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Absence of cognitive deficits following deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease

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Abstract

Electrical stimulation of the subthalamic nucleus is an effective treatment for the motor symptoms of Parkinson's disease. While most patients who undergo this procedure do not appear to suffer behavioral side effects, a minority experience cognitive or emotional deficits, and longitudinal studies have reported declines; however, the measures of cognitive function used have been limited. One explanation for the possible disturbance of cognitive functions is that electrical stimulation of the subthalamic nucleus disrupts the normal flow of information within cortico-striatal loops involving prefrontal, associative, or limbic cortex. We wished to assess the effect of high frequency electrical stimulation of the subthalamic nucleus in Parkinson's disease patients while they performed a comprehensive neuropsychological test battery. We selected cognitive tasks known to test the function of different cortical areas, including tests of executive function, cognitive flexibility, attention, memory, language and visual perception. Patients were tested on two separate days, with the stimulators turned on or off. Test scores were also compared to preoperative performance. In our sample of 15 patients without dementia or major depression there was no deterioration on any cognitive test as a result of stimulation. We conclude that electrical stimulation of the motor subthalamic nucleus does not cause appreciable declines in cognitive function in well-selected patients.

Keywords: High frequency stimulation; Neuropsychology; Executive function; Cognition; Movement disorder

1. Introduction

Chronic high frequency stimulation (HFS) of the subthalamic nucleus (STN) has proven to be a successful treatment in patients suffering from Parkinson's disease (PD) in whom pharmacological therapy has become inadequate. Early studies reported a reduction of motor disability (Benabid, 2003; Benabid et al., 1994; Limousin et al., 1998), in addition to the alleviation of dyskinesia, possibly due to a reduction of dopaminergic medication requirements (Moro et al.,

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1999). Recent studies investigating the long-term outcomes of HFS STN report a continued beneficial effect on motor signs and symptoms, although a worsening of speech and gait, and the development of cognitive and mood disturbances have also been observed (Krack et al., 2003; Rodriguez-Oroz et al., 2005; Schupbach et al., 2005).

HFS STN is thought to improve bradykinesia by inhibiting or disrupting the abnormal and excessive neural outflow of the STN (Dostrovsky & Lozano, 2002). However, because neural circuits originating in associative, prefrontal and limbic cortex also pass through the STN (Parent & Hazrati, 1995), there is a theoretical risk that stimulation of this structure could lead to cognitive deficits. Thus, while the benefits offered by HFS STN for motor symptoms have been consistently replicated, evidence from studies investigating the effects of HFS STN on cognition have been discordant, with some, but not all, longitudinal studies showing a minimal effect of HFS STN on cognition (Ardouin et al., 1999; Daniele et al., 2003; Funkiewiez et al., 2004; Morrison et al., 2004). Two recent long-term follow-up studies demonstrated general as well as frontal cognitive decline 5 years after surgery (Krack et al., 2003; Schupbach et al., 2005); however, this may be compatible with normal disease progression. In contrast, two studies reported significant improvements in cognition due to HFS when comparing patients ON and OFF stimulation (Jahanshahi et al., 2000; Pillon et al., 2000). In these studies, however, patients were tested off medications, such that in the OFF stimulation condition severe bradykinesia, apathy (Czernecki et al., 2005), anxiety or fatigue (Funkiewiez et al., 2003) may have affected performance on a prolonged cognitive test battery.

The goal of the present study was to address these inconsistent findings by investigating the acute effect of HFS STN on the performance of a broad range of cognitive tasks and test the hypothesis that acute HFS STN may cause cognitive impairment. Our speculation was that behaviours sensitive to frontal lobe function would be predominantly at greater risk for cognitive deficits given this region's connections to the STN via the fronto-striatal circuit (Parent & Hazrati, 1995). In particular, we wished to test patients ON and OFF stimulation while they were still taking anti-parkinsonian medications, in order to remove the potential confound of poor performance due to a severe off state.

2. Patients and methods

2.1. Patients

Fifteen outpatients with advanced idiopathic PD were recruited from a group of 29 individuals having undergone bilateral implantation of HFS STN between January 2002 and December 2004. Among the 29 patients, 2 refused to participate in this study and another 12 were excluded because they met one or more of the following criteria that could independently affect cognitive function: (1) symptoms of dementia; (2) moderate to severe depression; (3) history of alcoholism. Patient demographics are presented in Table 1. Postoperative anti-parkinsonian medication doses are listed as a levodopa equivalent dose (Möller et al., 2005). This study was approved by the Research Ethics Board of the Montreal Neurological Institute and informed consent was obtained from all participants.

2.2. Surgery

The quadripolar stimulating electrodes (Model 3387, Medtronic, Minneapolis, MN) were implanted under stereotaxic guidance using magnetic resonance imaging (MRI) for targeting and ventriculography for intraoperative guidance. Physiologic confirmation of the stereotactic target was obtained with monopolar macrostimulation of the neighboring motor fibres of the internal capsule using a curved retractable electrode (St-Jean et al., 1998). Microelectrode recording was then performed using a grid consisting of a 5-microelectrode array (Benazzouz et al., 2002). All patients met accepted criteria for PD, namely two of the three cardinal signs (bradykinesia, tremor, rigidity), response to L-dopa or dopamine agonists, and lack of evidence of other causes of parkinsonism.

2.3. Study design

A repeated measures design was used to assess the same group of participants on tasks listed in Table 2 during two separate sessions: stimulation ON, with the stimulator set at the individual's optimum therapeutic level, and stimulation OFF. To minimize practice effects, the order of the ON- and OFF-stimulation conditions was counterbalanced, put differently, some patients underwent the ON session first while other patients were tested OFF first. The mean interval between sessions was 27.3 days (S.D. $\pm$ 20.95) with all sessions performed in the morning. Each

Table 1
Demographic and clinical patient characteristics

Variable	Mean (S.D.)	Range
Females	6	
Males	9	
Current age (years)	58.1 (7.46)	45–70
Education (years)	11.3 (3.97)	5–19
Pre-surgical		
Full Scale IQ	97.7 (14.8)	77–132
Verbal IQ	98.4 (14.5)	78–132
Performance IQ	97.9 (14.9)	75–122
Post-surgical		
Full Scale IQ	96.0 (15.9)	75–128
Verbal IQ	95.6 (16.4)	72–132
Performance IQ	96.3 (14.1)	76–117
Disease duration (years)	13.6 (4.39)	8–26
Months since surgery	15.9 (12.74)	4–49
Mini-Mental State Examination	28.4 (2.01)	24–30
Beck Depression Inventory-II	8.6 (2.94)	2–12
Postoperative LED (mg/day)	854.7 (500.03)	0–1900
Stimulation parameters		
Right		
Frequency (Hz)	185 (0)	185
Pulse width (μs)	94.0 (10.56)	90–120
Amplitude (V)	2.8 (0.64)	1.8–3.6
Left		
Frequency (Hz)	185 (0)	185
Pulse width (μs)	94.0 (10.56)	90–120
Amplitude (V)	2.8 (0.82)	1.5–4.1
UPDRS		
Preoperative ON medication (100 mg)	27.2 (10.2)	13–46
Preoperative OFF medication	39.5 (12.5)	12–56
Stimulation, ON	8.4 (5.1)	3.7–19.0
Stimulation, OFF	20.1 (8.2)	5.5–38.0

Abbreviations: LED, levodopa equivalent dose.

session lasted approximately 4 h. To minimize fatigue effects and decreased motivation, all patients remained on their regular daily dosage of anti-parkinsonian medication. In addition, rest periods were interspersed throughout the sessions. Practice effects were minimized by using parallel forms of tests, where available. Tests with alternate versions include the Wechsler Memory Scale-R, Rey Auditory Verbal Memory Test, Tower of London and the Rey-Osterreith Figure (Taylor Figure). Test versions were counterbalanced across conditions; in other words, some patients received test version 1 during the ON session while in other patients, it was administered during the OFF session. Both test versions used in our study have been standardized and versions have previously been tested for equivalency (Lezak, Howieson, & Loring, 2004; Spreen & Strauss, 1998). For the ON session, stimulators were left on at the patient's usual settings. For the OFF session, stimulators were turned off 60 min before the start of the testing session, a period chosen to allow the reappearance of parkinsonian features, but to minimize subjective feelings of anxiety and discomfort due to physical disturbances. Previous neuropsychological studies using an ON versus OFF design set a stimulator time OFF time between 30 and 60 min prior to testing (Daniele et al., 2003; Jahanshahi et al., 2000). As part of their pre-surgical clinical workup, all patients also underwent a preoperative neuropsychological evaluation. The battery of tests was a subset of the one used for this study and outlined in Table 1, so that all patients underwent three testing sessions in all. The mean interval between

Table 2
Measures and assessment tools

Domain	Test	Behavior measured
Verbal memory	Rey Auditory Verbal Memory Test (form 1 and 2)	Verbal learning, free recall and recognition of unconnected concrete words
	Wechsler Memory Scale (form 1 and 2), logical memory test	Free recall of contextual material (short prose passages)
Visual memory	Rey Osterreith Figure/Taylor Figure, delayed recall	Free recall complex geometric design
Working memory	Externally Ordered Working Memory Test	Monitoring verbal stimuli
	WAIS-Digit Span (backward)	Monitoring auditory stimuli
Executive function	Tower of London	Planning, problem solving
	Wisconsin Card Sorting Test	Concept formation, set shifting, set maintenance, feedback utilization
Attention	Stroop (Golden, 1978)	Suppression of habitual responses, sensitivity to interfering stimuli, processing speed
	Symbol Digital Modalities Test	Visual scanning and tracking ability
	WAIS-Digit Span (forward)	Auditory attention
Visuospatial	Hooper Visual Organizational Test	Ability to mentally manipulate and reorganize fragmented stimuli
	Rey Figure/Taylor Figure (form 1 and 2), copy	Measure visuoconstructional organization (fragmentation, planning, placement and size distortion)
Language	Boston Naming Test	Object-naming ability
	Controlled Oral Word Association Test	Cognitive flexibility and verbal fluency
Motor function	Sequential and Simple Tapping (Thurstone, 1944)	Speed and manual coordination
	Grooved Pegboard	Manual dexterity
Motor disability	United Parkinson's disease Rating Scale (UPDRS part III)	Rating of motor symptoms

pre-surgical evaluation and the first of the two post-surgical evaluations (either ON or OFF) was 19.5 months (S.D. $\pm$ 13.29).

2.4. Measures

The Mini-Mental State Examination and the Beck Depression Inventory-II were used to screen for dementia and depression, respectively. Both were administered preoperatively and during the stimulator ON condition, as part of patient's clinical assessments. Cut-off scores for exclusion from this study were 24 for the Mini-Mental State Examination and 15 for the Beck Depression Inventory-II (Lezak, Howieson, & Loring, 2004; Spreen & Strauss, 1998).

Colour perception was assessed using Dvorine pseudo-isochromatic plates (Dvorine, 1953). Two patients showed a moderate deficit and one showed a severe deficit. As all patients were able to discriminate the task stimulus colours for the Tower of London, all results were included in statistical analyses. However, scores for the Stroop test and the Wisconsin Card Sort task for the patient with severe colour perception defect were excluded because they could have contaminated the results. The two patients with the moderate colour perception deficit were able to clearly distinguish the stimulus colours for the Stroop and Wisconsin Card Sort task, and their data are included in the analysis for both tests.

Multiple cognitive domains were assessed including executive function, verbal working memory, attention, language, visual perception, verbal and visuospatial memory and motor function. The Unified Parkinson's Disease Rating Scale (UPDRS) III–motor section (Fahn & Elton, 1987) was administered by one of us (MF) to assess motor disability. Tests used and the functions they are purported to measure are outlined in Table 2.

2.5. Statistical analysis

A paired *t*-test analysis was performed to compare performances of the motor and neuropsychological measures administered during stimulation ON and OFF conditions. Since paired *t*-tests did not reveal significant differences between the ON and OFF stimulation conditions on tests assessing cognitive function, post hoc analyses were performed to better understand these non-significant results. 95% confidence intervals were calculated to give an estimate of the maximum difference we could have potentially overlooked given our study design. Using this range, we were able to determine whether scores could have potentially declined to clinically meaningful levels as a result of stimulation.

In addition, in a smaller subset of tests a separate paired *t*-test was performed to compare baseline (preoperative) test performances to postoperative (ON condition) test performances. A significance level of $p < 0.05$ was used for all analyses. Analyses were performed with SPSS version 11 (SPSS Inc., Chicago, IL) and G-Power (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/).

3. Results

Comparison of ON and OFF stimulation conditions revealed no difference in task performances on measures of executive function, working memory, attention, language, visuospatial perception, visual memory, and verbal memory (Table 3). Ratings on the UPDRS III motor section indicated a significant 12-point improvement of clinical motor signs during stimulation ($p < 0.0001$). Similar results were obtained for skilled motor function. On the grooved pegboard test, time interval for peg insertion (a measure of fine manual dexterity) was significantly improved by stimulation when using the dominant hand ($t\,(14) = -3.343$, $p < 0.005$) or the non-dominant hand ($t\,(14) = -4.633$, $p < 0.0001$). On the sequential tapping task stimulation significantly improved motor speed for the non-dominant hand ($t\,(14) = 2.287$, $p < 0.038$) but not for the dominant hand ($p > 0.05$). A trend towards significance was observed for bimanual sequential tapping ($t\,(14) = 1.881$, $p = 0.081$).

In a subset of tests, we compared baseline performances to post-surgical outcome (ON condition). As seen in Table 4, a paired *t*-test revealed no significant differences between preoperative and current Full Scale IQ ratings ($p > 0.05$). No significant differences in task performance on measures of executive function, working memory, language, visuoperception, visuospatial memory, and verbal memory were observed; however, on the Stroop-Interference, a significantly higher sensitivity to interfering stimuli was observed postoperatively ($t\,(13) = 3.626$, $p < 0.003$). Processing speed (word reading) was also significantly reduced ($t\,(13) = 3.434$, $p < 0.004$).

4. Discussion

4.1. Acute effect of stimulation

We administered an extensive battery of tests known to be sensitive to dysfunction of various brain regions to PD patients with implanted STN stimulators. The main finding is that stimulation did not cause detectable impairments in cognitive performance in this group of non-demented, non-depressed, relatively young PD patients (all but two were under 65 years of age).

As expected, there was a significant beneficial effect of STN stimulation on parkinsonian motor features, as demonstrated by a mean 12-point decrease in the UPDRS-III motor score. The effect was most notable on the rigidity and bradykinesia scores, consistent with previous data (Kumar et al., 1998; Limousin et al., 1998, 1995). In addition, skilled motor function showed a moderate improvement with stimulation. Manual dexterity was significantly improved bilaterally, however sequential tapping was ameliorated to a lesser extent. The sequential tapping task used here has previously been found to be reliant on frontal and temporal cortices (Leonard, Milner, & Jones, 1988), suggesting that it is testing relatively complex cognitive aspects of movement beyond simple bradykinesia. Therefore, as we failed to find an improvement on other tasks reliant on the integrity of temporal or frontal lobe functions, it is perhaps not surprising that HFS STN should not increase sequential tapping speed or coordination to the same extent as fine manual dexterity.

Previous studies on the cognitive effects of HFS STN, mainly on neuropsychological tasks sensitive to frontal lobe function, have yielded conflicting results. Two early studies reported significant improvements in psychomotor speed

Table 3
ON vs. OFF test performance results

	N	ON (S.D.)	OFF (S.D.)	*p*-Value	*d*	95% C.I.
Executive function						
Wisconsin Card Sorting Test						
Total categories	14	4.3 (2.2)	3.9 (2.1)	0.535	0.186	3.5–4.2
Total perseverative errors	14	25.0 (23.3)	29.1 (21.4)	0.778	0.183	25.7–32.4
Total nonperseverative errors	14	3.1 (3.6)	3.1 (2.7)	0.947	0.000	2.6–3.5
Tower of London						
Total correct	15	6.3 (2.5)	5.7 (2.6)	0.508	0.235	5.3–6.7
Total moves	15	22.5 (28.9)	25.1 (20.3)	0.589	0.092	22.2–28.0
Total rule violation	15	0.5 (1.1)	0.2 (0.4)	0.413	0.361	0.1–0.3
Working memory						
Petrides externally ordered task (%)	15	77.7 (17.4)	81.8 (14.7)	0.170	0.255	79.6–83.9
Digit Span-backward	13	5.4 (2.3)	5.4 (2.3)	1.000	0.000	5.0–5.8
Attention						
Stroop test						
Colour naming (# in 45 s)	14	57.6 (10.1)	54.8 (14.5)	0.129	0.224	52.5–57.0
Word reading (# in 45 s)	14	77.4 (17.3)	79.3 (20.2)	0.562	0.101	76.2–82.4
Interference index (C/W) (# in 45 s)	14	31.9 (10.1)	32.3 (11.2)	0.797	0.038	30.5–34.0
SDMT-oral (# in 90 s)	14	33.5 (11.4)	34.8 (12.0)	0.336	0.111	33.8–35.8
Digit Span-forward	15	7.0 (2.3)	6.5 (2.5)	0.327	0.208	6.2–6.7
Language						
FAS						
Letter F	15	8.5 (4.3)	8.4 (4.6)	0.884	0.064	7.7–9.1
Animals	15	14.7 (4.9)	14.0 (5.6)	0.494	0.133	13.1–14.8
Letter S	15	8.3 (4.4)	7.3 (4.0)	0.207	0.168	6.9–7.6
Boston Naming	15	46.0 (8.9)	45.5 (8.2)	0.389	0.041	44.3–46.7
Visuospatial function						
Rey Osterreith Figure, copy	15	17.8 (5.3)	17.6 (4.9)	0.887	0.039	17.4–17.8
Hooper Visuospatial Organization	13	21.7 (5.3)	21.0 (5.2)	0.407	0.133	20.1–21.8
Memory						
Rey Auditory Verbal Learning Test						
Total learning score	15	42.1 (10.8)	41.9 (9.3)	0.914	0.016	40.5–43.2
Delayed recall	15	7.9 (3.2)	8.3 (2.5)	0.509	0.139	7.9–8.7
Delayed recognition	15	11.9 (3.5)	11.1 (3.2)	0.176	0.239	10.6–11.6
Wechsler Logical Memory Test						
Immediate recall	15	10.0 (3.3)	9.7 (3.1)	0.690	0.093	9.3–10.2
Delayed recall	15	6.7 (3.1)	6.5 (3.5)	0.825	0.042	5.9–7.0
REY Osterreith Figure, delayed recall	15	10.5 (5.3)	9.7 (4.6)	0.281	0.161	9.0–10.4
Motor function						
Unimanual Sequential Tapping						
Dominant	15	95.4 (25.3)	94.9 (25.9)	0.870	0.019	91.9–98.6
Non-dominant	15	88.1 (26.5)	82.3 (27.1)	0.038		
Bimanual Tapping	15	16.8 (4.9)	15.4 (4.9)	0.081		
Grooved Pegboard, dominant (sec)	15	139.1 (45.8)	183.4 (74.4)	0.005		
Grooved Pegboard, non-dominant (sec)	15	137.1 (31.0)	177.1 (48.8)	0.000		
UPDRS-Part III	14	8.4 (4.5)	20.1 (8.2)	0.000		

S.D.: standard deviation; C.I.: confidence interval; *d*: Cohen's *d* (effect size, defined as difference of the means over the pooled standard deviation; 0.2 is indicative of a small effect, 0.5 a medium and 0.8 a large effect size).

Table 4
Preoperative vs. postoperative (ON) test performance results

	N	PRE (S.D.)	ON (S.D.)	*p*-Value	*d*	95% C.I.
Intelligence						
Full-Scale IQ rating	15	97.7 (14.8)	96.0 (15.9)	0.357	0.111	95.4–100.0
Verbal IQ rating	15	98.4 (14.5)	95.6 (16.4)	0.137	0.181	96.0–100.7
Performance IQ rating	15	97.9 (14.9)	96.3 (14.1)	0.568	0.110	95.8–100.0
Executive function						
Wisconsin Card Sorting Test						
Total categories	14	4.0 (2.1)	4.3 (2.2)	0.513	0.140	3.6–4.3
Total perseverative errors	14	34.8 (29.3)	26.3 (23.7)	0.362	0.319	30.2–39.3
Total nonperseverative errors	14	2.4 (2.3)	3.4 (3.7)	0.133	0.325	1.8–3.0
Tower of London, total correct	14	6.7 (2.2)	6.3 (2.5)	0.633	0.170	6.3–7.1
Working memory						
Digit Span-backward	15	5.9 (2.2)	5.9 (2.5)	0.876	0.000	5.5–6.2
Attention						
Stroop test						
Colour naming (# in 45 s)	14	64.7 (16.7)	57.8 (10.6)	0.061		
Word reading (# in 45 s)	14	93.1 (23.0)	77.4 (17.3)	0.004		
Interference index (c/w) (# in 45 s)	14	36.4 (10.3)	31.9 (10.1)	0.003		
Digit Span-forward	15	7.0 (2.4)	7.2 (2.6)	0.678	0.080	6.6–7.3
Language						
Boston Naming	15	47.7 (7.7)	46.0 (8.9)	0.128	0.204	46.5–48.8
Visuospatial function						
Rey Osterreith Figure, copy	15	21.0 (6.2)	17.8 (5.3)	0.120	0.555	20.11–21.88
Memory						
Rey Auditory Verbal Learning Test						
Total learning score	15	43.2 (8.2)	42.1(10.8)	0.494	0.115	42.0–44.4
Delayed recall	15	7.9 (3.4)	7.9 (3.2)	0.918	0.000	7.4–8.3
Delayed recognition	15	11.7 (3.9)	11.9 (3.5)	0.785	0.054	11.1–12.3
Wechsler Logical Memory Test						
Immediate recall	15	9.3 (4.1)	10.0 (3.3)	0.479	0.188	8.7–9.9
Delayed recall	15	6.4 (4.3)	6.7 (3.1)	0.798	0.083	5.7–7.0
REY Osterreith Figure, delayed recall	15	10.6 (6.4)	10.5 (5.3)	0.946	0.017	9.6–11.5
Motor Function						
Unimanual Sequential Tapping						
Dominant	15	96.3 (34.5)	92.9 (32.0)	0.652	0.102	91.4–101.2
Non-dominant	15	92.7 (32.2)	84.2 (28.8)	0.270	0.278	88.1–97.3
Bimanual Sequential Tapping	15	20.5 (14.8)	16.7 (5.4)	0.336	0.341	18.4–22.6
Grooved Pegboard	15					
Dominant	15	148.6 (73.6)	128.0 (38.4)	0.572	0.351	138.1–159.1
Non-dominant	15	149.0 (44.6)	125.9 (22.4)	0.248	0.654	142.6–155.4
UPDRS	15	27.2 (10.2)	8.4 (5.1)	0.000		

For abbreviations see notes to Table 3.

and working memory (Jahanshahi et al., 2000; Pillon et al., 2000). In both of these studies, however, patients were tested off anti-parkinsonian medication. It is possible that, when testing was done OFF stimulation and OFF medication, performance on certain tasks worsened because of motor disability and discomfort, reduced motivation and arousal, or increased apathy. Both dopaminergic therapy and HFS STN have been shown to reduce apathy (Czernecki et al., 2005), fatigue, anxiety and tension (Funkiewiez et al., 2003) in PD patients.

More recent studies have shown that when patients remain on regular doses of medication, stimulation of the STN produces either minimal or no changes in cognitive function (Halbig et al., 2004; Morrison et al., 2004; Witt et al., 2004). In a comparison of two learning tasks it was shown that STN stimulation improved non-declarative memory while simultaneously causing impairment in declarative memory (Halbig et al., 2004). Similarly, another group found that STN stimulation improved random number generation while impairing the Stroop task (Witt et al., 2004), with no effect on other neurocognitive tasks. Both of these studies suggest that the improvement in one domain may be accompanied by impairment in another. Specific cognitive deficits on patients tested OFF medication have also been reported with HFS STN in the domains of response interference (Schroeder et al., 2002), verbal fluency (Schroeder et al., 2003), and conditional associative learning (Jahanshahi et al., 2000). In the first two studies, impaired performance with stimulation was associated with reduced neuronal activation in relevant cortical areas as assessed by positron emission tomography.

Longitudinal studies have generally demonstrated a lack of clinically significant cognitive impairment for well-selected patients undergoing STN stimulator surgery (Daniele et al., 2003; Funkiewiez et al., 2004; Rodriguez-Oroz et al., 2005; Witt et al., 2004), although this is not a universal finding (see review by Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005). Two long-term studies did report a slight but significant decline in the Mattis dementia rating scale over 5 years (Krack et al., 2003; Schupbach et al., 2005), a result that could be related to normal disease progression. Although global measures of cognitive function tend to be unaffected by STN stimulation, impairments in specific cognitive functions have been described. The most commonly reported of these is impaired verbal fluency (Alegret et al., 2001; Ardouin et al., 1999; Daniele et al., 2003; Funkiewiez et al., 2004; Morrison et al., 2004; Pillon et al., 2000). An imaging study in 7 patients showed that STN stimulation impaired verbal fluency while disrupting cerebral blood flow in speech areas in the left frontal and temporal cortices (Schroeder et al., 2003). However, we did not find a reduction in verbal fluency as a result of STN stimulation, using the Controlled Oral Word Association Test. This suggests that electrical stimulation per se may not be the cause of the postoperative decline in verbal fluency. Indeed, one longitudinal study found that verbal fluency was impaired at 3 months postoperatively with the stimulator turned off, but that it improved at 6 and 12 months with the stimulator turned on (Daniele et al., 2003), while several studies with ON vs. OFF designs have failed to detect a deleterious effect of STN stimulation on verbal fluency (Jahanshahi et al., 2000; Morrison et al., 2004; Pillon et al., 2000; Witt et al., 2004).

4.2. Preoperative versus postoperative

We were able to compare preoperative performances to postoperative (ON condition) performances in a subset of tests used in this study, although this was not the main objective. During the preoperative evaluation, patients remained on their daily dosage of medication. As seen in Table 4, here again we did not detect significant differences between condition means with the exception of the Stroop test. During the postoperative condition, a significantly higher sensitivity to distraction, as well as slowed processing speed (colour and word naming), were observed. This finding concurs with previous studies reporting on preoperative versus postoperative outcome (Alegret et al., 2001; Dujardin, Defebvre, Krystkowiak, Blond, & Destee, 2001). Note however that there was a broad range in the timing of the postoperative evaluation (4–49 months).

4.3. Limitations and conclusion

There are limitations to our study. As in previous studies, our patient sample was relatively small. This, of course, prevents us from generalizing our findings to a wider and more heterogeneous population of PD patients. In order to determine whether clinically meaningful changes were overlooked because of low power, further analyses were performed. On almost all of our cognitive tasks, confidence intervals remained outside of the ranges indicative of clinical impairment (Table 3). Although confidence intervals did point to possible stimulation-induced decreases on tests measuring verbal working memory and planning (rule violation), test score decreases were not within a range indicative of clinically significant decrease or impairment. Possible stimulation-induced increases for results on tests measuring immediate memory for digits and word fluency (phonemic category) were also clinically insignificant. Concerning pre- versus postoperative test results (Table 4), similarly, on a task measuring cognitive flexibility, confidence intervals indicated possible stimulation-induced changes that were, as well, not clinically relevant. However, test scores for visuospatial construction were within a range indicative of possible clinically relevant impairments.

The second limitation concerns the nature of repeated designs and the possibility of practice effects. We took great care to control for learning effects by counterbalancing ON versus OFF test sessions and using alternative versions of tests when possible. We also selected tests that were known to be insensitive to practice effects across short periods of time. For test-retest data, the reader is referred to McCaffrey, Duff, and Westervelt (2000). Additionally, we compared the results of postoperative Session 1 to those of postoperative Session 2, and did not observe significant differences irrespective of whether patients were ON or OFF stimulation for Session 1, for most of the tests. There were however two exceptions: results showed a decline in the mean performance score for the second testing session for the recognition segment of the Rey Auditory Verbal Learning Test, and a significant increase in scores was observed for the Boston Naming Test, suggesting the possible existence of order effects. These order effects cannot account for our null results as we counterbalanced the ON and OFF sessions.

The results of the present study extend previous investigations that have sought to define the cognitive effects of HFS STN in Parkinson's disease patients. Within our group of non-demented and non-depressed patients, our findings do not support the notion that HFS STN produces significant deterioration in cognitive function. These results, however, should be interpreted with caution. Our patients, for the most part, were relatively young (under 65 years of age) and did not show evidence of cognitive impairment, dementia or psychiatric symptoms preoperatively. As well, this study can only address acute and relatively short-term effects of the HFS to the STN. Nonetheless, our results confirm previous studies showing that, for appropriately selected patients, HFS STN is a cognitively safe procedure.

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