

# Behavioural disorders, Parkinson's disease and subthalamic stimulation

J L Houeto, V Mesnage, L Mallet, B Pillon, M Gargiulo, S Tezenas du Moncel, A M Bonnet, B Pidoux, D Dormont, P Cornu, Y Agid

*J Neurol Neurosurg Psychiatry* 2002;**72**:701–707

See end of article for authors' affiliations

Correspondence to:  
Dr Y Agid, Centre  
d'Investigation Clinique,  
Hôpital de la Salpêtrière,  
47 Boulevard de l'Hôpital,  
75013 Paris, France;  
agid@ccr.jussieu.fr

Received 25 May 2001  
In revised form  
25 September 2001  
Accepted  
11 October 2001

**Objective:** to analyse 24 parkinsonian patients successfully treated by bilateral STN stimulation for the presence of behavioural disorders.

**Method:** patients were evaluated retrospectively for adjustment disorders (social adjustment scale, SAS), psychiatric disorders (comparison of the results of psychiatric interview and the mini international neuropsychiatric inventory) and personality changes (IOWA scale of personality changes).

**Results:** parkinsonian motor disability was improved by 69.5% and the levodopa equivalent daily dosage was reduced by 60.5%. Social adjustment (SAS) was considered good or excellent in nine patients, moderately (n=14), or severely (n=1) impaired in 15 patients. Psychiatric disorders consisted of amplification or decompensation of previously existing disorders that had sometimes passed unnoticed, such as depressive episodes (n=4), generalised anxiety (n=18), and behavioural disorders with drug dependence (n=2). Appearance of mild to moderate emotional hyperreactivity was reported in 15 patients. Personality traits (IOWA scale) were improved in eight patients, unchanged in seven, and aggravated in eight

**Conclusion:** Improvement in parkinsonian motor disability induced by STN stimulation is not necessarily accompanied by improvement in psychic function and quality of life. Attention is drawn to the possible appearance of personality disorders and decompensation of previous psychiatric disorders in parkinsonian patients who are suitable candidates for neurosurgery. We suggest that a careful psychological and psychiatric interview be performed before surgery, and emphasise the need for psychological follow up to ensure the best possible outcome.

Bilateral continuous high frequency stimulation of the subthalamic nucleus (STN) was recently introduced to treat advanced forms of Parkinson's disease.<sup>1</sup> The method currently used improves motor disability by 33%–67%, motor fluctuations by 73%–83%, and levodopa induced dyskinesias by 55%–88%, and permits a 40%–80% reduction in the doses of antiparkinsonian medication, compared with the preoperative state.<sup>2–6</sup>

Several factors contribute to the efficacy of the treatment: the stringency of the inclusion criteria, the accuracy of electrode implantation in the STN, and long term optimisation of the stimulation parameters.<sup>5</sup> The surgical intervention has little or no effect on cognitive function. Two recent studies showed that chronic bilateral subthalamic stimulation affects neither memory nor executive functions.<sup>7,8</sup> A third study, however, showed that frontal lobe-like symptomatology can be aggravated in patients 70 years of age or older.<sup>9</sup> The question of behavioural effects of the treatment has not yet been addressed directly, except in a few isolated case reports.<sup>9</sup> We report the results of a retrospective study designed to explore the range of behavioural disorders in 24 patients successfully treated by bilateral STN stimulation.

## PATIENTS

Twenty four out of 28 consecutive patients agreed to participate in the study. One patient (reported in the discussion of the paper) committed suicide before the inclusion period and was not enrolled in the study; three others refused to participate. Consent was obtained in accordance with the Declaration of Helsinki, and the local ethics committee approved the study. At the time of surgery, age at onset of the disease and duration of the disease were 43 (SD 6.5) and 16 (SD 4.5) years, respectively. All patients were significantly improved by levodopa therapy but had severe

disease (Hoehn and Yahr score<sup>10</sup> off medication >4) and levodopa related motor complications (UPDRS IV score<sup>11</sup>: 12 (SD 4) that could not be controlled despite optimised treatment (daily dose levodopa equivalent<sup>12</sup> 1400 (SD 620) mg). None of the patients had significant psychiatric disorders or dementia. Electrodes were implanted bilaterally in the subthalamic nucleus with an approach combining three dimensional MRI and intraoperative electrophysiological guidance.<sup>13</sup> Except for subdural aeroma in most patients and a transient acute confusional state in one patient, no significant direct complications of surgery were found. The position of the electrodes was checked by MRI performed postoperatively.<sup>14</sup> In the 24 patients (48 electrodes), continuous monopolar stimulation at 2.75 (SD 0.4) V was applied through one (n=40 electrodes) or two (n=8 electrodes) contacts, with a frequency of 144 (SD 27) Hz and a pulse width of 60 (n=46) or 90 (n=2)  $\mu$ s. The present study was performed 19 (SD 11) months (range 3–38) after implantation of the electrodes. Five cases are reported, illustrating the main behavioural disorders found in the study: personality changes, psychiatric disorders, modified control of emotional responses, and affective blunting.

## CASE REPORTS

### Patient 1

A 61 year old man had a history of depression, which began 16 years ago, a few months before the onset of an akinetorigid syndrome in the right lower limb. He developed severe motor

**Abbreviations:** STN, subthalamic nucleus; SAS, social adjustment scale; UPDRS, unified Parkinson's disease rating scale; MINI, mini international neuropsychiatric inventory; ISPC, IOWA scales of personality change

fluctuations and levodopa induced dyskinesias. Non-motor fluctuations, such as impulsive behaviour and aggressiveness during motor “off” periods and excitation during “on” periods, were seen. An optimised regimen of antiparkinsonian medications did not improve his condition. Stimulation of the subthalamic nucleus was proposed, and electrodes were implanted. Stimulation improved motor disability by 86% (UPDRS III) but the daily doses of levodopa equivalents decreased by only 12%. The following electrical parameters were applied: left electrode contact 2, amplitude 2.8 V, 60  $\mu$ s, 130 Hz; right electrode contact 3, 3.0 V, 60  $\mu$ s, 130 Hz. Although motor status was satisfactory, the patient wanted his wife to stay at home all day to look after him. He spontaneously increased his daily dose of levodopa, preferentially in a quick acting form (“There’s something missing. I need more energy, more pep”). He developed devious strategies to increase his stimulation parameters and tried to obtain new medications from physicians with little experience of treating Parkinson’s disease. His wife reported mood swings in the course of the day, passing from aggressiveness, irritability with low tolerance to frustration, depressed mood to excitation and abnormal sexual behaviour with exhibitionism, and gambling. A 4 month treatment with lithium and several modifications of the stimulation parameters failed to improve his condition. Clozapine administration and supportive psychotherapy were not effective. We discovered a period of alcohol misuse and an episode of hypomania that occurred 10 years before the onset of the disease that had been concealed by the patient. We concluded that this patient had worsened an affective disorder with addictive behaviour (hedonistic homeostatic dysregulation<sup>15</sup>) with previous evidence of bipolar disorder.

#### Patient 2

A 58 year old man had a 13 year history of Parkinson’s disease with severe levodopa induced dyskinesias and motor fluctuations. He reported a transient period during which he experimented with illicit drugs. Continuous bilateral subthalamic stimulation improved his motor status by 81% and his daily dose of levodopa was decreased by 68%. Monopolar stimulation was applied through left electrode contact 2, 3.2 V, 60  $\mu$ s, 130 Hz and right electrode contact 1, 3.2 V, 60  $\mu$ s, and 130 Hz. Four months after stimulation, while the patient’s condition was dramatically improved, his father died, and his marriage deteriorated. His wife reported that he had behavioural disorders with sexual deviancy, exhibitionism, and heightened libido, but poor conjugal relations. She no longer felt secure and was constantly afraid that something might happen to the children in the neighbourhood. The couple maintained their relationship although they lived apart, but finally divorced. During the subsequent months, the patient showed an interest in games of chance and travelled to foreign countries where he was suspected of leisure tourism. In summary, this patient with severe Parkinson’s disease was considered to be a novelty seeker and had manifested sexual deviancy that had not been noted when he was selected for neurosurgery. We suspect that the improvement in his motor condition after stimulation therapy favoured full expression of his behavioural abnormalities.

#### Patient 3

This 62 year old schoolteacher had an 11 year history of Parkinson’s disease with severe levodopa induced dyskinesias and on-off phenomena. Twelve months after his operation, his parkinsonian motor score (UPDRS III) and daily doses of levodopa equivalent were reduced by 78% and 66%, respectively. Monopolar stimulation was applied through the contact 2, 2.9 V, 60  $\mu$ s, 130 Hz on both sides. In the weeks after the operation, the patient reported conflicts with his daughter, and complained of sexual dysfunction and difficulty in

communicating with his wife. Within the 6 months after the neurosurgical procedure, several episodes of depression were seen, associated with decreased appetite and sleep disorders. His wife reported loss of interest and inertia (“he refuses to communicate and takes advantage of his sadness”). Supportive psychotherapy and antidepressant drugs were ineffective and therefore discontinued. When examined for the present study, the psychiatric interview showed two episodes of major depression 20 and 18 years before the operation, which had been considered to result from the loss of his first child. The patient said that he had experienced sadness and anxious ruminations ever since, but that these worsened after his motor disability improved after neurosurgery. In view of a major risk of suicide, psychological and pharmacological therapies have been resumed. In summary, this patient was successfully treated by bilateral STN stimulation, despite two severe episodes of depression that had not been detected during selection. The reappearance of a severe anxious-depressive state during the stimulation therapy and the exacerbation of familial conflicts, strongly suggest that this patient would not have been selected for surgery if a more careful neuropsychiatric examination had been performed.

#### Patient 4

A 60 year old man with a 16 year history of Parkinson’s disease and no history of psychiatric disorders had severe motor fluctuations (including off period freezing) despite a combined treatment with a dopamine agonist (35 mg ropinirole daily) and levodopa (1000 mg daily). Forty eight hours after bilateral electrode implantation, he reported that “words did not come as easily as before”. Although stimulation improved his motor disability score by 61% and his daily doses of levodopa equivalent were reduced by 68%, his gait was hindered by a start hesitation and freezing at corners, significantly improved with a combination of ropinirole (20 mg daily) and levodopa (150 mg daily). Monopolar continuous stimulation was applied through contact 2, 2.7 V, 60  $\mu$ s, and 130 Hz for both sides. Although his motor status was satisfactory, the patient reported difficulty controlling his emotions. “I’m overtaken by feelings that I cannot control”, he said. This emotional hyperreactivity was described as a difficulty in controlling the magnitude and the range of his emotions. The affect expressed was congruent and syntonic. Memory and behaviour remained unimpaired. There were no mood or anxiety disorders. Neurological examination was otherwise normal. Briefly, this patient presented emotional hyperreactivity and a mild reduction in verbal fluency after surgery.

#### Patient 5

A 57 year old man, with a history of anxiety with phobia but no significant psychological disability in daily living, had had Parkinson’s disease for 20 years. He presented severe motor fluctuations and levodopa induced dyskinesias despite optimal adjustment of his antiparkinsonian treatment. Stimulation of the STN dramatically improved his condition, and all antiparkinsonian medications were withdrawn. Monopolar continuous stimulation was applied through contact 2, 2.9 V, 60  $\mu$ s, and 130 Hz on both sides. Four months after neurosurgery, the patient began to complain of fatigue and loss of initiative. He was no longer interested in seeing his friends. His wife reported decreased libido. “Before stimulation, I wanted to be like everybody else. I fought against my disease. Now, I have lost my motivation, I no longer want to do anything, I miss the period when I was fighting”. There were no feelings of sadness, guilt, or uselessness, nor ideas of death or suicide. After an unsuccessful 3 month trial with paroxetine (20 mg daily), a significant improvement was obtained after 1 month of treatment with bromocriptine (30 mg daily). Interest and motivation became “as before” although a clear difficulty in controlling emotions appeared, for instance while watching

television. In summary, despite satisfactory motor results, this patient, without a relevant history of psychiatric disorders, had affective blunting which disappeared under treatment with a dopaminergic D2 agonist. The appearance of emotional hyperreactivity, which was not present pre-operatively, was attributed to the neurosurgical operation.

## METHODS

### Parkinsonian motor disability

Parkinsonian motor disability (UPDRS III)<sup>11</sup> and levodopa related motor complications (UPDRS IV),<sup>11</sup> while patients were under stimulation and taking their usual antiparkinsonian medication (on medication/on stimulation) were compared with the baseline scores obtained 1 month before surgery. Baseline scores were assessed 12 hours after withdrawal of antiparkinsonian drugs (off medication). Under both levodopa and continuous bilateral STN stimulation, the severity of motor disability and motor complications improved by 69.5% (UPDRS III score from 49 (SD 16) to 15 (9)) and 75% (UPDRS IV score from 12 (4) to 3 (3)), respectively, compared with the preoperative state, and the daily doses of levodopa equivalent<sup>12</sup> decreased by 60.5% (from 1400 (SD 620) to 550 (SD 400) mg/day). Two patients no longer needed medication.

### Cognitive functions were evaluated

Cognitive functions were evaluated 1 month before and 6 months after surgery, as described elsewhere.<sup>7</sup> The neuropsychological tests included the Mattis dementia rating scale<sup>16</sup> (before surgery, 140 (SD 4); after surgery 140 (SD 4); maximal score: 144) and the "frontal score"<sup>7</sup> (before surgery, 40 (SD 8); after surgery, 42 (SD 6); maximal score: 50). There were no significant differences between the scores obtained before and after 6 months of continuous bilateral STN stimulation.

### Behavioural disorders were assessed retrospectively using three different approaches

#### The social adjustment scale

The social adjustment scale (SAS)<sup>17</sup> is a semistructured interview, performed in the presence of the spouse by a highly trained psychologist (by MG in our study), that evaluates current social adjustment according to 44 items. These are classified into five main sections: work, social life and leisure activities, family life, marital relations, interaction with children. Each item, rated from 1 to 5 (excellent to bad), permits an estimation of "efficiency", "interpersonal behaviour", and "disagreement-conflict" in each section. Two additional sections explore economic status and global adjustment (a social adjustment score and the opinion of the interviewer).

#### The mini international neuropsychiatric inventory

The mini international neuropsychiatric inventory (MINI 500, French version)<sup>18</sup> is a structured diagnostic interview, which explores the principal psychiatric disorders classified under DSM-IV.<sup>19</sup> The interview elicits information on both previous and current psychiatric episodes. Differences between pre-stimulation and poststimulation behaviour can thus be detected. To further evaluate behaviour in daily life and the psychiatric profile of each patient, a non-standardised psychiatric interview was performed by one of us (LM), blind to the results of the MINI. The results of this examination were compared with the data obtained from the MINI to determine whether the responses were reliable and to make a tentative diagnosis.

#### The IOWA scales of personality change

The IOWA scales of personality change (ISPC)<sup>20</sup> give a quantitative estimate of the affective, behavioural, and social disturbances that may occur after brain lesions, and assess the

extent of changes from premorbid levels. The information is elicited from the spouse or other family member who has had the best opportunity to watch the subjects in daily life. Behavioural guidelines with examples are provided with each scale to enhance reliability. Twenty six "clinical scales" assess disturbances in behavioural control, goal directed behaviour, decision making, emotional expression, interpersonal relations, and insight. There are also four "control scales" (type A behaviour, vanity, frugality, and manipulativeness) to detect possible biases in the ratings. Versions for male and female patients are identical except for the use of sex appropriate pronouns. Each behavioural characteristic is introduced by a brief definition. Lack of initiative, for example, is defined as the extent to which the patient has difficulty starting tasks he must perform or activities he enjoys. The spouse first rates the current level of the item on a scale of 1 to 7: a rating of 1 reflects excellent initiative ("He is very good about getting to work on tasks that need to be done"); a rating of 3 is average ("He is about as good as most people at getting started on tasks that need to be done"); a rating of 5 reflects a moderate disturbance ("He often has difficulty in getting started on a task or project"); a rating of 7 reflects severe disability ("He has a great deal of difficulty getting started with activities"). Besides these behavioural guidelines, examples are provided for ratings 1, 3, 5, and 7 of each characteristic. The patient's behaviour during the 6 months preceding surgery was also evaluated with the same scale. The difference between the two ratings provides a measure of the extent of the changes.

### Statistical analysis

Items of the MINI were grouped together in four domains: mood disorders (major depressive episodes, dysthymia, mania, risk of suicide); anxiety disorders (agoraphobia, social phobia, panic attacks, generalised anxiety); behavioural disability (obsessive-compulsive behaviour, alcohol or drug misuse, bulimia, and anorexia); psychosis. This classification was validated using Spearman's correlation test (not shown). Means of quantitative variables were compared with the Kruskal-Wallis test and qualitative variables with Fisher's exact test. The analyses were performed with SAS software (SAS Institute Inc).

## RESULTS

### Social adjustment scale

Two patients were able to pursue their work, which markedly improved after the operation (table 1). Eight patients had good to excellent adjustment in terms of social life and leisure activities, maladjustment was slight or moderate in 14, and marked to severe in two (variable degree of loneliness, little interest in the outside world, low investment in social relationships, sense of uselessness). Family life was considered well adjusted in 14 patients, whereas 10 complained of conflicts with one or several members of the family. Married life was good or excellent in 11 patients, but a variable degree of conflict was found in 11. Altogether, global social adjustment was good in nine patients, moderately impaired in 14, and severely abnormal in one. There were no correlations between the scores for family life or married life, and age at onset, duration of the disease, percentage reduction in levodopa treatment, percentage improvement of levodopa induced motor complications, and daily dose of levodopa (not shown). However, age at onset of the disease was inversely correlated with the global social adjustment score ( $p < 0.05$ ). There was a negative correlation between the scores for maladjustment in social life and leisure activities ( $p < 0.01$ ) and in global social adaptation ( $p < 0.01$ ) and the degree of improvement of levodopa induced complications. In brief, late onset of the disease was associated with a poor postoperative

**Table 1** Social adjustment scale (SAS)<sup>17</sup> in 24 parkinsonian patients treated by bilateral continuous stimulation of the STN\*

	Adjustment good to excellent	Maladjustment	
		slight to moderate	marked to severe
Work (n=2)	2		
Social living and leisure (n=24)	8	14	2
Family (n=24)	14	8	2
Married life (n=22)	11	9	2
Children relation (n=21)	14	6	1
Global social adjustment (n=24)	9	14	1

\*Expressed as number of patients; n, total number of patients who responded to the questions.

global social adjustment; maladjustment in social life and leisure activities, and a poor global social adaptation were associated with the persistence of levodopa induced motor complications.

### Neuropsychiatric profile: the mini international neuropsychiatric inventory (MINI)

#### Depressive episodes

Depressive episodes, experienced by half of the patients (12/24) during the course of the disease (not referred for medical attention in eight patients) before surgery, were seen in five out of 24 patients after surgery (table 2). Four of these patients had had a history of depression before stimulation. In patient 2 (see case report) who had no history of depression, the depressive episode could not be considered with certainty to have resulted from stimulation.

#### Suicidal risk

A suicidal risk was noted in three out of 12 patients who had had a history of depression before stimulation and in four patients after stimulation therapy.

#### Hypomania

An episode of hypomania, which resolved spontaneously within 2 weeks, was seen 1 month after neurosurgery in one patient. However, a moderate and transient euphoria occurred in the days subsequent to surgery in 18 patients.

#### Agoraphobia

Agoraphobia was noted in four patients. The symptom worsened dramatically postoperatively in two patients, who continued to have episodes of freezing, although STN stimulation provided satisfactory relief from the other parkinsonian symptoms.

**Table 2** Number of patients with psychiatric disorders among 24 parkinsonian patients treated by continuous bilateral STN stimulation

	Observed at any point before neurosurgery	Observed after neurosurgery
Major depressive episode	12	5 (4)
Suicide risk	3	4 (3)
Hypomania	2	1 (1)
Agoraphobia	4	4 (4)
Obsessive-compulsive disorder	1	1 (1)
General anxiety	17	18 (17)
Alcohol dependence	1	0
Drug dependence	2	2 (2)
Psychosis	2	1 (0)
Post-traumatic stress disorder	1	1 (1)

Values in parentheses are results found both after and at some stage before surgery.

#### Anxiety

Anxiety, identified in 17 out of 24 patients before surgery, was noted in 18 patients after STN stimulation. Generalised anxiety with fear of sudden failure of the stimulator was experienced by 15 patients, 10 of whom also developed anxiety without specific concerns. In the three other patients, we failed to identify a specific focus for their anxiety.

#### Drug dependence

Drug dependence was noticed in two patients (case reports 1 and 2), who developed addictive behaviour with respect to levodopa treatment. A transient period of alcohol dependence was found in the anamnesis of patient 1 and a history of misuse of cannabis in patient 2.

#### Psychosis

Two patients had had an episode of psychosis before surgery, one of whom developed an episode of psychosis after surgery. In the first patient, drug induced psychosis (70 mg bromocriptine a day) occurred 3 years before neurosurgery but resolved within a few days after withdrawal of the medication. In the second patient, florid psychosis with mystic delusions appeared a few weeks after electrode implantation, concomitant with the withdrawal of subcutaneous administration of apomorphine (no follow up).

No correlations were found between the presence of depression, agoraphobia, anxiety, psychosis, drug dependence, and the general characteristics of the patients (not shown). There was a significant positive correlation between the presence of anxiety and both the percentage reduction in the daily dose of levodopa equivalent ( $p < 0.01$ ) and the postoperative UPDRS IV score ( $p < 0.05$ ). In brief, the presence of anxiety was associated with a marked reduction in the daily dose of levodopa equivalent and in motor complications score (UPDRS IV).

#### IOWA scales of personality change (ISPC)

Stimulation caused no significant changes in either the global score or scores for specific characteristics of ISPC (table 3). The variance was large, however, suggesting that subgroups of patients may exist. An analysis of the distribution of the scores disclosed the existence of three subgroups: a group in which the ratings before and after surgery were "identical" (global change  $< 10$ ), a group that was "ameliorated" (global score decreased  $> 10$ ), and a group that was "aggravated" (global score increased  $> 10$ ). For the "identical" subgroup ( $n = 7$ ), the global score was 97 (SD 16) before and 95 (SD 16) after surgery. None of the 30 characteristics analysed individually differed significantly. For the "ameliorated" subgroup ( $n = 8$ ), the global score was 116 (SD 19) before and 83 (SD 16) after surgery, and the scores for the following 10 characteristics decreased significantly ( $p < 0.05$ ) after surgery: lack of initiative, perseveration, depression, lack of persistence, lack of stamina, lack of planning, dependency, social withdrawal, apathy, and vulnerability to pressure. None of the 30 scores

**Table 3** Change in the IOWA scales of personality in 24 patients treated by continuous bilateral STN stimulation

	Identical (n=7)	Ameliorated (n=8)	Aggravated (n=8)
Irritability	-1.3 (1.9)	-0.8 (2.0)	<b>1.7 (1.4)</b>
Lack of initiative	1.0 (1.5)	<b>-2.8 (2.0)</b>	<b>2.6 (1.7)</b>
Perseveration	0.1 (0.4)	<b>-3.4 (1.8)</b>	<b>1.8 (1.3)</b>
Depression	0.1 (1.9)	<b>-2.9 (1.8)</b>	1.3 (2.0)
Impulsivity	0.0 (0.0)	-0.5 (0.9)	1.2 (1.6)
Obsessiveness	-0.3 (0.8)	0.5 (2.3)	-0.1 (1.8)
Lability/moodiness	-1.1 (1.9)	0.0 (1.8)	<b>1.1 (1.0)</b>
Lack of persistence	0.4 (0.8)	<b>-3.1 (2.0)</b>	<b>2.5 (1.5)</b>
Lack of stamina	0.1 (0.4)	<b>-2.4 (0.7)</b>	1.0 (3.7)
Lack of planning	0.3 (0.8)	<b>-2.0 (2.1)</b>	<b>2.4 (1.9)</b>
Inflexibility	-0.4 (1.6)	-1.1 (1.5)	<b>1.4 (1.2)</b>
Poor judgment	0.0 (0.0)	-1.0 (1.5)	<b>1.3 (1.2)</b>
Anxiety	-0.3 (0.9)	-0.9 (1.0)	0.8 (3.0)
Insensitivity	-0.3 (1.8)	-0.4 (1.1)	<b>1.4 (0.9)</b>
Social inappropriateness	-0.1 (0.9)	-0.4 (1.1)	0.6 (1.4)
Dependency	0.3 (0.5)	<b>-2.0 (2.1)</b>	1.0 (1.9)
Impatience	0.0 (0.0)	-1.2 (2.1)	<b>1.3 (1.0)</b>
Type A behaviour	0.0 (0.6)	-0.9 (2.0)	-0.6 (1.4)
Blunted affect/unemotional	-0.3 (2.6)	-0.6 (1.2)	0.6 (2.1)
Social withdrawal	0.1 (0.4)	<b>-2.4 (2.4)</b>	0.9 (2.0)
Aggression	-0.7 (1.9)	-0.2 (0.7)	1.4 (1.6)
Indecisiveness	0.3 (0.9)	-0.7 (1.2)	<b>1.6 (1.8)</b>
Vanity	0.0 (0.0)	0.2 (0.7)	0.1 (1.1)
Suspiciousness	-0.1 (0.4)	-0.1 (0.8)	1.2 (1.9)
Apathy	0.3 (1.8)	<b>-1.9 (1.6)</b>	<b>2.0 (1.5)</b>
Frugality	-0.4 (0.8)	-0.1 (0.3)	-0.8 (2.6)
Inappropriate affect/emotion	0.6 (2.0)	-0.3 (0.7)	1.1 (1.6)
Manipulativeness	-0.1 (0.4)	0.3 (0.7)	0.4 (0.5)
Vulnerability to pressure	0.0 (0.0)	<b>-1.0 (1.1)</b>	<b>2.3 (1.6)</b>
Lack of insight	-0.3 (0.8)	-0.4 (1.1)	0.6 (1.4)
Total	-2.1 (6.4)	<b>-32.6 (16.8)</b>	<b>33.5 (14.1)</b>

Numbers in parentheses are SD. Boldface type:  $p < 0.05$ .

increased. For the "aggravated" subgroup (n=8), the global score was 106 (SD 25) before and 140 (SD 26) after surgery, and scores for the following 13 characteristics increased significantly ( $p < 0.05$ ) after surgery: irritability, lack of initiative, perseveration, lability/moodiness, lack of persistence, lack of planning, inflexibility, poor judgement, insensitivity, impatience, indecisiveness, apathy, and vulnerability to pressure. None of the 30 characteristics decreased. The six characteristics that improved significantly in one group and worsened in the other (lack of initiative, perseveration, lack of persistence, lack of planning, apathy, vulnerability to pressure) can therefore be considered to be the most sensitive to high frequency stimulation of the STN.

The results of this investigation (SAS, ISPC, and MINI) were coherent and consistent with those obtained during the psychiatric examination. In addition, 15 of the 24 patients reported mild to moderate emotional hyperreactivity. According to the patients' spouses, the amplitude of emotions increased after surgery, and they were triggered more readily by trivial factors compared to the preoperative state. The affect expressed was congruent and syntonic. This higher emotional reactivity was not accompanied by bulbar or pseudobulbar palsy or pyramidal signs, and was not influenced by levodopa treatment.

## DISCUSSION

Parkinsonian motor disability was markedly improved bilaterally in all patients studied, in agreement with previous reports.<sup>2-5,6</sup> This efficacy of the neurosurgical procedure in all patients strongly suggests that the electrodes were correctly placed in both STNs. This was in accordance with the position of the electrode checked on the postoperative MRI. Despite the efficacy of neurosurgery, psychiatric and behavioural disorders were found in a few but not all patients. Although the data presented were obtained in a representative population of

patients with Parkinson's disease treated by bilateral STN stimulation, the results should be considered with caution as this was a retrospective study performed on a limited number of patients (n=24). Moreover, a bias in the selection of the patients cannot be excluded, as those who agreed to participate in the study might well be those expected to experience psychiatric complications or difficulties in social life after surgery. The main abnormalities seen postoperatively in aggravated patients can be schematically divided into the following categories: social maladjustment, decompensation of psychiatric disorders, anxiety, emotional hyperreactivity, and severe behavioural disorders.

### Social maladjustment

Several factors may have contributed to the slight to severe global social maladjustment found in 15 out of 24 patients. (1) The marked motor improvement and the consequent regaining of autonomy after surgery in most of the patients was followed in some cases by the deterioration of conjugal relationships (six patients). These interpersonal conflicts were interpreted as having resulted from problems of communication between the patients, who suddenly regained their autonomy, and their devoted spouses, who lost their function after years of more or less permanent disease related compassion and care. In three of these patients, additional existential problems emerged, due to the impossibility of integrating into a new sociofamilial environment after years of severe motor disability. (2) These difficulties were triggered or aggravated postoperatively by the emergence of severe anxiety, which probably prolonged the state of dependence, exacerbated depression, and favoured the expression of behavioural disturbances in some patients. In accordance with a previous report,<sup>9</sup> older patients were most vulnerable to postoperative problems of social adjustment, as shown by the negative correlation between the global adjustment score and the age at

onset of the disease. Briefly, the results indicate that difficulties in social and conjugal adjustment can occur postoperatively, in particular in aged patients, and suggest that a careful assessment of the sociofamilial situation should be performed before selection of patients for neurosurgery.

### Depression

Twelve out of the 24 patients examined in this study had experienced depression before surgery, a prevalence which is in agreement with previous epidemiological reports in Parkinson's disease.<sup>21</sup> After surgery, depression occurred in five patients, four of whom had had depressive episodes in the past. The persistence of depression in these patients was not expected, given their satisfactory postoperative motor status. Although psychiatric disorders were a contraindication, these patients were nevertheless selected for continuous stimulation of the STN. The severity of the history of depression was overlooked when the patients were selected for surgery, probably because the severity of parkinsonian motor disability and levodopa related motor complications predominated over the psychiatric disorders. No psychiatric history was present in the anamnesis of one patient (case report 2), who developed a transient depressive episode under emotionally straining circumstances. This suggests that the neurosurgical procedure did not contribute to the depressive episode in this patient. In addition, a patient not included in this study, a 56 year old woman with a 13 year history of severe Parkinson's disease, committed suicide 9 months after surgery. The operation had been a success and all antiparkinsonian medications were withdrawn. Five months after continuous bilateral stimulation of the STN, she developed severe melancholia with feelings of guilt and major delusions, in a context of marked anxiety. We discovered at that time that she had had a severe depression at the age of 19 and that her father had committed suicide. After 2 months of treatment with serotonin reuptake inhibitors and anxiolytic drugs, the depressive state regressed, but sadly she hanged herself 2 months later. In brief, a history of major depressive episodes is predictive of severe postoperative mood disorders.

Given the marked improvement in motor disability resulting from neurosurgery, the reactivation of depression in these patients is difficult to understand. The contrary was expected. Mood disorders are usually improved in conjunction with motor handicap in *de novo* patients with Parkinson's disease treated with levodopa<sup>22</sup> or at time of maximal clinical improvement in patients with Parkinson's disease with motor fluctuations.<sup>23</sup> Given the close temporal relation between the occurrence of depression in our patients and the date of neurosurgery, a causal role of STN stimulation cannot be excluded. A transient depressive episode was seen during stimulation of the left substantia nigra (below the subthalamic site) in a woman with longstanding Parkinson's disease and no history of depression, whereas stimulation of the STN, the therapeutic target, had no such effect.<sup>24</sup> In the patients studied here, this explanation is unlikely as motor disabilities were markedly improved in all patients and it was checked that the therapeutic electrode was in the STN area.

A direct effect of stimulation induced inhibition of the STN<sup>25</sup> might possibly explain the emotional blunting found in one patient (case report No 5), who remained psychologically unsatisfied despite a marked improvement of his motor disability. The fact that this unexpected reaction was ameliorated by the administration of dopamine agonists (without additional improvement in motor disability) suggests a persistence of the residual impairment of extrastriatal dopaminergic pathways (mesolimbic), which was not compensated for by STN stimulation. The possibility that other factors contributed to the appearance of mood disorders in our patients cannot be ruled out. In particular, episodes of depression have been reported after the positive outcome of radical

treatment for other chronic disabling diseases. A prospective study performed in 60 epileptic patients, who underwent temporal lobe surgery found depression in 21% of patients before surgery versus 38% after surgery.<sup>26</sup> Similar findings have been reported in patients with end stage kidney<sup>27</sup> and cardiac failures and transplantation<sup>28</sup>, suggesting that depression found in these studies may share common mechanisms with that found in our study.

Taken together, the results suggest that caution should be exercised when selecting patients with Parkinson's disease with a history of severe depression for treatment by continuous STN stimulation, with particular attention being given to suicidal tendencies.

### Anxiety and emotional lability

The prevalence of anxiety (75%; 18/24 patients) in the operated patients was higher than that reported for the general population of patients with Parkinson's disease.<sup>21</sup> The reason why anxiety did not improve but, on the contrary, was accentuated after surgery is not clear. Because anxious patients took higher daily doses of levodopa than the others, the role of the still reduced brain dopaminergic transmission might be postulated.<sup>23</sup>

Most patients operated on (75%) experienced disabling difficulty in controlling their emotions. The affects expressed were congruent and syntonetic and not dissociated as observed in pseudobulbar palsy and gelastic states (emotional lability). The fact that bulbar or pyramidal signs did not accompany this emotional hyperreactivity argues against pseudobulbar palsy, although a form fruste of this clinical entity cannot be excluded. Because this symptom was not influenced by levodopa treatment, the residual decreased brain dopaminergic transmission very likely did not play a part, although this possibility cannot be excluded. The mechanism by which stimulation of the STN contributed to emotional hyperreactivity in our patients therefore remains to be established. The fact that a clinical picture of thymoaffective disinhibition<sup>29</sup> has been described after lesions of the STN, and the fact that stimulation induced laughing has been reported in a patient treated by bilateral STN stimulation<sup>30</sup> suggests that stimulation induced STN dysfunction might have played a part in this emotional process.

### Behavioural disorders

In this series of 24 patients treated by STN stimulation, a serious therapeutic problem was posed by two patients (case reports Nos 1 and 2). Both had had transient periods of drug dependence in the past, and both became addicted to levodopa therapy<sup>15 31 32</sup> before and after surgery. Whether this dependency on drugs in general, and on levodopa in particular, was caused or aggravated by the still present nigrostriatal dopaminergic deficiency is unknown. In addition, patient 2 expressed previously overlooked sexual deviancy after neurosurgery. It is highly probable that improvement of parkinsonian motor disability after neurosurgery in this patient favoured the full expression of his behavioural abnormalities. Taken together, these results suggest that the decision to operate on a parkinsonian patient with addictive behaviour towards levodopa should be very carefully considered, especially in patients with affective disorders.

### CONCLUSION

The results of this study confirm that bilateral continuous high frequency stimulation of the STN remains one of the most effective treatments of advanced forms of Parkinson's disease with levodopa induced motor complications, provided that the patients are carefully selected. We were surprised by the unexpected appearance of behavioural disorders that counteracted the advantages of motor improvement in a few

patients. We found familial and social maladjustment in several patients who remained unsatisfied and anxious despite satisfactory motor improvement. Moreover, severe behavioural disorders, in particular depressive disorders, became decompensated after neurosurgery in others. However, in view of the retrospective nature of this study and the lack of case controls these results need to be confirmed prospectively. Nevertheless, we suggest that patients should undergo a careful psychological and psychiatric interview before surgery to evaluate the sociofamilial environment and the existence of prior personality disorders, addictive behaviour, or depressive episodes. The frequency with which anxiety and emotional hyperreactivity were found after surgery, and the possibility that unnoticed behavioural disorders might become decompensated, points to the need for an appropriate psychological follow up to ensure a favourable outcome.

## ACKNOWLEDGEMENTS

INSERM and the National Parkinson Foundation-Miami supported the study. We would like to thank Drs I Arnulf, P B Bejjani, and P Damier for their assistance, the nurses of the Centre d'Investigation Clinique for providing the patients with care, and Dr M Ruberg for reviewing the manuscript. We are indebted to Dr Barrash, Mrs Juillerat Van der Linden and Mrs Peter-Favre for providing us with the French version of the IOWA Scales of personality changes and to Dr Lecrubier for the French version of the MINI.

## Authors' affiliations

**J L Houeto, V Mesnage, M Gargiulo, A M Bonnet, Y Agid**, Centre d'Investigation Clinique, Fédération de Neurologie and INSERM U 289, France

**B Pillon**, INSERM E 007, France

**B Pidoux**, Fédération de Neurophysiologie Clinique, Hôpital de la Salpêtrière, Paris, France

**D Dormont**, Services de Neuroradiologie, Hôpital de la Salpêtrière, Paris, France

**P Cornu**, Services de Neurochirurgie, Hôpital de la Salpêtrière, Paris, France

**L Mallet**, Services de Psychiatrie, Hôpital de la Salpêtrière, Paris, France

**S Tezenas du Moncel**, Services de Informatique Médicale, Hôpital de la Salpêtrière, Paris, France

## REFERENCES

- 1 **Limousin P**, Pollak P, Benazzou A, *et al*. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995;**345**:91–5.
- 2 **Limousin P**, Krack P, Pollak P, *et al*. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998;**339**:1105–11.
- 3 **Kumar R**, Lozano M, Kim YJ, *et al*. Double blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 1998;**51**:850–5.
- 4 **Moro E**, Scerrati M, Romito LMA, *et al*. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. *Neurology* 1999;**53**:85–90.
- 5 **Houeto JL**, Damier P, Bejjani PB, *et al*. Subthalamic stimulation in Parkinson's disease: a multidisciplinary approach. *Arch Neurol* 2000;**57**:461–5.
- 6 **Molinuevo JL**, Valldeoriola F, Tolosa E, *et al*. Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson's disease. *Arch Neurol*. 2000;**57**:983–8.
- 7 **Ardouin C**, Pillon B, Peiffer E, *et al*. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. *Ann Neurol*. 1999;**46**:217–23.
- 8 **Pillon B**, Ardouin C, Damier P, *et al*. Neuropsychological changes between "off" and "on" STN or Gpi stimulation in Parkinson's disease. *Neurology* 2000;**55**:411–18.
- 9 **Saint-Cyr JA**, Trepanier LL, Kumar R, *et al*. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain* 2000;**123**:2091–108.
- 10 **Hoehn MM**, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;**17**:427–42.
- 11 **Fahn S**, Elton RL, UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne D, *et al*, eds. *Recent development in Parkinson's disease*. Vol 2. Florham Park, NJ: MacMillan Healthcare Information, 1987:153–63.
- 12 **Krack P**, Pollak P, Limousin P, *et al*. Subthalamus nucleus or internal pallidal stimulation in young onset Parkinson's disease. *Brain* 1998;**121**:451–7.
- 13 **Bejjani BP**, Dormont D, Pidoux B, *et al*. Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. *J Neurosurg* 2000;**92**:615–25.
- 14 **Yelnik J**, Damier P, Bejjani P, *et al*. Functional mapping of the human globus pallidus: contrasting effect of stimulation in the internal and external pallidum in Parkinson's disease. *Neuroscience*. 2000;**101**:77–87.
- 15 **Giovannoni G**, O'Sullivan JD, Turner K, *et al*. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry* 2000;**68**:423–8.
- 16 **Mattis S**. *Dementia rating scale*. Odessa, FL: Psychological Assessment Resources, 1988.
- 17 **Weissman MM**. The assessment of social adjustment: a review of techniques. *Arch Gen Psychiatry* 1975;**32**:357–65.
- 18 **Sheehan DV**, Lecrubier Y, Sheehan KH, *et al*. The mini-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;**59**(suppl 20):22–33, quiz 34–57.
- 19 **American Psychiatric Association**. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: APA, 1994.
- 20 **Barrash J**, Anderson SW, Jones RD, *et al*. The Iowa rating scales of personality change: reliability and validity. *Journal of the International Neuropsychological Society* 1997;**3**:27–8.
- 21 **Aarsland D**, Larsen JP, Lim NG, *et al*. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999;**67**:492–6.
- 22 **Cummings JL**. Depression and Parkinson's disease: a review. *Am J Psychiatry* 1992;**149**:443–54.
- 23 **Maricle RA**, Nutt JG, Valentine RJ, *et al*. Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: a double-blind, placebo-controlled study. *Neurology* 1995;**45**:1757–60.
- 24 **Bejjani BP**, Damier P, Arnulf I, *et al*. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* 1999;**340**:1476–80.
- 25 **Benabid AL**, Benazzou A, Hoffmann D, *et al*. Long-term electrical inhibition of deep brain targets in movement disorders. *Mov Disord* 1998;**13**(suppl 3):119–25.
- 26 **Ring HA**, Moriarty J, Trimble MR. A prospective study of the early postsurgical psychiatric associations of epilepsy surgery. *J Neurol Neurosurg Psychiatry* 1998;**64**:601–4.
- 27 **Fukunishi I**. Psychosomatic problems surrounding kidney transplantation: incidence of alexithymia and psychiatric disturbances. *Psychother Psychosom* 1992;**57**:42–9.
- 28 **Bunzel B**, Laederach-Hofmann K. Long-term effects of heart transplantation: the gap between physical performance and emotional well being. *Scand J Rehabil Med* 1999;**31**:214–22.
- 29 **Trillet M**, Vighetto A, Croisile B, *et al*. Hemiballismus with logorrhea and thymo-affective desinhibition caused by haematoma of the left subthalamic nucleus. *Rev Neurol (Paris)* 1995;**151**:416–9.
- 30 **Kumar R**, Krack P, Pollak P. Transient acute depression induced by high-frequency deep brain stimulation. *N Engl J Med* 1999;**341**:1003–4.
- 31 **Tack E**, De Cuyper G, Jannes C, *et al*. Levodopa addiction: a case study. *Acta Psychiatr Scand* 1988;**78**:356–60.
- 32 **Soyka M**, Huppert D. Ldopa abuse in a patient with former alcoholism. *British Journal of Addiction* 1992;**87**:117–8.