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Effects of Levodopa and Subthalamic Nucleus Stimulation on Cognitive and Affective Functioning in Parkinson's Disease

Aurélie Funkiewiez, MA, PhD,[1]* Claire Ardouin,[1] Roshan Cools,[2] Paul Krack,[1] Valérie Fraix,[1] Alina Batir,[1] Stephan Chabardès,[1] Alim-Louis Benabid,[1] Trevor W. Robbins,[2] and Pierre Pollak[1]

[1]*Department of Clinical and Biological Neurosciences, University Hospital of Grenoble, and INSERM U318, Joseph Fourier University of Grenoble, Grenoble, France*
[2]*Department of Experimental Psychology, University of Cambridge, United Kingdom*

Abstract: In Parkinson's disease (PD), levodopa and subthalamic nucleus (STN) stimulation lead to major improvement in motor symptoms. Effects of both treatments on cognition and affective status are less well understood. Motor, cognitive, and affective symptoms may relate to the dysfunctioning of parallel cortico–striatal loops. The aim of this study was to assess cognition, behavior, and mood, with and without both treatments in the same group of PD patients. A group of 22 nondemented PD patients was included in this study. Patients were tested twice before surgery (*off* and *on* levodopa) and twice 3 months after surgery (OFF and ON STN stimulation, *off* levodopa). Cognitive and affective effects of STN stimulation and levodopa had some common, but also different, effects. STN stimulation improved performance on the planning test, associated with the dorsolateral prefrontal cortex. However, the treatments had opposite effects on tests associated with the orbitofrontal cortex; specifically, levodopa impaired while STN stimulation improved performance on the extinction phase of a reversal/extinction task. Acutely, both treatments improved motivation and decreased fatigue and anxiety. On chronic treatment (3 months after surgery), depression improved, whereas apathy worsened 3 months after surgery. To conclude, there were significant but contrasting effects of levodopa and STN stimulation on cognition and affective functions. © 2006 Movement Disorder Society

Key words: levodopa; subthalamic nucleus stimulation; basal ganglia frontal loops; Parkinson's disease; neuropsychology

Chronic bilateral subthalamic nucleus (STN) stimulation may be used to treat patients with idiopathic Parkinson's disease (PD) in whom long-term pharmacological treatment has failed. This surgery has been shown to improve motor symptoms of PD,[1,2] but the effects on cognitive functions and mood are not well characterized, with contradictory results in the literature.[3]

Usually, studies have shown no global cognitive deterioration after STN stimulation in the short term[4–6] or in the long term,[2,7] except for small groups of elderly patients where cognitive deficits are more frequent.[8] Comparisons between preoperative and postoperative evaluations have shown minor improvements in executive function.[4,9] On the other hand, mild cognitive impairments have also been reported, such as diminished verbal fluency,[4,5,7,9] delayed free recall,[6] and working memory (with high memory load).[10] An alternative way to study the effects of STN stimulation more specifically is to compare the patients' performances with their stimulators turned ON and OFF. Studies using this methodology have shown that stimulation improves executive functioning.[5,11] By contrast, with stimulators turned ON, visual conditional learning was impaired,[11] and patients also made a greater number of errors on the interference condition of the Stroop test.[11,12]

Concerning behavior, an assessment of acute subjective psychic effects of STN stimulation has shown an increased feeling of well-being when stimulators are turned ON.[13] Hilarity has been described following increases in stimulation parameters[14] and mania can occur with chronic STN stimulation.[15,16] On the other hand, cases of depression have also been reported[17,18] and

*Correspondence to: Dr. Aurélie Funkiewiez, INSERM U610, Pavillon Claude Bernard, Hôpital de la Salpêtrière, 47 Bd de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: a.funkiewiez@tiscali.fr

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apathy has been described following chronic STN stimulation.[8,19,20]

How could we explain these nonmotor effects of STN stimulation? Parallel basal ganglia–thalamo–cortical circuits have been described with different functions that may be relevant to the motor, cognitive, and affective dimensions of PD.[21] These so-called nonmotor loops include dorsolateral prefrontal cortex (PFC), orbitofrontal, and anterior cingulate circuits. Many studies suggest that executive functions, such as planning and working memory, depend on the dorsolateral PFC loop. Both patients with dorsolateral PFC lesions and PD patients perform worse than controls on tests of planning and spatial working memory.[22–24] The orbitofrontal loop has been shown to be sensitive to specific tests, such as decision-making[22,25] and reversal/extinction learning tests.[26] Lesions of the anterior cingulate loop lead to changes in mood and motivation, such as depression and apathy.[22] Several functional imaging studies of STN stimulation in PD with paradigms involving motor and cognitive aspects have shown modifications of cerebral blood flow of the supplementary motor area, premotor cortex, orbitofrontal, dorsolateral, and cingulate cortex,[27,28] suggesting that STN stimulation might influence the limbic and associative, as well as the motor, loops.

In this study, considering this anatomo–functional model of cortico–striatal circuits, we have investigated each circuit with specific neuropsychological tests in order to know if STN stimulation could have specific effects on the different circuits.

In addition to this question, we have investigated the same aspects with levodopa treatment. It is well accepted now that the motor effects of STN stimulation closely resemble those of levodopa treatment.[29] What about the nonmotor effects? The literature about the nonmotor effects of levodopa is partly contradictory. Executive functions have been improved or not changed with levodopa, depending on the tests used.[30,31] One study showed impairment on a verbal fluency task only when patients were *off* levodopa, whereas on two other measures, associative conditional learning and subject-ordered pointing, patients were impaired only when *on* levodopa.[32] In another study, medication remediated impairments in switching between two tasks, but in contrast, the same medication impaired probabilistic reversal learning.[33] Effects of levodopa on mood and behavior have also been described, with an improvement of anxiety[13,34] and depression.[34–36]

The aim of the current study, performed in the same group of patients, was to compare the effects of dopaminergic medication and STN stimulation on these distinct functional domains using cognitive, behavioral, and mood assessments.

PATIENTS AND METHODS

Patients

Twenty-two PD patients who had surgery for STN stimulation in our center were included in this study. Characteristics of patients are shown in Table 1. These patients were not demented (all patients had a score above 130 on the Mattis Dementia Rating Scale) and had no ongoing psychiatric impairment, except one patient who was severely depressed (Beck Depression Inventory = 26) at the time of surgery. One of these patients has not been tested 3 months after surgery because the parameters of stimulation were not stabilized. The levodopa equivalent daily doses were calculated as described

TABLE 1. *Characteristics of parkinsonian patients before and 3 months after surgery*

	Before surgery, mean (SD)	3 months after surgery, mean (SD)
Total number	22	21
Sex (female/male)	10/12	10/11
Age (yr)	54.5 (7.5)	
Education (yr)	12.5 (5.2)	
Mattis Dementia Rating Scale	137.6 (4.2)	
Duration of the disease (yr)	10.7 (3.9)	
Levodopa equivalent daily doses (mg)	1,420.0 (643.8)	319.9 (380.0)
UPDRS III scores		
On L-dopa	13.1 (7.7)	
Off L-dopa	43.1 (12.6)	
Off L-dopa/OFF STN stimulation		42.4 (16.7)
Off L-dopa/ON STN stimulation		18.1 (11.7)
Parameters of STN stimulation (for both sides)		
Voltage (V)		2.8 (0.5)
Rate (Hz)		132.4 (10.9)
Pulse width (μS)		60 (0)

elsewhere.[19] All patients gave informed consent to participate in this study, which was approved by the Grenoble University Hospital ethics committee.

Procedure

All patients were tested four times: twice before surgery, *off* and *on* drug, and twice 3 months after surgery, *off* drug, OFF and ON STN stimulation. The order of testing was counterbalanced between patients. The preoperative *off* drug condition corresponded to 12-hour withdrawal of all antiparkinsonian treatments and the *on* drug condition corresponded to the period of improved motor function after the intake of the usual antiparkinsonian drugs. Postoperatively, the tests began 20 minutes after turning OFF the stimulator. The order of computerized tests was counterbalanced between patients to control for possible fatigue effects and interactions between tests.

Neuropsychological Tests

Planning Task: Cambridge Neuropsychological Test Automated Battery (CANTAB)[37]

There were three "pockets" in each half of the screen, which respectively could hold three, two, and one balls. Three balls were placed in predetermined positions in the pockets of each of the two displays. The subjects were told that they had to make the bottom arrangement look like the top one. There were four levels of difficulty, with problems of two, three, four, and five moves. The measure of this test was the mean number of moves for each level of difficulty.

Reversal/Extinction Task

A reversal/extinction task adapted from Rolls and colleagues[26] was used. This was a visual discrimination reversal, in which patients could learn to obtain points by choosing one stimulus, but had to withhold a response when a different visual stimulus appeared, otherwise a point was lost. When subjects reached a learning criterion of 9 correct responses within a sequence of 10 consecutive trials, the contingencies unexpectedly reversed. In the third phase, the extinction, points could only be won by refraining from choosing both of the patterns. The scores were the total number of trials to reach criterion (with a maximum of 30 trials) for the three phases.

Addiction Research Center Inventory (ARCI) Questionnaire

Patients filled out the French version[38] of the short form of the ARCI[39] in order to assess the acute psychic effects of all conditions of treatment. The ARCI is a true/false questionnaire of 49 items designed to differentiate classes of psychoactive drugs. It yields scores for five different scales: amphetamine (A) and benzedrine group (BG), sensitive to amphetamine-like stimulating effects; morphine–benzedrine group (MBG), sensitive to euphoric effects; pentobarbital–chlorpromazine–alcohol group (PCAG), sensitive to sedative effects (calming, relaxing); and lysergic acid diethylamide (LSD), sensitive to somatic and dysphoric effects (anxiety, sensation of illness).

Apathy Scale

Apathy was assessed with the apathy scale adapted by Starkstein and colleagues[40] from Marin.[41] This questionnaire is composed of 14 items. Patients with a score greater than or equal to 14 (maximum = 42) were considered as apathetic, as proposed by Starkstein and colleagues.[40]

Beck Depression Inventory

Depression was assessed with the Beck Depression Inventory,[42] and scores range from 0 to 63. Patients had to select the response that corresponded to how they felt during the past 2 weeks.

Both the apathy and the depression scales were completed by patients, but in only two conditions: *on* drug before surgery and *on* drug and ON stimulation after surgery. This is because patients had to answer according to how they felt over the past 2 weeks. Thus, they did not experience the *off* conditions for a sufficient amount of time to be able to answer this question.

Statistical Analysis

The data were analyzed using the software Statistica (StatSoft, Tulsa, OK). Analysis of variance (ANOVA) for repeated measures were conducted, with two within-subject factors: treatment (levodopa vs. stimulation) and condition (*off* vs. *on*). Local comparisons were done using contrasts, to compare data two by two, when interactions were significant. A $P < 0.05$ was considered significant.

RESULTS

Motor Functioning

The postoperative motor scores are shown in Table 1. All patients had a postsurgical MRI to check for the correct placement of the active contact of the electrodes in the STN. All electrodes were correctly implanted in STN. One patient had a clinically asymptomatic contusion of the right caudate nucleus.

Neuropsychological Tests

The mean scores are shown in Table 2.

Planning Task

Only data for problems of four and five movements were normally distributed and analyzed. The contrasts analysis showed a significant improvement of performances with STN stimulation for the five-move problems.

Extinction/Reversal Task

The mean numbers of trials to reach criterion during the learning, reversal, and extinction phases are shown in Figure 1. For the initial acquisition phase, there were no significant effects of condition or treatment. For the reversal phase, the effect of treatment was significant ($F_{1,13} = 6.39$; $P = 0.025$) due to an improvement of performance after surgery relative to presurgery. This effect is driven entirely by an impairment before surgery for *on* levodopa condition; the *off* levodopa score is identical to the postsurgery scores. For the extinction phase, there was a significant interaction between treatment and condition ($F_{1,15} = 12.22$; $P = 0.0032$). Contrast analyses revealed that the effect of condition (i.e., the difference between the *off* and *on* conditions) was significant for both treatments. Patients needed significantly more trials to reach criterion when they were *on* levodopa relative to their *off* levodopa state ($F_{1,19} = 13.14$; $P = 0.0018$). By contrast, the same patients needed significantly fewer trials when they were ON stimulation relative to their OFF stimulation state ($F_{1,16} = 8.72$; $P = 0.0094$). No other effect reached significance.

ARCI

The ARCI scores are shown in Figure 2. The analysis revealed a main effect of subscale ($F_{4,80} = 16.71$; $P < 0.0001$), a main effect of condition (*off* vs. *on*; $F_{1,20} = 9.13$; $P = 0.007$), and an interaction between subscales and condition ($F_{4,80} = 37.17$; $P < 0.0001$). Contrasts analyses revealed effects of conditions for all subscales and both treatments due to higher well-being and lower fatigue and anxiety scores with levodopa and/or STN stimulation. Comparisons between levodopa and STN stimulation were not significant.

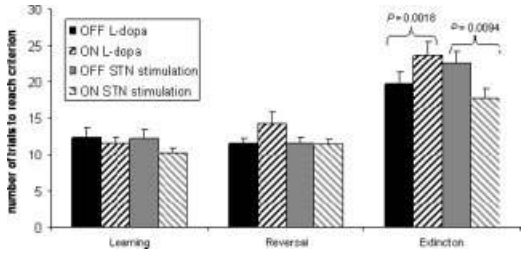

FIG. 1. Mean number (SEM) of trials to reach criterion for the three phases of the reversal/extinction test.

Depression and Apathy

Depression and apathy scores are shown in Figure 3. Depression scores were significantly lower after surgery ($F_{1,20} = 14.65$; $P = 0.001$). Apathy scores were significantly greater after surgery ($F_{1,18} = 5.68$; $P = 0.028$). The mean score of apathy was under the cutoff score of 14, showing no apathy. Nevertheless, five patients were apathetic (with a score above 14) 3 months after surgery; only one of them was apathetic before surgery.

DISCUSSION

In summary, there were significant beneficial effects of STN stimulation on several aspects of cognitive and behavioral function, including planning and extinction, confirming earlier findings from related tasks.[5,11] By contrast, levodopa appears to impair performance on the extinction phase of the reversal/extinction task, consistent with the findings of Cools and colleagues.[43] Both STN stimulation and levodopa, when administered acutely, improved subjective feelings of well-being. On

TABLE 2. *Mean (SD) performances of parkinsonian patients for the planning task, before surgery (off and on L-dopa) and 3 months after surgery (OFF and ON STN stimulation)*

	L-dopa			STN stimulation		
	Off	*On*	*P**	OFF	ON	*P***
Number of subjects	22	22		20	21	
Mean number of moves						
Four-move problem	5.9 (1.1)	5.5 (1.0)	NS	5.2 (1.0)	5.4 (1.1)	NS
Five-move problem	7.5 (1.6)	7.8 (1.4)	NS	8.1 (1.8)	7.0 (1.5)	0.04

Global interaction significant: ($F_{1,19} = 8.43$; $P = 0.009$).
*Comparisons between *off* and *on* L-dopa.
**Comparisons between OFF and ON STN stimulation.
NS, non-significant.

chronic STN stimulation, depression was significantly reduced, although apathy increased.

There is a methodological limitation inherent to the study. We were unable to differentiate between effects of treatments and learning because the two treatments were always tested in the same order (levodopa before STN stimulation). Therefore, the improved performances after surgery (only for the reversal phase of the reversal/extinction test) could possibly be related to practice effect rather than surgery or stimulation. Nevertheless, the difference between the two treatments was significant only for the *on* conditions. Had there been a major learning effect between the two assessments (before and after surgery), the difference for the *off* conditions would also have been significant.

How could we explain the impairment induced by levodopa on some aspects of cognitive performance? Patients may have been more impulsive *on* than *off* levodopa, as described by Cools and colleagues.[43] This behavior could indicate an intolerance for waiting, leading to selection of immediate over delayed reward.[43] Performances on two other tests have been shown to be impaired with levodopa, a probabilistic reversal discrimination[33] and conditional associative learning.[32] There is considerable evidence that these tasks are mediated by ventral frontal circuitry, including the orbitofrontal cortex.[26,33,43] It has been proposed for PD that levodopa normalizes dopamine levels in severely depleted areas, such as the dorsolateral circuit, while overdosing the less depleted ventral circuit.[32,33,43] This difference in regional dopamine depletion may be less important for patients with a longer disease duration, who are typically candidates for STN stimulation. This overdose hypothesis postulates normal performances of PD patients *off* medication on ventral circuit tests. However, deficits have been described.[44] How could we explain differential effects of levodopa and STN stimulation on tests associated with orbitofrontal–ventral striatal circuitry? We hypothesize that levodopa affects more structures than STN stimulation. Thus, levodopa, when converted to dopamine, may activate not only the motor striatum, but also the frontal cortex, anterior cingulate cortex, hippocampus, amygdala, globus pallidus, thalamus, and STN.[45,46] An alternative hypothesis is that levodopa has a more potent effect on dopamine systems than does STN stimulation, the latter thus having fewer side effects resulting in dopaminergic overdose.

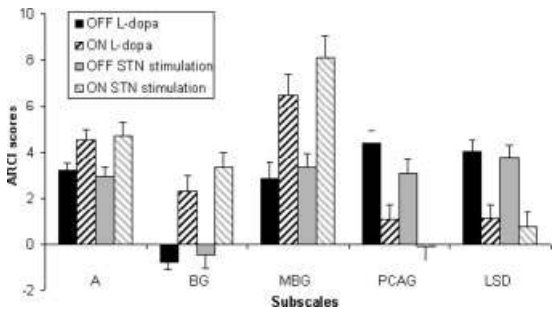

FIG. 2. Mean scores (SEM) for the five subscales of the ARCI for the four conditions of patients. A, amphetamine; BG, benzedrine group; MBG, morphine–benzedrine group; PCAG, pentobarbital–chlorpromazine–alcohol group; LSD, lysergic acid diethylamide. High scores indicate psychic stimulation (A and BG), euphoria (MBG), sedation (PCAG), and dysphoria (LSD). All comparisons between *off* and *on* conditions are significant for L-dopa and STN stimulation ($P < 0.01$).

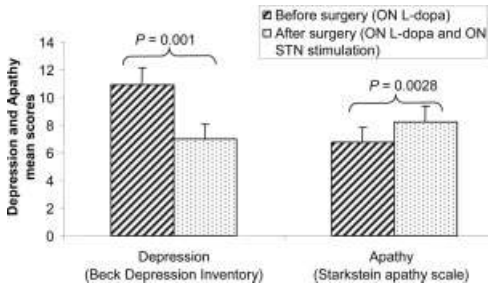

FIG. 3. Mean (SEM) scores of depression and apathy for PD patients before and after surgery.

STN stimulation and levodopa did share some common effects on affective processing, both reducing depressive symptoms. Emotional effects, acutely measured with the ARCI scale here under both treatments, similarly showed improvements in motivation and well-being. Contrary to our previous study,[13] which revealed greater efficacy of a suprathreshold dose of levodopa relative to chronic STN stimulation, both treatments had similar effects in the present study, using the chronic dopaminergic therapy rather than suprathreshold doses. Thus, the enhanced psychotropic effects of levodopa compared to STN stimulation in our previous study were probably related to drug dosage rather than a difference in specificity. Depression as measured by the Beck Depression Inventory was also improved after surgery, as shown previously.[4,20] Even if there is some evidence that STN stimulation has a direct effect on mood, we cannot reject an indirect effect due to the major motor improvement or an evaluation artifact related to improvement of somatic items of this scale. On the other hand, patients were more apathetic 3 months after surgery. Even though the mean score of apathy was below the cutoff score of 14, an increase in apathy frequently represents a complaint from patients and caregivers in the long term.[2] This apathy could be due to the massive reduction of dopaminergic treatments.[19] Patients and caregivers typically describe difficulty in self-initiating any activities,

even though the patients may have many if helped by external stimuli. This does not seem to be related to prefrontal dysfunction, because the patient's performances in the planning test do not change after surgery. Furthermore, it has been shown that STN stimulation does not worsen frontal executive function[4] and that postoperative apathy correlates with fluency, a typical sign of apathy, but not with other tests of executive function.[7] Future studies should specifically address postoperative apathy in PD patients in order to better understand the apathy that occurs in this context and to evaluate the most suitable therapy.

In conclusion, we have shown opposite effects of STN stimulation (improvement) and levodopa (worsening) on cognitive functions in a test sensitive to orbitofrontal–ventral striatal function. STN stimulation but not levodopa had minor effects on planning functions, associated with dorsolateral PFC–dorsal striatal circuits. Both treatments had equivalent positive subjective and mood-related effects.

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