Transient Executive Dysfunction Following STN-DBS in Parkinson's Disease

N. Auclair-Ouellet, S. Chantal, L. Cantin, M. Prud'homme, M. Langlois, J. Macoir

Can J Neurol Sci. 2011; 38: 360-363

Deep brain stimulation (DBS) is an alternative treatment for patients with advanced Parkinson's disease (PD) inadequately or insufficiently controlled with pharmacological treatments. It consists of implanting an electrode in a specific subcortical region to modulate its electrical activity. The structure most often targeted in PD is the subthalamic nucleus (STN). Chronic high frequency stimulation of the STN helps to reduce tremor, dyskynesia and medication doses, and its effectiveness is now well established[1]. However, there is also a risk that STN-DBS could lead to cognitive side effects but evidence of this is scarce and controversial. Some studies showed minimal influence of STN-DBS on cognition[2], while others reported decline[3,4] in cognitive efficiency in similar (verbal fluency, executive functions and working memory) or different domains (e.g. improved vs. reduced performance on procedural and declarative memory respectively[5]).

The purpose of this study was to characterize the cognitive performance of PD subjects having undergone bilateral STN-DBS and to identify short- and longer-term effects on various domains of cognition.

Method

Seven patients who underwent DBS surgery at the Hôpital de l'Enfant-Jésus in Quebec City, Canada were recruited. The participants' clinical and demographic characteristics at baseline are presented in Table 1.

Quadripolar DBS electrodes (Model #3389, Medtronic Inc., Toronto, Canada) were guided within each STN during the same surgical procedure using a stereotactic frame and magnetic resonance imaging (MRI) targeting. The accuracy of the electrode placement was confirmed by microelectrode recording followed by clinical examination with or without stimulation. Once the exact nerve cells were located, recording electrodes were replaced by permanent DBS leads. The location of each electrode contact was calculated according to the electrode's dimension and electrophysiological data. A Medtronic Kinetra stimulator was implanted subcutaneously two weeks after surgery. The active contact of the electrode is located above the STN (one patient), at the rostral border (three patients) or in the middle part (two patients) of the STN. Different electrode trajectories were tested in one patient and the definitive electrode location was difficult to evaluate. Patients remained conscious throughout the procedure so they could provide feedback on the stimulation and report on side effects (nausea, dizziness, etc.). Surgical complications occurred in two patients (thrombophlebitis), and one of them received anticoagulant therapy.

Motor performance of the participants was measured with a comprehensive test battery including the UPDRS and the Timed Up and Go (TUG) test. Patients' performance on a comprehensive neuropsychological test battery was also tracked over 12 months in three testing sessions: before surgery, while patients were taking medication, and at 6 and 12 months after activation of the stimulator while patients were 'on' medication and 'on' stimulation with the stimulator set at the individual's optimum therapeutic level. Parallel forms of the tests were used when available.

The neuropsychological battery comprised two questionnaires for the evaluation of levels of depression (Beck Depression Inventory; BDI) and anxiety (Beck Anxiety Inventory; BAI) as well as standardized tests assessing different cognitive functions in seven cognitive domains: 1) attention: digits forward from the Neuropsychological Assessment Battery; 2) speed of information processing: Stroop word and color subtests for visuo-oral modality, and symbol search and digit symbol coding from the Wechsler Adult Intelligence Scale 3rd Edition for visuo-motor modality; 3) working memory: digits backward from the Neuropsychological Assessment Battery and

Table 1: Clinical and demographic characteristics of participants at baseline

	1	2	3	4	5	6	7	Mean (S.D.)
Age	69	64	68	66	77	69	68	68.71 (4.07)
Sex	m	m	f	f	f	f	m	
Education	6	9	12	19	6	6	3	8.71 (5.35)
Disease duration	10	18	19	10	18	13	29	16.71 (6.63)

From the Faculté de médecine – Département de réadaptation (NAO, JM), Centre de recherche Université Laval (NAO, JM) – Robert-Giffard, Université Laval; Centre hospitalier affilié universitaire de Québec – Hôpital de l'Enfant-Jésus – Département des sciences neurologiques (SC, LC, MP, ML), Québec, Canada.

Received January 15, 2010. Final Revisions Submitted October 14, 2010.

Correspondence to: Joel Macoir, Faculté de médecine, Département de réadaptation, Université Laval, Pavillon Ferdinand-Vandry, Québec (Québec), G1K 7P4, Canada.

Table 2: Motor and behavioural characteristics of participants

	Baseline		6 months		12 months	
	ON	OFF	ON	OFF	ON	OFF
UPDRS-I	3.29 (1.50)	3.29 (1.50)	1.71 (0.95)	1.83 (0.98)	1.00 (1.29)*	0.71 (1.25) *
UPDRS-II	15.57 (5.41)	30.29 (5.02)	12.43 (6.60)	15.00 (5.01)	13.14 (4.38)	14.43 (4.08) **
UPDRS-III	23.29 (13.87)	47.14 (12.76)	19.86 (6.52)	25.17 (6.56)	22.29 (4.89)	26.57 (6.37) *
UPDRS-IV	6.29 (4.35)	4.71 (2.43)	1.57 (1.72)	2.75 (1.71)	0.86 (1.22) *	2.00 (2.83)
TUG[1]	12.52 (2.73)	24.86 (11.97)	10.28 (4.77)	15.38 (11.76)	9.93 (2.79) [t]	12.36 (6.17) [t]
BDI[2]	10.14 (4.98)	N/A	10 (5.70)	N/A	11.57 (6.85)	N/A
BAI[3]	11.57 (5.71)	N/A	8 (12.59)	N/A	6.71 (6.21)	N/A

1. Timed Up and Go, average for the two trials; 2. Beck Depression Inventory; 3. Beck Anxiety Inventory; ON: on medication; OFF: off medication; Comparison of performance between baseline and 12 month follow-up: * : $p < .05$; ** : $p < .01$; [t]: Statistical tendency

Brown-Peterson task; 4) learning and memory: California Verbal Learning Test-2nd Edition for verbal memory, and immediate and delayed recalls of the Rey Complex Figure Test and Benton Visual Retention Test for visual memory; 5) language: category verbal fluency and Boston Naming Test; 6) visuospatial/constructional abilities: copy of the Rey Complex Figure Test and clock copying from the Parietal Lobe Battery; and 7) executive functions: letter fluency, Stroop interference subtest, Tower of London and Clock Drawing Test.

A composite domain Z-score was calculated to represent the magnitude efficiency for each of these cognitive domains and to maximize the assessment of functional impairment. To accomplish this, a subset of representative variables was selected from each neuropsychological test and performances (raw scores) were converted to standardized scores. Composite domain scores were subsequently created for each patient by summing representative Z-scores (or scaled scores) and dividing by the number of measures. The composite domain Z-scores were compared between follow-up sessions using paired sample t-tests. The scores were also analyzed using a descriptive approach in order to position each patient in relation to the mean. To do this, the variation in Z-scores between the two follow-up sessions was calculated and categorized using a criterion of ±0.50 standard deviation considered as a relevant change. For scaled scores, a change was considered relevant when it was associated with a change in the level of impairment (e.g. from normal performance to mild impairment).

Results

A positive effect of STN-DBS surgery on medication dosage as well as on the symptom severity of Parkinson's disease was observed in all seven patients. The average Levodopa and Carbidopa dose for 24 hours decreased after STN-DBS (average Levodopa dose: before surgery = 1078.57mg (SD = 552.91); after surgery = 585.71mg (SD = 264.13); average Carbidopa dose: before surgery = 269.64mg (SD = 138.23); after surgery = 146.43mg (SD = 66.03)). As shown in Table 2, average UPDRS scores improved after STN-DBS. Significant improvement in performance (OFF-medication) between baseline and 12 months after surgery was observed in parts II (Activities of daily living) and III (Motor examination) of the scale. A tendency towards significant improvement on the TUG test (a test of functional mobility) was also observed when comparing the participants' performance at baseline and 12 months. No significant change was observed in the individual scores for depression (BDI) and anxiety (BAI) between baseline and follow-up at 6 and 12 months.

As shown in Table 3, a significant increase in performance was observed for learning and verbal memory between 6 and 12 months ($p < .05$). A significant decrease in executive functioning was observed between 0 and 6 months ($p < .01$), followed by a significant improvement in performance between 6 and 12 months ($p = .01$). A statistical tendency towards improvement was noted between 0 and 12 months for executive functions ($p = .056$).

Descriptive results showed a decline in performance in 24% of the cases (all patients and all cognitive domains included) between baseline and 6 months, compared to 12% between 6 and 12 months. With respect to specific domains, the scores of six of the seven patients (85.7%) diminished between baseline and 6 months in the domain of executive functions. For learning and verbal memory, 71.4% of the patients improved their score between 6 and 12 months. Therefore, results from the descriptive analyses were congruent with those reported with the statistical method. These two approaches allow change patterns to be identified, especially in the domain of executive functions.

Conclusion and Discussion

Except for executive functions, no cognitive domain was negatively affected by STN-DBS in the PD patients reported. Cognitive functions dependent on frontal lobes (such as executive functions) are suspected to be more vulnerable since

https://doi.org/10.1017/S031716710001163X Published online by Cambridge University Press

Table 3: Mean scores (SD) and comparison of the patients' performance at the three times of measure

	Z- scores (scaled score) (SD)			Comparison of measures		
Cognitive domains	Baseline	6 months	12 months	Baseline-6 months	6-12 months	Baseline-12 months
Attention	-1.07 (.56)	-1.25 (.88)	-1.3 (.94)	.13	.80	.09
Speed of information processing						
- Visuo-oral modality	-1.31 (.91)	-1.11 (.89)	-1.53 (1.15)	.20	.14	.22
- Visuo-motor modality	6.33 (2.52)	6.88 (2.78)	8.67 (1.15)	.74	.74	.66
Working memory	-.27 (1.15)	-.28 (1.09)	-.52 (.99)	.95	.29	.48
Learning and memory						
- Verbal modality	.47 (.81)	.05 (.66)	.93 (.98)	.21	.04*	.37
- Visual modality	-.71 (1.11)	-.26 (1.32)	-.27 (1.43)	.53	.55	.57
Language	.19 (1.11)	.22 (.94)	.11 (.68)	.92	.63	.79
Visuospatial/constructional abilities	-.97 (1.67)	-.54 (1.26)	-.26 (2.22)	.50	.70	.15
Executive functions	.26 (.47)	-.50 (.74)	-.03 (.43)	.006**	.015*	.056[t]

**: $p < .01$; *: $p < .05$; [t]: statistical tendency

the connection between the STN and the frontal lobe, via the fronto-striatal circuit, could be disrupted by the electrical stimulation. Our results are partly consistent with those reported in a meta-analysis conducted by Parsons et al[6], which found a significant decline not only in executive function but also in verbal learning and memory. In the present study, we showed that the decline in executive function seemed to be transient since performance at 12 months tended to return to the baseline level. This is consistent with the results reported by Zangaglia et al[7], who followed the cognitive evolution of 32 PD patients three years after STN-DBS surgery. In this study, the patients' performance in the domain of executive functions showed a decrease after six months. Twelve months after surgery however, their performance had returned close to the baseline value. This result was maintained three years after surgery and supports the finding of a transient deficit.

Age has been identified as a factor influencing cognitive performance after STN-DBS. Saint-Cyr et al[8] found that cognitive decline was more consistently observed in patients older than 69 years. In our study, only one patient was older than 69. With respect to UPDRS and TUG scores, as well as for neuropsychological measures, the performance of this patient was similar to that observed for younger patients.

This study also has some limitations. First, only a few patients were studied, which affects statistical power. Thus the conclusions drawn from the analyses should be interpreted with caution. Furthermore, the lack of statistical power prevented us from testing correlations between the participants' performance at the motor and cognitive level and other variables of interest, such as the programming parameters of the electrode. These parameters are adjusted many times during the first six months after surgery, and this could have influenced the results. The length of the follow-up is also shorter than in the majority of recent studies, which include follow-up as long as five years after surgery[3,9]. Interest in STN-DBS has increased in recent years and studies now include larger sample sizes. Some studies also include a comparison group[7,10], which helps to identify the respective effects of the surgery and the natural course of the disease on cognitive functions. Future studies should include a comparison group of PD patients receiving the best medical treatment. Another limitation is that the examiner was not blinded to the surgical status of the patients. This may be a source of bias in the study.

In conclusion, our results show that, in the seven patients reported, STN-DBS is "cognitively safe". Even if there are some differences in the nature and degree of cognitive impairment reported across studies, many of them acknowledge that "STN-DBS is associated with at least mild cognitive change"[11]. This underscores the importance of gathering detailed information on patients' preoperative cognitive profile and following their cognitive evolution closely after surgery.

Acknowledgements

The first author was supported by a grant from the Réseau provincial de recherche en adaptation-réadaptation (REPAR) of the Fonds de la recherche en santé du Québec (FRSQ). We are indebted to all the participants for their cooperation.

Author roles:

- Auclair-Ouellet, N. Execution of statistical analysis; writing of the first draft of the manuscript.
- Chantal, S. Selection and administration of neuro-psychological measures; supervision of statistical analysis; review and critique of the manuscript.
- Cantin, L. Neurosurgeon; implantation of STN-DBS.
- Prud'homme, M. Neurosurgeon; implantation of STN-DBS.
- Langlois, M. Neurologist; adjustment of stimulation parameters and medication.
- Macoir, J. Organization and supervision of the project; contribution to the writing of the first draft of the manuscript; completion and preparation of the article for submission.

References

1. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet. 2009;8(1):67-81.
2. Fraraccio M, Ptito A, Sadikot A, Panisset M, Dagher A. Absence of cognitive deficits following deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Arch Clin Neuropsychol. 2008;23(4):399-408.
3. Schupbach WM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry. 2005;76(12):1640-4.
4. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63-73.
5. Halbig TD, Gruber D, Kopp UA, et al. Subthalamic stimulation differentially modulates declarative and nondeclarative memory. Neuroreport. 2004;15(3):539-43.
6. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Troster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet. 2006; 5(7):578-88.
7. Zangaglia R, Pacchetti C, Pasotti C, et al. Deep brain stimulation and cognitive functions in Parkinson's disease: A three-year controlled study. Mov Disord. 2009; 24(11):1621-8.
8. Saint-Cyr JA, Trépanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain. 2000;123(10):2091-108.
9. Contarino MF, Daniele A, Sibilia AH, et al. Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007;78(3):248-52.
10. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet. 2008;7(7): 605-14.
11. Halpern CH, Rick JH, Danish SF, Grossman M, Baltuch GH. Cognition following bilateral deep brain stimulation surgery of the subthalamic nucleus for Parkinson's disease. Int J Geriatr Psychiatry. 2009;24(5):443-51.