

Subthalamic Nucleus Stimulation Affects Fear and Sadness Recognition in Parkinson's Disease

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Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson's disease (PD) can produce emotional disorders that have been linked to disturbance of the STN's limbic territory. The aim of this study was to confirm the impairment of the recognition of facial emotions (RFE) induced by STN DBS, not only ruling out the effect of the disease's natural progression in relation to the effect of DBS, but also assessing the influence of modifications in dopamine replacement therapy (DRT) following STN DBS. RFE was investigated in 24 PD patients who underwent STN DBS and 20 PD patients treated with apomorphine. They were assessed 3 months before and after treatment. The 2 patient groups were compared with a group of 30 healthy matched controls. The results showed that RFE for negative emotions (fear and sadness) was impaired in only the STN DBS group in the posttreatment condition and was unrelated to DRT. Results confirm the selective reduction of RFE induced by STN DBS, due neither to the disease's natural progression nor to modifications in DRT.

Keywords: subthalamic nucleus, deep brain stimulation, Parkinson's disease, emotion recognition, limbic system

Clinical studies have revealed a selective reduction in the recognition of facial emotions (RFE) following deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD); (Biseul et al., 2005; Drapier et al., 2008; Dujardin et al., 2004; Le Jeune et al., 2008; Schroeder et al., 2004). Although the materials and procedures differ across studies, one important and consistent finding is that the impairment seems to selectively concern negative emotions. Another important finding is that the impairment cannot be attributed to secondary variables, such as anxiety or depression, a visuospatial deficit, or general cognitive decline. These clinical changes have been related to disturbance of

the STN's limbic territory (Dujardin et al., 2004; Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005) and would appear to suggest that STN stimulation affects the processing of emotional information.

The involvement of the STN in emotional processing has been suggested by both peri- and postoperative case reports (Kuhn et al., 2005; Mallet et al., 2007), as well as by PET studies (Geday, Ostergaard, & Gjedde, 2006; Le Jeune et al., 2008). In one of these (Le Jeune et al., 2008), our group recently obtained a positive correlation between a reduction in the recognition of fearful facial expressions following STN DBS and changes in glucose metabo-

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lism, especially in the right orbitofrontal cortex (OFC), using ^{18}F FDG-PET. These results suggest that the STN may be part of a broadly distributed neural network involved in RFE, either via processing within the STN itself or by virtue of its impact on other limbic territories.

Nevertheless, this research has left several questions unanswered. First, even if the presence of emotional disturbances in PD is still a matter for debate (Adolphs, Schul, & Tranel, 1998), some authors argue that RFE impairments may occur in the natural course of PD (for a review, see Assogna, Pontieri, Caltagirone, & Spalletta, 2008). In this context, it is impossible to rule out the possibility that RFE impairment reported after STN DBS may be due to the disease's natural progression rather than being a specific effect of DBS. To answer this question, we adopted a design that allowed us to assess the effect of the disease's natural progression compared with the effect of DBS on RFE. Second, it is worth noting that after STN DBS, dopamine replacement therapy (DRT) is significantly reduced. In a recent study, Lawrence, Calder, McGowan, and Grasby (2002) showed that, in healthy subjects, a selective disruption of one dopamine receptor family can lead to impairment of RFE abilities, and it is now well-documented that dopamine is involved in emotional processing (for a review, see Salgado-Pineda, Delaveau, Blin, & Nieoullon, 2005). In PD, we do not yet know whether a significant reduction in DRT can explain the emotional modifications observed after STN DBS. Finally, in our previous study, we performed a *quantitative* analysis of RFE performances, and the question of the *qualitative* pattern of confusion therefore remains open.

In this context, the aim of the present study was to reinforce our previous results showing the impact of STN DBS on RFE in PD by assessing the effect of the disease's natural progression and the influence of modifications in DRT following STN DBS and by qualitatively describing the pattern of recognition errors.

Method

Participants

Two groups of patients with PD and a healthy control (HC) group took part in the study. All patients met the clinical criteria of the United Kingdom Parkinson's Disease Society Brain Bank for idiopathic PD (Hughes, Daniel, Kilford, & Lees, 1992). Sociodemographic, clinical, and motor data are shown in Table 1.

The first group included 24 consecutive patients with PD who were refractory to medical treatment and who underwent bilateral STN DBS (STN group) at Rennes University Hospital in Brittany, France. Standard selection and exclusion criteria for surgery were applied to all patients (Welter et al., 2002). There were 17 men and 7 women. Mean ($\pm SD$) age at surgery was 59 (± 8) years. Mean ($\pm SD$) educational level was 10 (± 3) years. Mean ($\pm SD$) disease duration at surgery was 11.9 (± 2.5) years. Mean ($\pm SD$) preoperative DRT was 1,307 mg dopa (± 338 , range 500–1,900) calculated on the basis of correspondences adapted from Lozano et al. (1995).

This group was compared with a pathological control group (APO group) of 20 consecutive patients with medically refractory PD who were eligible for surgery but who were treated instead with subcutaneous infusion of apomorphine (APO) because of the length of the waiting list. They were first assessed 3 months prior to the introduction of APO (M0), with a second assessment con-

Table 1

Motor Scores and Dopamine Replacement Therapy Before and After Treatment (DBS or APO)

Variable	STN stimulated PD patients ($n = 24$)					APO PD patients ($n = 20$)				
	Off-dopa period score			On-dopa period score		Off-dopa period score			On-dopa period score	
	Preop Mean \pm SD	Postop Mean \pm SD	Stat. value	Preop Mean \pm SD	Postop Mean \pm SD	Stat. value	Preop Mean \pm SD	Postop Mean \pm SD	Stat. value	Postop Mean \pm SD
Age (years)	59.0 \pm 10.4	NA	—	NA	NA	—	64.3 \pm 10.8	NA	—	NA
Education (years)	10.4 \pm 3.0	NA	—	NA	NA	—	10.8 \pm 4.1	NA	—	NA
Duration (years)	11.9 \pm 2.5	NA	—	NA	NA	—	11.3 \pm 5.2	NA	—	NA
UPDRS III	36.5 \pm 12.4	21.7 \pm 11.2*	5.00	8.2 \pm 4.5	8.8 \pm 6.6	—0.84	ND	ND	—	14.7 \pm 9.5
S&E (%)	61.9 \pm 19.1	74.1 \pm 17.9*	—3.23	87.8 \pm 12.4	88.7 \pm 13.6	—0.60	60.0 \pm 24.5	61.5 \pm 26.0	—0.57	87.5 \pm 8.6
H&Y	2.7 \pm 0.9	2.3 \pm 1.0	1.13	1.0 \pm 0.6	1.1 \pm 1.1	—1.78	2.8 \pm 1.3	2.6 \pm 1.3	0.62	1.7 \pm 0.7
DRT (mg)	NA	NA	—	1307 \pm 338	987 \pm 406*	4.42	—	—	—	1036 \pm 504
										1152 \pm 612*
										—2.55
										—0.02

Note. STN = subthalamic nucleus; PD = Parkinson's disease; APO = continuous subcutaneous infusion of apomorphine; M0 = first evaluation of the APO group; M6 = second evaluation (6 months later) of the APO group; Duration = disease duration; UPDRS III = Unified PD Rating Scale, Part III; S&E = Schwab & England scale; H&Y = Hoehn & Yahr scale; DRT = dopamine replacement therapy; NA = not applicable; ND = not done. Statistical values (stat. values) and p values between pre- and postconditions are reported (t test for matched pairs). Scores in the posttreatment condition marked with an asterisk were significantly different from those in the pretreatment condition ($p < .05$).

ducted 3 months after its introduction (M6). This control group allowed us to specifically assess the course of RFE abilities over a 6-month period. There were 8 men and 12 women. Mean ($\pm SD$) age at introduction of APO was 64.3 (± 10.8) years. Mean ($\pm SD$) educational level was 10.8 (± 4.1) years. Mean ($\pm SD$) disease duration at introduction of APO was 11.3 (± 5.2) years. Mean ($\pm SD$) pre-APO DRT was 1,023.8 (± 494.3) mg. Medication intake was defined as DRT, as it was for the STN group.

The two patient groups were comparable for disease duration, $t(2) = 0.49, p = .7$, and for severity of the disease, as measured by the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS III) in the on-dopa condition (Fahn & Elton, 1987), $t(2) = -2.02, p = .2$, the Hoehn and Yahr scale (H&Y; Hoehn & Yahr, 1967), $t(2) = 0.2, p = .9$, and the Schwab and England scale (S&E; Schwab & England, 1969), $t(2) = 0.45, p = .7$. The two patient groups were also comparable for DRT, $t(2) = 0.57, p = .6$, and for overall cognitive efficiency, as measured by the Mattis scale (Mattis, 1988), $t(2) = 1.59, p = .2$.

The HC group consisted of 30 healthy individuals who had no history of neurological disease, head injury, or alcohol abuse, and no signs of dementia as attested by their score on the Mini-Mental State Examination (Dérouesné, 2001); the mean ($\pm SD$) score was 28.7 (± 0.6). There were 15 men and 15 women. Mean ($\pm SD$) age was 59 (± 8) years. Mean ($\pm SD$) educational level was 11 (± 3) years.

All three groups (STN, APO, and HC) were comparable for educational level, $F(2, 73) = 0.25, p = .8$, and for age $F(2, 73) = 2.81, p = .07$.

After a complete description of the study, written informed consent was obtained for each participant, and the study was conducted in accordance with the Declaration of Helsinki.

Procedure

All STN PD patients were assessed 3 months before ($M - 3$) and 3 months after ($M + 3$) surgery using motor, neuropsychological, and emotional evaluations. For the neuropsychological and emotional assessments, all STN PD patients were on-dopa in the preoperative condition and on-dopa and on-stimulation in the postoperative condition. As we had already found in our previous study (Biseul et al., 2005) that there was no difference in RFE abilities between the on- and off-stim conditions, the STN PD group was postoperatively assessed in the on-stim condition only.

All APO PD patients were assessed twice over the same time interval as the STN DBS PD patients (i.e., first assessment = M0, second assessment 6 months later = M6) using motor, neuropsychological, and emotional evaluations. For the neuropsychological and emotional assessments, all APO PD patients were in the on-dopa condition.

Neurosurgery

Quadripolar DBS electrodes (3389 Medtronic, Minneapolis, MN) were implanted bilaterally in the STN in two successive operating sessions. The overall methodology was similar to that described previously by Benabid et al. (2000).

The location of the unipolar chronic electrode contacts at M3 was determined using a technique reported in detail elsewhere (Sauléau et al., 2005). The focus of each stimulation contact was

located in relation to the midpoint of the bicommissural line (AC-PC), by superimposing the electrode positioning picture on the corresponding ventriculogram. Distances were measured on a squared transparent sheet and then readjusted using a computerized spreadsheet. The contacts' coordinates were expressed as millimeters along three axes originating from the midpoint of the bicommissural line. The first axis was parallel to the bicommissural line, the second axis was perpendicular to the AC-PC line, and the third axis was perpendicular to the midsagittal plane. The mean coordinates of the selected contacts were 11.8 ± 1.0 mm lateral to the AC-PC line, 0.7 ± 1.2 mm above the AC-PC, and -0.8 ± 1.3 mm posterior to the AC-PC midpoint.

In all patients, chronic stimulation was monopolar, using a single contact of the quadripolar electrode. The stimulation characteristics were as follows: mean ($\pm SD$) electrical variables 2.7 (± 0.5) for voltage, 68.7 (± 13.9) for pulse width, and 138.1 (± 17.1) for frequency on the right side, and 2.7 (± 0.4) for voltage, 67.5 (± 13.22) for pulse width, and 138.7 (± 17.1) for frequency on the left side.

Motor Assessment

All STN patients were evaluated according to the Core Assessment Program for Intracerebral Transplantation (Langston et al., 1992) and were scored on the UPDRS III (Fahn & Elton, 1987), H&Y (Hoehn & Yahr, 1967), and S&E (Schwab & England, 1969) scales 3 months before and 3 months after surgery. All STN patients were assessed on- and off-dopa before and after surgery; stimulation remained on after surgery.

All APO patients were scored on the UPDRS III (Fahn & Elton, 1987) in the on-dopa condition only. The H&Y (Hoehn & Yahr, 1967) and S&E (Schwab & England, 1969) scores were recorded twice, at M0 and M6.

Neuropsychological and RFE Assessments

Neuropsychological background. A short neuropsychological battery was administered to all participants prior to the RFE sessions. This battery included the Mattis scale (Mattis, 1988) and a series of tests assessing frontal executive functions: Nelson's modified version of the Wisconsin Card Sorting Test (MCST; Nelson, 1976), the Trail Making Test (TMT; Reitan, 1958), the 2-min phonemic and semantic verbal fluency task (Cardebat, Doyon, Puel, Goulet, & Joannette, 1990), and the Stroop test (Stroop, 1935).

Benton Facial Recognition Test. To check that the early processing stages of face perception were intact, the Benton Facial Recognition Test (Benton, Hamsher, Varney, & Spreen, 1983) was administered to all participants. None of the participants included in this study presented any aperceptive prosopagnosia, as measured by the Benton Recognition Test.

RFE. After they had been familiarized with the task and the list of emotions, each participant was presented with a randomized sequence of 55 computerized photographic slides of seven facial expressions (happiness, sadness, fear, surprise, disgust, anger, and neutral) on a screen (Ekman & Friesen, 1976). To avoid a list effect between the pre- and posttreatment conditions, we used two versions of the facial affect recognition task, which were counter-balanced. In the pretreatment condition, half the participants were

assessed with Version A of the task and half with Version B. In the posttreatment condition, the first half were assessed with Version B and the second half with Version A. In line with the procedure described by Marinkovic, Trebon, Chauvel, and Halgren (2000), Biseul et al. (2005), and Le Jeune et al. (2008), each version contained between 7 and 10 pictures for each facial expression category (Version A: 10 for happiness, 9 for sadness, 7 for fear, 7 for surprise, 7 for disgust, 8 for anger, and 7 for neutral; Version B: 8 for happiness, 8 for sadness, 8 for fear, 7 for surprise, 8 for disgust, 9 for anger and 7 for neutral). After observing the picture for 3 s, participants were prompted to give an answer (verbally) by choosing the most suitable response from the list of the emotions. Responses were recorded on a scoresheet by the experimenter.

Statistical Analysis

Clinical, motor, and neuropsychological data. For the intergroup comparisons in the pretreatment condition, we compared the scores for the different variables between the STN, APO, and HC groups, using either a single-factor analysis of variance (ANOVA), where equal variances were assumed, or the Brown–Forsythe test. Whenever the ANOVA and Brown–Forsythe tests yielded a significant difference, Student–Newman–Keuls or Tamhane’s T_2 post hoc analyses were carried out to determine which groups differed from the others. In the posttreatment conditions, we compared the scores for the different variables between the STN and APO groups using independent group t tests.

For the intragroup comparisons, we compared the scores for the different variables within each of the two PD patient groups between the pre- and posttreatment conditions using matched-pairs t tests.

Emotional data. For the intergroup comparisons in the pretreatment condition, we compared the scores for the emotional variables between the STN, APO, and HC groups using either a single-factor ANOVA or the Brown–Forsythe test. Whenever these tests yielded a significant difference, post hoc analyses (Student–Newman–Keuls or Tamhane’s T_2 , respectively) were carried out to determine which groups differed from the others.

To evaluate the effect of the stimulation versus the effect of the disease’s progression, we conducted a repeated measures ANOVA on the RFE data obtained in the preoperative and postoperative conditions, with group (STN and APO) as a between-subjects variable. Moreover, to assess the influence of DRT modification on RFE changes, we included DRT modification after the introduction of treatment as a covariable. In addition, as the age difference between the three groups was not far from significance ($p = .07$), age was also considered in a second step as a covariable.

RFE confusion matrices were also studied. A confusion matrix gives an account of errors in an identification test. It consists of a table in which the columns represent the predicted (“right”) answers and the rows the actual answers (or vice versa). Values in the table represent the numbers or percentages of the responses actually given for each predicted response. Accordingly, if all judges consistently give the correct answer, the values along the main diagonal will be 100% and all the others will be 0. The cells along the diagonal indicate the rate of correct answers, and the others show which types of stimulus are most often confused. The patterns of confusion go beyond the classic right–wrong dichotomy and provide a more fine-grained characterization of the errors

made by the groups. RFE confusion patterns were compared between the PD groups and the HC group, and also within each PD group, using the chi-square test.

For the intragroup comparisons, we compared the scores for the different variables within each of the two PD patient groups between the pre- and posttreatment conditions using matched-pairs t tests.

Statistical analysis was performed with SPSS 13.0 software, and differences were considered to be significant at the 5% level.

Results

Clinical and Motor Results

Intergroup comparisons. The statistical comparisons of the clinical and motor results between the two groups of PD patients in the preoperative conditions are presented above, in the **Participants** section (see Table 1).

No significant difference was found between the two PD patient groups in the postoperative condition (all measures $p > .05$), except for the UPDRS III score in the on-dopa condition, $t(42) = 2.72$, $p = .01$. It should be noted that a trend toward significance was found between the two patient groups for the S&E score in the off-dopa condition, $t(42) = -1.84$, $p = .07$.

Intragroup comparisons. In the STN PD group, a significant motor improvement was observed 3 months after surgery, as shown by the changes in the motor UPDRS score in the off-dopa condition and the S&E score in the off-dopa condition. As far as the dopa therapy was concerned, there was a significant decrease in DRT at $M + 3$ compared with $M - 3$ (see Table 1).

In the APO PD group, no significant difference was found between the first and second evaluations, except for DRT (see Table 1).

Neuropsychological and RFE Results

Neuropsychological background and Benton Facial Recognition Test. Performances by the participants on the neuropsychological tests are presented in Table 2.

Intergroup comparisons. In the preoperative condition, no significant difference was found between the STN PD, APO PD, and HC groups for the neuropsychological background tests (all measures $p > .05$), except for the numbers of errors, $F = 8.21$, $p < .01$, and perseverations on the MCST, $F(\text{Brown–Forsythe}) = 3.32$, $p = .046$. It should be noted that analysis revealed a strong trend toward significance for semantic fluency, $F(\text{Brown–Forsythe}) = 3.16$, $p = .052$. For the number of errors on the MCST, post hoc analysis revealed a significant difference between the STN and HC groups ($p < .001$), a trend toward significance between the STN and APO groups ($p = .07$), and no significant difference between the APO and HC groups ($p = .24$). For the number of perseverations on the MCST, post hoc analysis revealed a significant difference between the STN and HC groups ($p = .003$), whereas there was no significant difference between the STN and APO groups ($p = .83$) or APO and HC groups ($p = .26$). For semantic fluency, post hoc analysis confirmed that it was only a trend, as it did not reveal any significant difference between the STN and HC groups ($p < .11$), STN and APO groups ($p = .11$), or APO and HC groups ($p = .1$). In addition, in the preoperative

Table 2

Neuropsychological Background Data Before (Preop or Pre-APO) and After (Postop or Post-APO) Treatment in PD Patients and HC Group

Test	STN PD patients (n = 24)				APO PD patients (n = 20)				HC (n = 30)
	Preop Mean \pm SD	Postop Mean \pm SD	Stat. value	p	M0 Mean \pm SD	M6 Mean \pm SD	Stat. value	p	
Benton (max. 54)	45.5 \pm 4.5	46.3 \pm 3.9	-0.89	.4	45.6 \pm 4.8	46.0 \pm 3.9	-3.34	.7	47.3 \pm 4.2
Mattis (max. 144)	139.7 \pm 2.4	138.7 \pm 4.3	1.39	.2	139.5 \pm 3.7	138.3 \pm 6.0	1.34	.2	140.7 \pm 1.6
Stroop									
Interference	0.9 \pm 8.8	-0.8 \pm 10.9	0.45	.7	0.9 \pm 8.0	0.6 \pm 7.8	0.62	.5	3.1 \pm 4.8
TMT									
B-A (s)	89.2 \pm 66.9	98.0 \pm 77.4	-0.58	.5	98.9 \pm 78.5	59.7 \pm 42.1	1.63	.1	70.5 \pm 29.3
Verbal fluency									
Semantic	20.2 \pm 7.1	16.0* \pm 5.4	2.21	.04	25.8 \pm 11.2	27.3 \pm 11.5	-0.40	.7	26.4 \pm 8.9
Phonemic	19.7 \pm 7.7	16.1* \pm 7.4	2.02	.05	19.7 \pm 10.1	20.4 \pm 9.5	0.28	.8	19.7 \pm 6.4
MCST									
Categories (max. 6)	5.4 \pm 0.6	5.0 \pm 1.3	1.94	.06	5.4 \pm 1.2	5.1 \pm 1.8	1.23	.2	5.8 \pm 0.3
Errors	8.2 \pm 4.4	7.5 \pm 6.2	0.57	.6	5.5 \pm 4.5	4.6 \pm 4.6	0.00	1.0	2.7 \pm 2.9
Perseverations	2.7 \pm 2.4	3.3 \pm 4.1	-0.78	.6	2.2 \pm 3.4	1.2 \pm 2.6	0.36	.7	0.6 \pm 1

Note. STN = subthalamic nucleus; PD = Parkinson's disease; APO = continuous subcutaneous infusion of apomorphine; HC = healthy controls; M0 = first evaluation of the APO group; M6 = second evaluation (6 months later) of the APO group; TMT = Trail Making Test; TMT B-A = time difference between completion of parts B and A on the Trail-Making test; MCST = modified Wisconsin Card Sorting Test. Statistical values (stat. values) and *p* values between pre- and postconditions are reported (*t* test for matched pairs).

Scores in the posttreatment condition marked with an asterisk were significantly different from those in the pretreatment condition (*p* < .05).

condition, no significant difference was found between the STN PD group, the APO PD group, and the HC group for the Benton Facial Recognition Test, *F* = 0.19, *p* = .8.

In the postoperative condition, no significant difference was found between the two PD patient groups (all measures *p* > .2) except for the TMT B-A (i. e., time difference between completion of parts B and A on the Trail-Making test), *t* = 2.72, *p* = .03, and semantic fluency, *t* = 0.00, *p* < .001.

Intragroup comparisons. In the STN PD group, no significant difference was found between the preoperative and postoperative conditions for the neuropsychological background tests, except for semantic and phonemic fluency (see Table 2).

In the APO PD group, no significant difference was found between the preoperative and postoperative conditions for the

neuropsychological background tests, except for the number of categories in the MCST (see Table 2).

RFE. Performances by the participants on the RFE task are presented in Table 3.

As gender is known to influence emotion recognition, with a recent study highlighting a female advantage in the recognition of negative emotion (Li, Yuan, & Lin, 2008), we performed an additional analysis to compare the RFE performances of male and female participants in the pretreatment condition. Analysis revealed no significant difference between men and women within the three groups for any of the seven individual expressions or for the total score: happiness, *t*(72) = 0.17, *p* = .8; sadness, *t*(72) = -1.61, *p* = .1; fear, *t*(72) = 0.01, *p* = .9; surprise, *t*(72) = 0.41, *p* = .7; anger, *t*(72) = 1.29, *p* = .2; neutral, *t*(72) = 0.31, *p* = .3;

Table 3

Percentage of Correct RFE Responses Before (Preop or Pre-APO) and After (Postop or Post-APO) Treatment in PD Patients and in HC Group

Emotion	STN PD patients (n = 24)				APO PD patients (n = 20)				HC (n = 30)
	Preop Mean \pm SD	Postop Mean \pm SD	Stat. value	p	M0 Mean \pm SD	M6 Mean \pm SD	Stat. value	p	
Happiness	97.0 \pm 5.5	97.1 \pm 5.8	0.83	.4	95.8 \pm 6.2	99.5* \pm 2.2	-2.05	.05	97.0 \pm 5.3
Sadness	69.2 \pm 20.9	57.8* \pm 21.5	2.43	.02	69.6 \pm 23.5	62.7 \pm 25.8	1.12	.3	65.0 \pm 21
Fear	62.8 \pm 23.9	42.5* \pm 25.3	2.41	.02	47.4 \pm 26.7	47.1 \pm 28.9	-0.04	.9	57.2 \pm 19.9
Surprise	93.4 \pm 9.4	92.2 \pm 11.9	1.07	.3	90.7 \pm 13.3	92.8 \pm 9.8	-0.29	.8	90.9 \pm 17.7
Disgust	90.6 \pm 13	90.3 \pm 14.1	0.82	.4	91.8 \pm 12.1	91.3 \pm 13.1	0.35	.7	92.1 \pm 9.3
Anger	65.8 \pm 24.6	66.7 \pm 20.2	0.36	.7	63.6 \pm 22.6	69.7 \pm 23.9	-0.51	.6	73.0 \pm 20.3
Neutral	79.1 \pm 23.4	81.5 \pm 24.4	-0.70	.5	87.8 \pm 16.9	88.5 \pm 12.7	-0.15	.9	90.0 \pm 13
Total score	79.7 \pm 7.3	75.9* \pm 8.0	2.35	.03	78.1 \pm 5.6	77.9 \pm 10.7	-0.26	.8	80.6 \pm 8.8

Note. RFE = recognition of facial emotion; STN = subthalamic nucleus; PD = Parkinson's disease; APO = continuous subcutaneous infusion of apomorphine; HC = healthy controls; M0 = first evaluation of the APO group; M6 = second evaluation (6 months later) of the APO group. Statistical values (stat. values) and *p* values between pre- and postconditions are reported (*t* test for matched pairs).

Scores in the posttreatment condition marked with an asterisk were significantly different from those in the pretreatment condition (*p* < .05).

total, $t(72) = -0.81$, $p = .4$. It should be noted that the analysis revealed a trend toward significance for disgust, $t(72) = -1.91$, $p = .06$.

In the pretreatment condition, no significant difference was found in RFE between the STN group, the APO group, and the HC group for any of the seven individual expressions or for the total score: happiness, $F(2, 73) = 0.56$, $p = .6$; sadness, $F(2, 73) = 0.71$, $p = .5$; fear, $F(2, 73) = 2.56$, $p = .08$; surprise, $F(2, 73) = 0.41$, $p = .7$; disgust, $F(2, 73) = 0.03$, $p = .9$; anger, $F(2, 73) = 0.91$, $p = .4$; neutral, $F(\text{Brown-Forsythe}) (2, 73) = 2.46$, $p = .1$; total, $t(2, 73) = 0.56$, $p = .6$.

A significant worsening of RFE for both fear and sadness was found in the STN group ($t(23) = 2.41$, $p = .02$ and $t(23) = 2.43$, $p = .02$, respectively), but not in the APO group ($t(19) = -0.04$, $p = .9$ and $t(19) = 1.12$, $p = .3$, respectively). Consequently, in the STN group, RFE was globally impaired in comparison with the preoperative evaluation (Table 3 and Figure 1).

A repeated measures ANOVA performed on fear scores before and after treatment showed a significant effect of group, $F(1, 42) = 4.77$, $p = .03$, without highlighting any effect of DRT modification, before and after treatment: $F(1, 42) = 1.51$, $p = .3$. These results remained consistent after adjusting for age at treatment: group, $F(1, 42) = 4.47$, $p = .041$; DRT modification, $F(1, 42) = 1.44$, $p = .2$; age, $F(1, 42) = 0.00$, $p = 1.0$. Concerning sadness scores, the repeated measures ANOVA failed to reveal any significant effect of group, $F(1, 42) = 0.35$, $p = .6$.

As far as the patterns of confusion were concerned, that is, the ways in which the different groups confused the different types of emotions, analyses revealed that there was no difference in the patterns of confusion either between the STN PD group and the APO PD group in the pretreatment and posttreatment conditions or between these groups and the HC group. In addition, there was no difference in the patterns of confusion between the first and second assessments, either for the STN PD group or for the APO PD group, except for sadness in the STN PD group ($p = .04$). In the pretreatment condition, instead of choosing sadness, patients se-

lected disgust (32%), then fear (22%), neutral (19%), surprise (17%), and anger (10%), whereas in the posttreatment condition, they chose neutral first (36%), followed by surprise (22%), disgust (15%), fear (14%), and anger (13%).

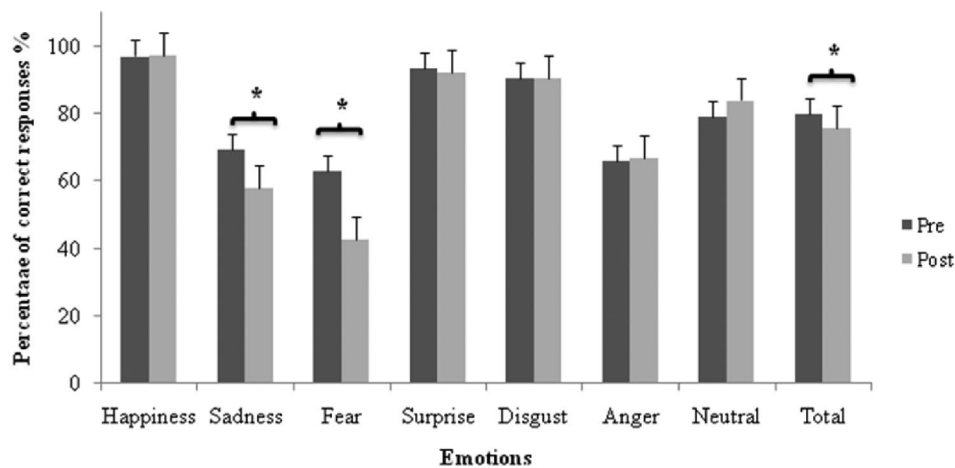
Discussion

The aim of this study was to confirm the impact of STN DBS in PD on RFE for negative emotions by controlling for the effect of the disease's natural progression as well as for modifications in DRT following STN DBS.

We explored the RFE performances of 24 PD patients 3 months before and 3 months after STN DBS, comparing them with a cohort of 20 PD patients 3 months before and 3 months after the introduction of APO.

Our results seem to confirm our initial hypothesis. We demonstrated that, prior to surgery, STN patients had no RFE impairment compared with the APO group and the HC group. Three months after surgery, however, STN patients displayed significant RFE impairment, not only for fear but also for sadness. This deficit was not related to DRT modifications. By contrast, in the APO group, RFE abilities remained unchanged after the 6-month interval except for a rise in the percentage of correct responses for happiness. In addition, we observed the same patterns of confusion in all three groups in the pretreatment condition (HC, STN DBS PD patients in the preoperative condition, and APO PD patients at M0). These patterns remained unchanged after the introduction of treatment for the APO PD patients. It is interesting that analyses revealed that the patterns of confusion were statistically different for sadness for the STN PD patients in the postoperative condition; in the preoperative condition, instead of choosing sadness, patients selected disgust (32%) and then fear (22%), whereas in the postoperative condition, they chose neutral first (36%), followed by surprise (22%).

Care was taken to ensure that the two patient groups were statistically comparable for age, education level, disease duration,



* $p < .05$

Figure 1. Mean percentages (and standard deviations) of correct responses for the subthalamic nucleus deep brain stimulation Parkinson's disease patient group in the pre- and postoperative conditions for all emotions (plus neutral condition) and total scores.

severity of the disease, and overall cognitive efficiency to avoid specific biases. Similarly, to rule out an overall visuospatial information processing deficit, which has already been described in PD (Finton, Lucas, Graff-Radford, & Uitti, 1998), we administered the Benton Recognition Test (Benton et al., 1983) to all participants. All the participants included in this study performed within the normal range (see Table 2). Although the STN DBS PD patient group showed a significant decrease on the semantic fluency test in the postoperative condition, which is consistently reported in the STN stimulation literature (e.g., Dujardin et al., 2004; for a meta-analysis, see Parsons, Rogers, Braaten, Woods, & Troster, 2006), a general cognitive deficit resulting from brain damage (Mandal, Tandon, & Asthana, 1991) between the pre- and postoperative situations can be excluded, given the absence of any significant difference in the general neuropsychological tests. In addition, the RFE deficit was due neither to the disease's natural progression nor to modifications in DRT, but rather to a specific effect of the DBS.

Some limitations have to be taken into account when interpreting our results. We need to bear in mind that the RFE task has several methodological drawbacks. First, the use of categorization and forced choice does not allow correlations to be made between the different scales. Second, the use of static facial expressions does not offer any opportunity to modulate the facial actions in terms of the smallest visible unit of muscular activity (action units; Ekman & Friesen, 1978). Another limitation of our study is that we studied PD patients, which limited the speculations we could make about a possible role of the STN in emotion processing in normal brains. That said, it is worth noting that our PD patients had a satisfactory neuropsychological status and their preoperative MRI scans were normal (Welter et al., 2002). In addition, the presence of emotional disturbances in PD remains under debate (Adolphs et al., 1998).

Our results seem to corroborate the potent regulatory function of the STN in the processing of limbic information sent to cortical and subcortical regions. The STN is described as being situated in a central position in all five corticobasal ganglia–thalamocortical circuits, each of which has specific motor, oculomotor, associative, and limbic functions (Alexander, Crutcher, & DeLong, 1990). As mentioned earlier, neuroanatomical and physiological studies in animals have demonstrated that the STN can be functionally divided into sensorimotor (dorsolateral), limbic (medial), and cognitive–associative (ventromedial) areas (Parent & Hazrati, 1995). Reports of emotional modifications following STN DBS in PD plead in favor of limbic dysfunction induced by DBS. Although the neurosurgical target for DBS in PD is the sensorimotor area of the STN (dorsolateral territory), the small size of the structure (approximately 3 mm [coronal] \times 6 mm [sagittal] \times 12 mm [axial]) compared with the size of each contact of the implanted electrode (1.5 mm high \times 1.27 mm wide) suggests that DBS may influence other compartments of the STN besides the motor one through current diffusion, specifically the limbic area.

Our present data confirming emotional modifications following STN DBS, coupled with previous clinical (Biseul et al., 2005; Dujardin et al., 2004; Schroeder et al., 2004), neuroimaging (Le Jeune et al., 2008; Schroeder et al., 2002, 2003), and perioperative (Kuhn et al., 2005) STN DBS studies in PD, not only suggest that this neurosurgery may disturb the functioning of the limbic loop but also suggest the probable involvement of the STN in the neural

systems for recognizing emotion from faces. It is now well documented that the recognition of emotion draws on a distributed set of structures that include the occipitotemporal neocortex, amygdala, OFC, and right frontoparietal cortices (Adolphs, 2002). Our present results confirm that the DBS model seems to offer arguments for including the STN structure in the cerebral network that subtends RFE.

The medial tip of the STN in animals is principally targeted by limbic cortices (Parent & Hazrati, 1995) such as the OFC and the anterior cingulate cortex (Canteras, Shammah-Lagnado, Silva, & Ricardo, 1990). A close functional connection between the STN and these two cortical structures has been further confirmed by PET studies of PD patients with STN DBS (Le Jeune et al., 2008; Schroeder et al., 2002, 2003). In our previous study using ^{18}F FDG-PET, we observed a significant reduction in fear recognition following surgery and obtained a positive correlation between these neuropsychological results and changes in glucose metabolism, especially in the right OFC (Brodman areas 10, 11, 47). We also reported modifications in glucose metabolism in brain areas other than the OFC, in particular the amygdala, with a negative correlation between changes in glucose metabolism and changes in RFE. RFE impairment, particularly for fear and sadness recognition, has been ascribed to the amygdala on the basis of observations of patients with amygdala damage and PET and fMRI studies of normal subjects (for a detailed review, see Adolphs, 2002).

Taking all these considerations into account, the findings of the present study support the hypothesis that the STN forms part of the neural network that subtends the recognition of emotion from facial expressions via either direct or indirect connections. The processing of RFE is important for normal social interaction. For this reason, the relationship between the impaired perception of negative facial expressions and the social maladjustment of STN PD patients needs to be studied in future work.

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