<td>0.8 (6.2)</td>
<td>-2.1 (5.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>change after 12 months</td>
<td>1.2 (6.1)</td>
<td>-3.2 (8.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Category fluency</td>
<td>34.4 (8.8)</td>
<td>36.0 (8.2)</td>
<td></td>
</tr>
<tr>
<td>change after 6 months</td>
<td>-1.2 (7.9)</td>
<td>-4.0 (8.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>change after 12 months</td>
<td>-1.4 (6.3)</td>
<td>-4.0 (7.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>COWAT letter fluency</td>
<td>31.8 (12.7)</td>
<td>31.9 (13.6)</td>
<td></td>
</tr>
<tr>
<td>change after 6 months</td>
<td>-2.4 (9.3)</td>
<td>-2.8 (8.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>change after 12 months</td>
<td>-0.6 (9.3)</td>
<td>-4.5 (8.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Alternating fluency</td>
<td>42.3 (13.4)</td>
<td>45.6 (14.4)</td>
<td></td>
</tr>
<tr>
<td>change after 6 months</td>
<td>-5.0 (11.0)</td>
<td>-9.6 (11.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>change after 12 months</td>
<td>-3.7 (11.5)</td>
<td>-3.4 (6.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>PASAT</td>
<td>33.4 (16.1)</td>
<td>34.1 (16.1)</td>
<td></td>
</tr>
<tr>
<td>change after 6 months</td>
<td>1.8 (8.5)</td>
<td>1.7 (11.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>change after 12 months</td>
<td>2.5 (9.7)</td>
<td>2.5 (7.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>AVLT total score</td>
<td>36.6 (10.8)</td>
<td>37.5 (9.2)</td>
<td></td>
</tr>
<tr>
<td>change after 6 months</td>
<td>-1.9 (6.5)</td>
<td>1.1 (11.1)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>change after 12 months</td>
<td>AVLT delayed score</td>
<td>change after 6 months</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>change after 12 months</td>
<td>-1.7 (7.2)</td>
<td>2.65 (10.8)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Values are mean (SD). Negative change scores indicate decline in performance except for speeded test variables and error scores. COWAT = Controlled Oral Word Association Test; PASAT = Paced Auditory Serial Addition Test; AVLT = Auditory Verbal Learning Test; GIT = Groningen Intelligence Test. p = level of significance Mann-Whitney U test
Follow-up at 6 months

Six months after surgery, the STN group and the pallidotomy group did not show significant differences in change from baseline on the majority of the neuropsychological tests. There were significant different change scores on two executive tests, the Stroop Color Word test and the Trailmaking test. Patients in the STN group showed a slight increase in number of errors and patients in the pallidotomy group showed a decrease in number of errors. The size of the effect is large (Stroop Color Word Cohen’s d =0.94; Trailmaking test part B Cohen’s d=0.80). The increase in errors on the Stroop Color Word test did correlate significantly with a lower baseline score on DRS (r= -.63); this was not the case for errors on Trailmaking test B(r= -.29). The change in errors did not correlate with age or education or with reduction of levodopa after surgery. There were no significant differences on the behaviour and mood rating scales.

Follow-up at 12 months

Twelve months after surgery, there were no significant differences between the groups in change from baseline on the cognitive measures. The STN group showed a trend towards a decline on the Dementia Rating scale compared to the pallidotomy group. This decline on the DRS was in the STN group significantly correlated with diminished category fluency (r=0.73), but not significantly correlated with a decrease in performance on the Stroop Color-Word card (r= -0.42), which measures selective attention, the Stroop Word card (r= -0.31), which measures pronunciation speed, changes in levodopa dose (r=0.04) or changes in positive affect (r=-0.21). The decline on the DRS was in the STN group not significantly correlated with preoperative DRS (r=0.09). The other fluency measures did not convey significantly different change scores between the groups, although the STN group declined slightly more after 12 months.

On the mood and behaviour questionnaires, the STN group reported less signs of positive affect on the PANAS compared to baseline than the pallidotomy group, which reported more positive affect (STN group: baseline mean 31.3 (8.0), change after 12 months mean -3.6 (8.4); pallidotomy group: baseline mean 30.7 (9.2), change after 12 months mean 3.4 (10.7); p=0.03). The decrease in positive affect was not related to changes in levodopa dose (r=0.08). There was no differential increase between the groups in symptoms of negative affect, or depression on the other questionnaires. Baseline and follow-up scores on the questionnaires may be obtained from the first author.
One STN patient showed severe confusion and cognitive decline after surgery, predominantly in the executive functions. Switching off the stimulator did not improve these symptoms. The CT scan showed that both electrodes were displaced and the right electrode ran through the genu of the internal capsule. Compared to the preoperative CT scan no new lesions were seen. Both electrodes were repositioned with good result on motor functioning. During test stimulation there were no signs that the electrode was outside the motor part of the STN. After the second operation the patient was able to complete both neuropsychological evaluations.
Repeated analyses after exclusion of the patient with the displaced electrode from the analyses did not change the results.

**Discussion**

On the major measures of the neuropsychological evaluation we found no significant differences between bilateral STN stimulation and pallidotomy in change from baseline. However, six months after surgery the STN group made more errors than the pallidotomy group on two executive tests. This may be interpreted as diminished response inhibition, which suggests executive deterioration. After 12 months there appeared a trend for a differential effect on a cognitive screening task unfavourable for the STN group. This decline is related to diminished category fluency, which is also part of the DRS. Although both groups did not differ significantly in decline on the verbal fluency measures, the STN group decreased more. On a mood questionnaire the STN group reported less signs of positive affect than the pallidotomy group after 12 months compared to baseline. This could be suggestive for a flattened affect often seen in a dysexecutive syndrome, although in our study the decrease in positive affect is not correlated with a decrease in executive function.

Our study is in line with Witt et al 41, who found that six months after bilateral STN stimulation surgery PD patients made more errors on the Stroop Color Word test when the stimulator was turned on. Similar to our results, this impaired response inhibition subsided after 12 months. In our study, the disappearance of the effect did not seem related to changes in stimulation parameters, because they did not
Neuropsychological effects of pallidotomy versus STN DBS

change essentially. Diminished response inhibition has not been reported after pallidotomy. Notwithstanding our findings of only small group differences in change from baseline, the diminished response inhibition and the decrease in positive affect may be considered as executive decline. It is not clear how executive dysfunction after bilateral STN stimulation could be explained. Schroeder et al. found in a PET study that poorer verbal fluency during STN stimulation was related to decreased activation of the inferior frontal cortex. The spread of electrical current from the stimulator is not restricted to the sensorimotor part of the STN but given its small size it may also affect the limbic and cognitive-associative part [35]. Furthermore, the lowering of the levodopa dose in the STN group (table 1) could lead to an increase in apathy and carelessness and thus to an increase in errors.31 However, in our study the reduction in levodopa did neither correlate with the tests that showed increased executive dysfunction nor with the decrease in positive affect. The decrease in positive affect corresponds with the results of several other studies, which recently reported emotional changes after bilateral STN stimulation.5,8,12,14,23,42

In a recent study Krack et al.16 related emotional changes to several factors: pre-existing psychiatric illness, surgery-related stress, changes in medication, alterations in social life associated with improvements in motor function and the mismatch between the final outcome of treatment and the patient’s expectations. After unilateral pallidotomy only a slight improvement in general mood has been reported.43 This is in agreement with our findings. Future studies should administer more comprehensive neuropsychiatric measurements to unveil the changes in emotion after stereotactic surgery.

One of our patients showed fluctuating cognitive and behavioural impairments after bilateral STN stimulation, probably due to a lesion in the right-sided capsular genu by the passing electrode. Confusion, executive dysfunction, and behavioural changes are part of the clinical syndrome of patients with a lesion in this region.37 Apart from this specific patient, a number of patients from both groups complained after surgery about forgetfulness or word finding difficulties. This could very well be signs of executive dysfunction. In the majority of cases the negative effect of the minor cognitive decline was said to be negligible in comparison to the benefit of the treatment on motor functioning. The small sample size is a shortcoming of this study. Because of the wide variability in test results, differences may not reach statistical significance. By now
it is clear that we have to expect only subtle differences between groups with different stereotactic procedures. We need larger sample sizes to be able to confirm our findings and elucidate the interrelations. Another shortcoming was that the subgroups were unevenly distributed. As a consequence, we could not analyse right-left differences for the pallidotomy group. This right-left distinction is important; because we know from the literature that left-sided pallidotomy gives in general more negative cognitive effects than right-sided pallidotomy.\textsuperscript{43} Finally, we do not know the exact location of the STN electrodes, because we were not able to undertake postoperative MRI. The good motor improvement of the individual patients indicates that the electrodes were well placed, although the electric field in the STN could influence cells or fibre structures not directly involved in motor functioning as well.

We conclude that bilateral STN stimulation has slightly more negative effects on executive function than unilateral pallidotomy.
References


