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Article abstract—*Background:* In a previous study on a consecutive series of 62 patients with PD, the authors showed that bilateral subthalamic or pallidal continuous high-frequency deep brain stimulation (DBS) affects neither memory nor executive functions 3 to 6 months after surgery. *Objective:* To investigate the specific effects of DBS by comparing the performance of patients with the stimulator turned "on" and "off." *Methods:* The performance of 56 patients on clinical tests of executive function was compared after 3 and 12 months of DBS of the subthalamic nucleus (STN; n = 48) or the internal globus pallidus (GPi; n = 8) with the stimulator "on" or "off." Global intellectual efficiency, verbal learning, and mood were also evaluated with the stimulator "on." The performance of another group of 20 patients was compared after 6 months of DBS of the STN (n = 15) or the GPi (n = 5) with the stimulator "on" or "off" on more experimental tests recently shown to be more sensitive to L-dopa therapy. *Results:* When the stimulator was "on," STN patients showed a mild but significant improvement in psychomotor speed and working memory. In comparison with the presurgical state, STN patients had no cognitive deficit at 12 months, except for lexical fluency. There was no differential effect of STN or GPi stimulation. *Conclusions:* 1) The specific effect of DBS seems to mimic the action of L-dopa treatment in the cognitive as in the motor domain; 2) the surgery associated with DBS does not appear to affect the cognitive performance of patients with PD 12 months later, except for a mild deficit in lexical fluency.

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The failure of levodopa and dopaminergic medication to achieve long-term symptom relief in patients with PD, coupled with an improvement in our knowledge of basal ganglia pathophysiology and advances in stereotactic techniques, have led to renewed interest in surgical treatments, through pallidotomy and continuous high-frequency deep brain stimulation (DBS). Posteroventral pallidotomy improves the cardinal symptoms of PD and levodopa-induced dyskinesias, particularly on the side contralateral to the surgical lesion,[1,2] but consistent cognitive deficits may be demonstrated when the group of patients is sufficiently large.[3,4] DBS, a reversible nonlesioning surgical treatment,[5] can be applied to the internal globus pallidus (GPi)[6] or subthalamic nucleus (STN)[7] with a significant bilateral reduction in parkinsonian disability.[8,9] Compared to before surgery, there was no significant change in memory or executive functions 3 to 6 months after DBS in a series of 62 patients with PD treated by bilateral STN or GPi stimulation.[10]

These results are, however, open to discussion.[11] For instance, surgery could have provoked cognitive deficits compensated for by stimulation. The primaryaim of this new study was thus to distinguish the effects of DBS from those of surgery by comparing the postsurgical performance of patients with the stimulator turned "on" and "off." In the motor domain, the effects of DBS are reported to mimic those of L-dopa therapy.[12] To ascertain whether this is also the case in the cognitive domain, we compared the neuropsychological performance of patients with the stimulator turned "on" and "off," first on classic cognitive tests sensitive to PD[13] and then on more experimental tasks recently shown to be more specifically sensitive to the action of L-dopa.[14,15] Alternatively, cognitive deficits could appear later as a result of repetitive and prolonged stimulation. Thus, the second aim of the study was to assess cognitive function over a 12-month follow-up.

Methods. *Patients.* The study included 76 patients with PD (table 1). A first group of 56 patients underwent bilateral implantation of electrodes in Grenoble, 48 in the STN (STN1 group) and 8 in the GPi (GPi1 group). A second group of 20 patients underwent bilateral implantation of

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Table 1 *Characteristics of the four groups of patients**

Characteristics	STN1	GPi1	STN2	GPi2
No. of patients	48	8	15	5
Age, y	55.7 (7.5)	52.5 (6.5)	53.5 (9.7)	55.2 (10.2)
Level of education, y	12.4 (3.8)	13.0 (3.9)	11.1 (2.7)	9.6 (0.9)
Men/women	27/21	6/2	10/5	3/2
Disease duration, y	15.0 (4.9)	16.3 (3.4)	14.2 (5.5)	12.6 (2.7)
UPDRS-III ("off")	55.4 (12.8)	55.4 (8.5)	56.1 (17.9)	41.6 (14.1)
UPDRS-III ("on")	13.8 (8.2)	20.4 (8.4)	14.9 (8.1)	14.0 (7.5)
UPDRS-III ("off"; DBS−)	44.7 (15.0)	49.8 (14.8)	48.4 (19.7)	35.8 (18.7)
UPDRS-III ("off"; DBS+)	18.1 (11.8)	37.1 (13.3)	19.4 (20.4)	27.0 (12.5)
Levodopa before surgery	1110 (570)	744 (264)	1063 (496)	850 (514)
Levodopa after surgery	348 (292)	873 (478)	465 (405)	725 (308)

Values are n or mean (SD).

* Two groups with stimulation of the subthalamic nucleus; STN1 and STN2; two groups with stimulation of the internal globus pallidus: GPi1 and GPi2.

UPDRS = Unified Parkinson's Disease Rating Scale; "off" = without levodopa for 12 hours; "on" = under the maximum effect of levodopa; DBS−/+ = deep brain stimulator turned off/on.

electrodes in Paris, 15 in the STN (STN2 group) and 5 in the GPi (GPi2 group). All had a severe form of the disease and the response to levodopa was clear in all patients as shown by the Unified PD Rating Scale scores.[16] Despite optimal medication based on a combination of levodopa and dopamine receptor agonists, severe motor fluctuations were observed in all patients. No other neurologic impairment was found and brain MRI was normal. Patients were relatively young and had no significant cognitive or mood impairment before surgery. The four groups of patients did not differ in terms of age, level of education, gender, or disease duration or severity.

The neurosurgical procedures, all of which were approved by the relevant French Ethics Committee, have already been described.[7,17] For all patients, the electrodes were implanted stereotactically in a single session in accordance with preoperative MRI and ventriculography and intraoperative microrecordings and stimulations. The implanted quadripolar electrodes were positioned as closely as possible to the location where motor benefit was induced by the lowest electrical intensity and adverse effects by the highest electrical intensity using monopolar stimulation.

A brain MRI was performed a few days after electrode implantation to check the final location of the electrodes and detect any possible surgical complications. Seven patients had intracranial bleeding or edema, but had recovered without sequelae by the time of the neuropsychological examination. All patients had some degree of mental slowness or confusion from a few hours to days, except two patients who recovered after 1 month. Postoperative MRI showed mild extracerebral bleeding in three patients, small intraventricular bleeding in two patients, and frontal area contusion along one electrode tract in two other patients. No other serious adverse events associated with electrode implantation were detected.

Electrical parameters (pulse width, frequency, and voltage) were progressively adjusted by telemetry, using a console programmer, until an optimal effect was reached, in both the "on" and "off" drug conditions. In all patients stimulation was monopolar, using one contact of the quadripolar electrode. Parkinsonian motor features improved in all patients. The improvement was more pronounced with STN stimulation and the antiparkinsonian medication could be decreased in these patients (see table 1). At the time of the study, the mean (SD) voltage of stimulation was 2.4 (0.7) V for the STN and 3.1 (0.6) V for the GPi; the mean pulse width was 60.5 (10.9) μs for the STN and 78.5 (28.8) μs for the GPi; the mean frequency was 137.0 (27.6) Hz for the STN and 139.6 (20.6) Hz for the GPi.

Neuropsychological assessment. Clinical tests of executive function that usually indicate impairment in PD[13] were performed in 56 patients (groups STN1 and GPi1) before (during the preceding month) and 3 and 12 months after electrode implantation. After surgery, the performance was also compared with the stimulator turned "on" and "off," in a counterbalanced order. The conditions of stimulation were set from 15 to 30 minutes before beginning the neuropsychological examination. Most of the patients were assessed without levodopa (after 12 hours' withdrawal): 51 of 56 at 3 months and 56 of 56 at 12 months. The assessment included the simplified version of the Wisconsin Card Sorting Test,[18] verbal fluency tests,[19] and graphic and motor series.[20] To limit test–retest effects, parallel forms were used; for instance, for category fluency the names of fruit or furniture in 1 minute, and for literal fluency words beginning with "V" or "R" for 1 minute each. For the Wisconsin Card Sorting Test a parallel form was established with background, position, and form as criteria. The performance in both forms of the test was found to be similar in two groups of 40 normal subjects matched for age and educational level (form 1: 5.2 [1.2] criteria; form 2: 5.2 [1.2] criteria). The order of presentation of the parallel forms was counterbalanced. Given the potential role of control of attention on task performance, we added the Stroop Test,[21] which estimates the inhibition of interference, and the Trail Making Test,[22] which evaluates set-shifting.

Because clinical tests may lack sensitivity to subtle cognitive changes, we used more experimental tests of executive functions previously shown to be sensitive to L-dopa therapy. These tests were assessed in 20 patients (groups STN2 and GPi2) 6 months after electrode implantation and performance was compared with the stimulator turned "on" and with it turned "off" in a counterbalanced order. Given the patients' difficulty in carrying out the tasks when in the L-dopa "off" and stimulation "off" condition, their L-dopa dose (see table 1) was maintained in both the "off" and "on" stimulation conditions. We selected tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB): Motor Screening and Big Little Circle for simple and choice reaction times, Intra and Extradimensional Set Shifting for cognitive flexibility, and Spatial Working Memory.[14] We added the Digit Ordering Test for verbal working memory.[15]

Global intellectual efficiency, verbal learning, and mood were also evaluated in 56 patients (groups STN1 and GPi1) before (during the preceding month) and 3 and 12 months after electrode implantation (with the stimulators

"on"). The Mattis Dementia Rating Scale allowed attention, initiation, construction, conceptualization, and memory to be assessed.[23] To investigate verbal learning, we used the Grober and Buschke Test, which allows a comparison of free and cued recall.[24,25] The 16 to-be-learned words, belonging to 16 different semantic categories, were presented to the subject on four different cards. The encoding phase was controlled by asking the subject to point to and read aloud each word when its category cue was verbally provided. Then, the card was removed and immediate cued recall was tested by providing each category cue. Whenever the subject was unable to recall a given item, the encoding procedure was performed again for this item until the correct answer was obtained. The recall phase for the 16 words included three trials. Each trial consisted of an extended period of free recall (up to 2 minutes), immediately followed by cued recall for those items not retrieved at free recall. Selective reminding was used for any item missed at cued recall. The verbal learning free recall score (from 0 to 48) was determined by the total number of words correctly evoked in the three trials. The verbal learning total recall score (from 0 to 48) was determined by the number of words correctly evoked at free or cued recall. Delayed verbal free recall and delayed verbal total recall scores were also measured after a 15-minute delay. Two parallel forms were used to control for retest effects. Mood was assessed by the Beck Depression Inventory.[26]

Data analysis. Given the possible influence of locus of implantation (STN versus GPi), analysis of variance (ANOVA) with repeated measures was performed on each of the variables for each group separately, using condition (stimulator "off" and "on") and assessment time (before surgery, 3 months and 12 months after surgery) as repeated measures. For variables that showed significant differences, the pattern of differences was examined by two-tailed *t*-tests. Nonparametric analysis (Freedman and Wilcoxon tests) was effected when required by small groups of patients or variance heterogeneity. Two-way ANOVA was also performed on each of the variables, using group as a between factor, condition (stimulator "off" and "on") and assessment time (before surgery, 3 months and 12 months after surgery) as repeated measures.

Results. For the STN group, there was a significant improvement under stimulation (stimulator "on" versus stimulator "off") in: 1) graphic series, word and color conditions of the Stroop Test, and part A and B of the Trail Making Test, notably at 12 months (table 2); 2) psychomotor latency in simple and choice reaction times (table 3); and 3) the number of errors in spatial working memory, particularly for the more complex level (see table 3). There was also a trend toward significance for verbal working memory (see table 3). These positive changes were less than one SD for most of the patients. There was a significant effect of time of assessment (before surgery, 3 months and 12 months after surgery) on: 1) category fluency, with a poorer performance after surgery with or without stimulation (table 2); 2) part B of the Trail Making Test, with a better performance at 12 months under stimulation (see table 2); 3) verbal free recall, with a lower performance at 3 months, but recovery at 12 months (table 4); and 4) mood, with a lower depression score after surgery (see table 4).

For the GPi groups there was no significant improvement under stimulation (stimulator "on" versus stimulator "off"). There was a significant effect of time of assessment (before surgery, 3 months and 12 months after surgery) only on the Initiation subtest of the Mattis Dementia Rating Scale with an improvement at 12 months (see table 4).

There was only one significant group effect (STN versus GPi; $p < 0.05$) with a longer response latency in simple choice reaction time for the GPi2 group (see table 3). There was only one significant interaction ($p < 0.05$) between group and condition of stimulation: the number of errors in the more complex level of spatial working memory decreased under stimulation in the STN2 group, whereas it increased in the GPi2 group (see table 3). There was also only one significant interaction between group and time of assessment: the score of the subtest of Initiation of the Mattis Dementia Scale increased at 12 months in the GPi1 group but not in the STN1 group (see table 4).

Discussion. Our results showed cognitive improvement in psychomotor speed and working memory in STN patients when the stimulator was turned "on," no overall differential effect between STN and GPi stimulation, and no cognitive long-term effect of DBS 12 months after surgery except for a mild lexical fluency deficit in STN patients.

On clinical tests of executive functions, the performance of STN patients improved with the stimulator turned "on" for the word and color condition of the Stroop test and the forms A and B of the Trail Making Test. This was mainly related to an increase in psychomotor speed, as there was no significant change in cognitive speed under stimulation for the interference condition of the Stroop test and the difference in time of execution between condition B (cognitive shifting) and condition A (simple tracking) of the Trail Making Test just failed significance. This increase in psychomotor speed was also found in simple (Motor Screening) and choice (Big Little Circle) reaction time tests from the CANTAB. The effects of STN stimulation were comparable to those found in patients treated with L-dopa or dopamine agonists in similar tasks.[27] The improved performance on psychomotor tasks was congruent with the significant improvement of upper limb akinesia observed with the stimulator "on"[7,9] and associated with a slight improvement of initiation time and a more marked improvement of movement execution time.[12]

More unexpected was the effect of stimulation on purely cognitive functions, given the relative independence of motor and cognitive subcorticofrontal circuits.[28] This effect was significant in spatial working memory and showed a trend toward significance in verbal working memory. In spatial working memory, subjects were required to collect blue tokens randomly hidden inside boxes and not to reopen a box in which a blue token has already been found. This test was impaired by L-dopa withdrawal in levodopa-treated parkinsonian patients with more than 9 years of disease duration.[14] In verbal working memory, subjects were read random series of seven digits and were required to reorder the items in

Table 2 *Comparison of performance on tests of executive function before electrode implantation and after, with stimulator turned "off" and "on"*

Test	Before	3 months		*p* Value*	12 months		*p* Value†	Time, *p* Value‡
		"off"	"on"		"off"	"on"		
Wisconsin Card Sorting Test								
Criteria								
STN1	5.1 (1.1)	5.1 (1.2)	5.3 (1.0)	0.18	5.1 (1.5)	5.2 (1.2)	0.39	0.52
GPi1	5.1 (1.4)	4.9 (1.7)	5.1 (1.1)	0.79	5.5 (1.4)	5.0 (0.9)	0.10	0.69
Perseverations								
STN1	2.4 (2.1)	2.0 (2.5)	1.8 (1.8)	0.49	2.8 (3.6)	2.5 (2.6)	0.49	0.11
GPi1	2.9 (2.2)	1.6 (1.8)	3.1 (2.6)	0.24	3.1 (4.9)	2.3 (2.2)	0.92	0.48
Abandons								
STN1	1.0 (1.3)	1.1 (1.3)	1.0 (1.2)	0.34	1.0 (1.3)	1.2 (1.9)	0.52	0.43
GPi1	1.0 (1.2)	1.6 (2.3)	0.9 (1.4)	0.11	0.5 (0.8)	1.1 (1.1)	0.06	0.69
Lexical fluency								
Category								
STN1	14.6 (3.9)	12.3 (4.1)	12.7 (4.2)	0.43	12.1 (4.0)	12.9 (3.7)	0.21	**0.0006**
GPi1	14.8 (3.9)	12.4 (1.3)	12.9 (3.9)	0.93	13.5 (5.0)	13.8 (1.8)	0.78	0.34
Literal								
STN1	12.3 (5.0)	10.8 (4.8)	11.0 (4.9)	0.65	11.1 (4.7)	11.3 (4.9)	0.64	0.08
GPi1	10.6 (4.6)	11.1 (3.3)	11.5 (3.5)	0.46	12.8 (4.5)	12.3 (4.1)	0.73	0.27
Series								
Graphic								
STN1	8.2 (2.2)	7.5 (3.1)	7.9 (2.9)	0.22	7.4 (2.7)	8.2 (2.6)	**0.02**	0.56
GPi1	8.1 (2.7)	8.1 (2.8)	7.0 (3.3)	0.29	6.0 (3.7)	6.7 (2.6)	0.60	0.23
Motor								
STN1	8.5 (2.5)	8.8 (2.1)	8.6 (2.1)	0.34	8.5 (1.9)	8.8 (1.9)	0.18	0.73
GPi1	9.3 (0.7)	8.1 (3.5)	8.9 (1.6)	0.29	9.7 (0.8)	9.0 (2.2)	0.69	0.78
Stroop Test								
Words								
STN1	96.4 (17.5)	96.0 (15.8)	96.0 (13.6)	0.52	90.4 (16.0)	96.9 (18.8)	**0.0014**	0.92
GPi1	87.0 (16.0)	92.2 (12.1)	93.6 (16.8)	0.75	97.6 (9.7)	92.6 (13.1)	0.93	0.88
Colors								
STN1	62.9 (10.6)	60.0 (13.1)	61.1 (11.1)	0.38	57.6 (15.0)	60.0 (13.2)	**0.02**	0.89
GPi1	62.8 (5.3)	63.0 (3.1)	62.6 (7.5)	0.50	65.4 (6.1)	63.6 (11.0)	0.67	0.85
Colors of words								
STN1	35.7 (8.6)	33.8 (10.1)	34.8 (7.6)	0.21	34.4 (10.0)	35.6 (10.0)	0.26	0.93
GPi1	36.0 (10.8)	39.0 (8.3)	35.0 (5.2)	0.17	40.0 (12.6)	40.9 (11.6)	0.50	0.74
Trail Making Test								
A								
STN1	57.2 (20.6)	59.6 (31.7)	54.2 (30.4)	**0.04**	62.2 (30.3)	53.6 (15.4)	**0.05**	0.16
GPi1	59.6 (24.7)	53.0 (13.7)	44.9 (13.0)	0.11	54.0 (7.7)	44.7 (9.5)	0.17	0.22
B								
STN1	136.8 (64.8)	154.7 (129.7)	136.9 (142.4)	0.13	142.0 (75.0)	119.1 (47.6)	**0.01**	**0.01**
GPi1	131.6 (50.3)	130.0 (75.4)	111.9 (57.2)	0.13	105.3 (37.8)	97.0 (30.8)	0.69	0.22
B-A								
STN1	79.6 (50.4)	102.4 (111.3)	89.5 (119.1)	0.23	79.9 (53.9)	66.4 (36.9)	0.06	0.16
GPi1	72.0 (27.6)	77.0 (64.8)	67.0 (49.2)	0.24	50.8 (32.2)	52.3 (27.7)	0.68	0.31

Values are mean (SD). Boldface indicates statistical significance.
Two groups are described, one with stimulation of the subthalamic nucleus (STN1), one with stimulation of the internal globus pallidus (GPi1).

* *p*, † *p*, effect of stimulation; ‡, *p*, global effect of time of assessment.

Table 3 *Psychomotor speed, cognitive flexibility, verbal and spatial working memory with the stimulator turned "off" and "on"*

Test	STN2		*p* Value*	GPi2		*p* Value
	"off"	"on"		"off"	"on"	
Motor screening						
Latency	1277.9 (467.1)	1045.8 (195.2)	**0.05**	872.6 (116.7)	814.2 (143.6)	0.14
Precision	20.7 (4.0)	21.4 (4.2)	0.57	52.6 (79.6)	25.2 (20.7)	0.46
Big Little Circle						
Latency	951.9 (398.4)	729.4 (117.1)	**0.02**	642.8 (112.8)	648.8 (89.7)	0.68
Set shifting						
Stage	8.1 (2.0)	8.0 (2.2)	0.59	8.0 (2.2)	8.2 (1.8)	0.37
Errors	38.3 (40.3)	40.0 (40.1)	0.62	39.0 (63.0)	43.8 (51.3)	0.50
Verbal working memory						
Errors	19.1 (8.4)	17.3 (8.7)	0.09	17.8 (10.3)	13.6 (6.3)	0.20
Spatial working memory						
Strategy	36.6 (5.4)	36.5 (5.1)	0.88	36.4 (4.7)	38.0 (2.4)	0.27
Errors	46.9 (15.9)	40.3 (19.0)	**0.02**	29.6 (21.7)	31.0 (22.2)	0.89
6 boxes	12.7 (11.2)	11.9 (10.6)	0.81	9.0 (6.0)	6.4 (6.3)	0.34
8 boxes	32.9 (8.8)	26.3 (9.6)	**0.005**	19.8 (17.2)	23.6 (14.7)	0.59

Values are mean (SD). Boldface indicates statistical significance.
Two groups are described; one with stimulation of the subthalamic nucleus (STN2), one with stimulation of the internal globus pallidus (GPi2). The effect of stimulation was significant for the STN group alone (*p).

memory and to repeat them in ascending fashion. This Digit Ordering Test was specifically improved from the untreated to the levodopa-treated state in de novo parkinsonian patients.[15] Therefore, in the cognitive as in the motor domain, DBS appears to mimic the effects of levodopa therapy. This similarity is mainly phenomenologic, because levodopa acts by restoring dopamine neurotransmission in the striatum, whereas DBS is supposed to inhibit the STN or GPi. It turns out that close effects can be obtained through different neurophysiologic mechanisms, which are, however, functionally linked, as the striatal dopaminergic activation leads to a decrease in the subthalamic–pallidal pathway activity. This was shown both in animal models of PD and patients with PD.[29,30] The degree of improvement of working memory was lower with DBS in our study than with levodopa therapy in the previous studies. However, a dose of L-dopa (see table 1) had to be maintained for these experimental tasks both at baseline (stimulator "off") and under stimulation, due to the difficulty patients experienced in performing these tasks with stimulation "off" and levodopa "off." This dose of levodopa may have improved the baseline condition. These working memory tasks require processes of self-ordering and monitoring that depend on the integrity of the dorsolateral prefrontal cortex.[31] A same or adjacent area, as far as the resolution of PET imaging can show, was significantly activated when STN stimulation was applied during random joystick movement.[32]

Why were the cognitive effects of DBS limited to tests of working memory? Patients with PD are known to be impaired in many tests of executive function.[13] It should be emphasized that DBS had no significant effect on such cognitive clinical tests (see table 2) despite levodopa withdrawal in both conditions of stimulation for most of the patients (51/56) at 3 months and all patients at 12 months. The contribution of dopaminergic dysfunction to these frontal lobe–like deficits is, however, not clear. Levodopa has been reported to improve,[33] impair,[34] or not affect[35,36] frontal cognitive performance of parkinsonian patients, depending on the tests used and the selection of patients.[37] Different neural networks are probably involved in the various tasks. Some of these networks might be unaffected by the dopamine deficiency, but also by stimulation of the STN or the GPi. The level of difficulty of the task may also play a role. For instance, in spatial working memory the effect of stimulation was observed for eight but not for six boxes. The cognitive deficits of patients selected for DBS were very limited (see tables 2 and 4). Ceiling effects may explain the lack of influence of DBS on tasks such as the Wisconsin Card Sorting Test (see table 2) or Attentional Set Shifting (see table 3).

The results shown in table 3 suggest a greater improvement under stimulation for STN patients, but there was no group effect and no interaction between group and stimulation condition given high between-subject variability. This is surprising given recent models of frontostriatal circuitry suggesting that the direct pathway between the putamen and the GPi and the indirect pathway from the STN to the GPi via the GPe produce contrasting effects with

Table 4 *Comparison of performance on tests of global cognitive efficiency, memory, and mood before and after electrode implantation (stimulator turned "on")*

Test	Before	3 months	12 months	*p* Value
Mattis Dementia Rating Scale				
Total score				
STN1	137.0 (4.7)	136.6 (5.5)	136.7 (7.0)	0.80
GPi1	137.3 (5.3)	134.8 (4.8)	139.5 (3.0)	0.07
Attention				
STN1	36.0 (0.9)	36.0 (0.9)	35.8 (1.1)	0.60
GPi1	36.0 (0.8)	35.9 (0.6)	35.8 (1.2)	0.86
Initiation				
STN1	33.9 (3.8)	33.4 (3.9)	33.2 (4.5)	0.50
GPi1	33.9 (3.4)	32.3 (3.7)	36.6 (0.7)	**0.02**
Construction				
STN1	6.0 (0.0)	6.0 (0.0)	6.0 (0.0)	1.0
GPi1	6.0 (0.0)	6.0 (0.0)	6.0 (0.0)	1.0
Conceptualization				
STN1	37.4 (1.7)	37.2 (2.0)	37.4 (1.8)	0.39
GPi1	36.6 (1.8)	36.3 (1.8)	36.5 (1.8)	0.88
Memory				
STN1	23.9 (1.1)	24.0 (1.2)	24.2 (1.1)	0.33
GPi1	24.8 (0.5)	24.4 (0.7)	24.6 (1.1)	0.23
Grober and Buschke Verbal Learning Test				
Free recall				
STN1	28.8 (5.8)	26.4 (6.3)	28.5 (7.5)	**0.02**
GPi1	26.0 (7.2)	25.7 (7.1)	27.0 (7.1)	0.86
Total recall				
STN1	46.4 (2.2)	45.8 (3.1)	46.6 (1.8)	0.13
GPi1	46.2 (3.1)	45.8 (1.8)	45.2 (3.8)	0.70
Delayed free recall				
STN1	10.8 (2.5)	9.9 (2.8)	10.2 (3.0)	0.18
GPi1	10.2 (2.1)	10.3 (2.7)	11.7 (2.7)	0.35
Delayed total recall				
STN1	15.9 (0.3)	15.6 (0.9)	15.7 (0.7)	0.16
GPi1	15.7 (0.5)	15.2 (1.6)	15.7 (0.5)	0.63
Beck Depression Scale				
STN1	15.1 (7.0)	11.0 (7.8)	11.9 (7.8)	**0.0005**
GPi1	13.7 (7.2)	9.1 (6.1)	10.0 (5.4)	0.35

Values are mean (SD). Boldface indicates statistical significance. Two groups are described, one with stimulation of the subthalamic nucleus (STN1), one with stimulation of the internal globus pallidus (GPi1). p = global effect of time of assessment.

facilitation or suppression of cortical activity.[38] However, the number of patients with GPi stimulation may have been insufficient to allow the detection of such contrasting effects. Alternatively, such models may be questioned: dendritic domains in the STN and the GPi are quite large and the axonal plexi of afferents span territories far beyond the proposed independent circuits.[39]

By comparison with the preoperative state, there was no cognitive decrease at 12 months postsurgery in attention, construction, initiation, conceptualization, or memory scores on the Mattis Dementia Rating Scale, in verbal learning immediate or delayed free or cued recall, in the Wisconsin Card Sorting Test (number of criteria, perseverative errors or abandons), in graphic or motor series, or in the Stroop or the Trail Making Test, whichever the condition. The single long-term decrease in performance was observed in category fluency at 3 and 12 months in STN patients, with a trend for a similar deficit in literal fluency. Previously observed in DBS of the GPi,[11] the deficit in category fluency persisted 12

months after surgery in pallidotomy.[4] It might be a consequence of surgery, related to the parasagittal trajectory close to the anterior cingulate cortex used for electrode implantation. Indeed, functional activity of paracingulate and cingulate sulci increased during word generation in an fMRI study.[40] It might be argued that the circuits underlying this task are decommissioned by the surgery and that a whole new circuit is brought into play.[41] That new circuit would be untouched by DBS, because it was not modified by the stimulation state (stimulator "on" or "off"). From a cognitive or behavioral point of view, this lexical fluency deficit is difficult to explain. It is not related to a cognitive or phonologic slowing because there was an increase in performance in the Trail Making and Stroop Tests after surgery. Neither is it related to a mood change, as there was a mild but significant improvement of mood on the Beck Depression Inventory after surgery. It may be suggested that lexical fluency is less externally guided than other tests of executive functions and requires greater self-initiation. It would therefore be more sensitive to subtle personality changes, such as a decrease in self-activation.[42] Behavioral scales would be necessary to determine such subtleties and would allow this question to be answered.[4]

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Hypoglycemia-induced cerebellar dysfunction and quantitative positron emission tomography study

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Article abstract—*Objective:* To describe an unusual case of hypoglycemia-induced bilateral cerebellar dysfunction. *Background:* The cerebellum is known to be resistant to hypoglycemia, and selective cerebellar dysfunction caused by hypoglycemia has not been reported. Previous studies showed that the ratio between the rate constants for glucose uptake and phosphorylation (K_1 and k_3) is reversed in the cerebellum compared with the cerebral cortex; higher K_1 in the cerebellum and higher k_3 in the cerebral cortex. *Methods:* Quantitative dynamic PET scanning with labeled fluorodeoxyglucose (^{18}F-FDG) was performed to prove altered glucose kinetics in the cerebellum of a patient who presented with episodic cerebellar dysfunction associated with hypoglycemia. Four control subjects underwent the same study. *Results:* The ratio between K_1 and k_3 was not reversed in the cerebellum of our patient (K_1 = 0.082, k_3 = 0.192). On the contrary, the ratio was reversed in the control subjects (mean K_1 = 0.109, mean k_3 = 0.080). In addition, the patient's cerebellar metabolic rate of glucose ($rCMR_{glu}$ = 27.9 μmol/100 g/minute) and the rate constant of glucose egress (k_2 = 0.543) were relatively increased compared with those of control subjects (mean $rCMR_{glu}$ = 21.9 μmol/100 g/minute, mean k_2 = 0.352). *Conclusions:* In a case of episodic bilateral cerebellar dysfunction caused by hypoglycemia, quantitative dynamic PET study demonstrated decreased glucose uptake-to-utilization ratio and increased leak of glucose in the cerebellum. The cerebellum is not invariably resistant to hypoglycemia.

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The cerebellum is relatively resistant to hypoglycemia according to studies on the severity of metabolic alteration[1-6] or pathologic change.[2,7-9] In addition, many studies have indicated the following possible mechanisms: a more efficient glucose transporter system,[10,11] a denser capillary network,[12] or less reduction of the autoregulatory capacity during hypoglycemia[13] in the cerebellum than in other brain regions.

In a PET study of men with diabetes,[14] it was demonstrated that the cerebellum has different glucose kinetics compared with the cerebral cortex; a higher K_1 (rate constant for glucose uptake) and a lower k_3 (rate constant for glucose phosphorylation). Accordingly, the higher rate of glucose extraction from the blood and its lower utilization rate—the rate of phosphorylation and rate of utilization can be used interchangeably[15]—in the cerebellum account for its resistance to hypoglycemia.

We describe a case of selective cerebellar dysfunction due to hypoglycemia and its possible mechanism. We assessed the regional glucose kinetics of

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