Subthalamic nucleus stimulation affects orbitofrontal cortex in facial emotion recognition: a pet study

F. Le Jeune,[1,2,*] J. Péron,[2,3,*] I. Biseul,[3] S. Fournier,[2,3] P. Sauleau,[2,4] S. Drapier,[2,3] C. Haegelen,[2,5] D. Drapier,[2,6] B. Millet,[2,6] E. Garin,[1] J.-Y. Herry,[1] C.-H. Malbert[7] and M. Vérin[2,3]

[1]Service de Médecine Nucléaire, Centre Eugène Marquis, rue de la Bataille Flandres Dunkerque, 35042 Rennes, [2]Unité de Recherche Universitaire 425 'Comportement et Noyaux Gris Centraux', Université Rennes I, [3]Clinique neurologique, [4]Service des Explorations Fonctionnelles, [5]Service de Neurochirurgie, Hôpital Pontchaillou, CHU de Rennes, rue Henri Le Guilloux, 35033 Rennes, [6]S.H.U. Psychiatrie Adulte, CH Guillaume Régnier, 108 avenue du Général Leclerc, 35703 Rennes and [7]UMR SENAH, Ingestive Behaviour Department, 35590 Saint Gilles, France

*These authors contributed equally to this work.

Correspondence to: Prof. M. Vérin, Service de Neurologie, Hôpital Pontchaillou, CHU de Rennes, rue Henri Le Guilloux, 35033 Rennes, France
E-mail: marc.verin@chu-rennes.fr

Deep brain stimulation (DBS) of the bilateral subthalamic nucleus (STN) in Parkinson's disease is thought to produce adverse events such as emotional disorders, and in a recent study, we found fear recognition to be impaired as a result. These changes have been attributed to disturbance of the STN's limbic territory and would appear to confirm that the negative emotion recognition network passes through the STN. In addition, it is now widely acknowledged that damage to the orbitofrontal cortex (OFC), especially the right side, can result in impaired recognition of facial emotions (RFE). In this context, we hypothesized that this reduced recognition of fear is correlated with modifications in the cerebral glucose metabolism of the right OFC. The objective of the present study was first, to reinforce our previous results by demonstrating reduced fear recognition in our Parkinson's disease patient group following STN DBS and, second, to correlate these emotional performances with glucose metabolism using [18]FDG-PET. The [18]FDG-PET and RFE tasks were both performed by a cohort of 13 Parkinson's disease patients 3 months before and 3 months after surgery for STN DBS. As predicted, 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. These results confirm the role of the STN as a key basal ganglia structure in limbic circuits.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN), a small structure within the brain, is recognized as a treatment of choice for patients with medically intractable Parkinson's disease (Limousin-Dowsey *et al.*, 1999; Krack *et al.*, 2002).

Although this treatment appears to have a low morbidity rate and despite manifest improvements in motor performance after surgery, some behavioural disturbances have been reported. In particular, anxiety, mood disorders, apathy, indifference, personality changes, modified control of emotional responses and affective blunting have been observed in a small cohort of patients (Saint-Cyr *et al.*, 2000; Trepanier *et al.*, 2000; Bejjani *et al.*, 2002; Houeto *et al.*, 2002; Drapier *et al.*, 2006). Cognitive functions would also appear to be affected by chronic bilateral stimulation. According to Temel's review, the three most important behavioural changes after STN DBS are cognitive dysfunctions (41% of patients), depression (8%) and mania (4%) (Temel *et al.*, 2006). The most frequently reported adverse

effect is reduced word fluency (Pillon et al., 2000; Saint-Cyr et al., 2000).

These neuropsychological modifications induced by STN DBS suggest that this neurosurgery may disturb the functioning of associative and limbic circuits: neuroanatomical studies in animals have already demonstrated that the STN can be divided into sensorimotor (dorsolateral), limbic (medial) and cognitive-associative (ventromedial) areas (Parent and Hazrati, 1995; Joel and Weiner, 1997). Thus, although the target of surgery is the motor area, the adverse neuropsychological effects suggest that the other two areas may be affected by current diffusion (Dujardin et al., 2004b).

Some neuroimaging studies using ^{15}O-H$_2$O-PET have confirmed these hypotheses by demonstrating modifications in brain activation associated with neuropsychological impairments following STN DBS. One PET study showed decreased activity in both the right anterior cingulate cortex and the right ventral striatum during a response conflict task (Stroop task) (Schroeder et al., 2002). In a second study, Schroeder et al. (2003) reported decreased activity in the right orbitofrontal cortex (OFC), the left temporal gyrus and the left inferior frontal/insular cortex, associated with poorer performances on verbal fluency and counting tasks (Schroeder et al., 2003).

Dujardin et al. (2004b) and Schroeder et al. (2003) have both reported reduced recognition of negative facial emotions following STN DBS, and more recently our own group (Biseul et al., 2005) demonstrated that the surgery can induce selective fear recognition impairment. Damage to the OFC can result in impaired recognition of facial expressions (Adolphs, 2002a, b), and the STN is indeed closely connected to the OFC (Canteras et al., 1990). Accordingly, in the present study, we hypothesized that the impaired recognition of fear in Parkinson's disease patients following STN DBS is correlated with modifications in the glucose metabolism of the OFC. To test this hypothesis we conducted a ^{18}F-FDG-PET study of 13 Parkinson's disease patients in pre- and post-STN DBS conditions and correlated changes in their glucose metabolism with modified performances on a recognition of facial emotion (RFE) task.

Participants and Methods
Participants
One group of patients with Parkinson's disease and one 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 Parkinson's disease (Hughes et al., 1992).

The patient group consisted of a series of 13 consecutive patients with medically intractable Parkinson's disease, who underwent bilateral STN DBS at Rennes University Hospital (France). Standard selection and exclusion criteria for surgery were applied to all patients (Welter et al., 2002). In particular, brain atrophy was excluded on the basis of the preoperative MRI. There were nine men and four women. Mean (±SD) age at surgery was 57 (±7.8) years. All 13 Parkinson's disease patients

were right-handed, according to the criteria of the Edinburgh Handedness Inventory (Oldfield, 1971). Mean (±SD) disease duration at surgery was 10.9 (±2.2) years. The total levodopa-equivalent dose was calculated on the basis of the following correspondences adapted from (Lozano et al., 1995): mean (±SD) 1066.2 mg (±347) before STN DBS and 957.3 mg (±494.6) after STN DBS.

The HC group consisted of 30 healthy individuals who had no history of neurological disease, head injury or alcohol abuse and displayed no signs of dementia, as attested by their scores on the MMSE (Dérouesné, 2001).

The two groups were matched for age, sex ratio, handedness and education level. 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.

Methods
All the patients were assessed 3 months before and 3 months after surgery, using motor, PET and neuropsychological assessments. These evaluations were all performed in the same week. All the patients were on stimulation and on dopa for the PET and neuropsychological evaluations.

Prior to the STN DBS, all patients were neuropsychologically assessed to rule out cognitive impairments, using the Mattis scale (Mattis, 1988) and executive tasks, and depression, using the Montgomery and Asberg Depression Rating Scale, (MADRS) (Montgomery and Asberg, 1979). Following surgery, they were followed up clinically by a movement disorder specialist. None of the patients included in this study suffered from dementia [Mattis: mean (±SD) = 139.8 (±2.4)] or depression [MADRS: mean (±SD) = 4.2 (±6.4)].

Motor evaluations
All patients were evaluated according the Core Assessment Program for Intracerebral Transplantation (Langston et al., 1992) and were scored on the Unified Parkinson's Disease Rating Scale (UPDRS) I–IV (Fahn and Elton, 1987), the Hoehn and Yahr score (Hoehn and Yahr, 1967) and the Schwab and England score (Schwab and England, 1969) 3 months before and 3 months after surgery. Patients were assessed on and off dopa before and after surgery. Stimulation remained on after surgery.

Neurosurgery
Methodology. Quadripolar (from '0' for the most ventral contact to '3' for the most dorsal one) DBS electrodes (3389 Medtronic, Minneapolis, MN, USA) were implanted bilaterally in the subthalamic nucleus in two successive operating sessions. The overall methodology was similar to that previously described by Benabid et al. (2000). The location of the two selected electrode contacts (one on the left and one on the right) was determined using the stereotactic coordinates of the ventriculogram performed at the onset of the surgical procedure. During the operation, the final course and depth of the electrode were determined by the best effect obtained on rigidity with no side effect and at the lowest voltage. A 3D CT brain scan performed a few days later confirmed the position of the electrodes.

Electrode location. The contacts' coordinates were expressed as millimetres along three axes originating from the middle of the

Table 1 Stimulator parameters for each patient [electrodes: stimulated (−) contacts]

Subjects	Electrodes		Frequency (Hz)		Amplitude (V)		Impulse duration (μs)	
	Right	Left	Right	Left	Right	Left	Right	Left
1	2−	1−	130	130	2.2	3.3	60	60
2	1−	1−	130	130	1.6	1.6	60	60
3	2−	2−	130	130	2.6	2.6	60	60
4	1−	2−	185	185	3	3	60	60
5	2−	1−	130	130	3	3	60	60
6	1−	1−	130	130	3	2.5	60	60
7	2−	2−	130	130	2.5	1.8	90	90
8	1−	1−	145	145	2.2	2.3	60	60
9	1−	2−	130	145	1.3	2	60	60
10	2−	3−	130	130	3	3	90	90
11	2−	2−	130	130	2.8	2.8	60	60
12	0−	1−	130	130	1.3	1.8	60	60
13	1−	1−	130	130	2	2	60	60

Hz = hertz; V = volts; μs = microseconds.

bicommissural line: the first axis was parallel to the bicommissural line, the second axis was perpendicular to the anterior commissure–posterior commissure line and the third axis was perpendicular to the midsagittal plane. The mean coordinates of the selected contacts were 11.8 ± 1.4 mm lateral to the anterior commissure–posterior commissure line, 0.8 ± 2.1 mm below the anterior commissure–posterior commissure and 1.1 ± 1.6 mm posterior to the middle anterior commissure–posterior commissure. In all patients, chronic stimulation was monopolar, using a single contact of the quadripolar electrode. The stimulation characteristics were as follows: mean pulse width 64.6 μs for the right side (SD = 11.2) and 64.6 μs (SD = 11.2) for the left side, mean frequency 135.3 Hz (SD = 15.4) for the right side and 136.5 Hz (SD = 15.6) for the left side and mean voltage 2.3 V (SD = 0.6) for the right side and 2.4 V (SD = 0.6) for the left side. The stimulation characteristics for each patient are set out in Table 1.

Neuropsychological and RFE assessments

Neuropsychological background. A short neuropsychological battery was administered to all subjects before the RFE session(s). This battery included the Mattis scale (Mattis, 1988) and a series of tests assessing frontal executive functions: the Nelson simplified version of the Wisconsin Card Sorting Test (Nelson, 1976), the Trail Making Test (Reitan, 1958), Category and Literal Fluency Test (Cardebat *et al.*, 1990) and the Stroop Test (Stroop, 1935).

Benton Facial Recognition Test. To ensure that the early processing stages of face perception were intact, the Benton Facial Recognition Test (Benton *et al.*, 1983) was administered to all subjects before the RFE session(s). Subjects were excluded from the study, if face recognition as measured by the Benton Recognition Test was impaired.

RFE. After familiarizing themselves with the task and the list of emotions, the subjects were presented with a randomized sequence of 55 computerized photographic slides of seven facial expressions (happiness, sadness, fear, surprise, disgust, anger and no emotion) on a screen (Ekman and Friesen, 1976). After observing a picture for 3 s, the subjects were prompted to give an answer by choosing the most suitable response among the seven expressions.

The percentage of correct responses was calculated for each of the seven emotions as well as for the total score.

PET imaging procedure

All subjects were studied using ^{18}F-FDG PET in a resting state with eyes open. They underwent two scans: the first was performed 3 months before surgery and the second 3 months after surgery, with the stimulator switched on and on their anti-parkinsonian medication.

PET measurements were performed using a dedicated Discovery ST PET scanner (GEMS, Milwaukee, USA) in 2D mode with an axial field of view of 15.2 cm.

A 222–296 MBq injection of ^{18}F-FDG was administered intravenously under standardized conditions (in a quiet, dimly lit room with the patient's eyes and ears open). During acquisition, the patient's head was immobilized using a head holder. A cross-laser system were used to achieve stable and reproducible positioning. A 20 min 2D emission scan was performed 30 min post-injection and after X-ray-based attenuation correction. These studies were performed with the subjects positioned at the centre of the field of view. Following scatter, dead time and random corrections, PET images were reconstructed by 2D filtered back projection, providing 47 contiguous transaxial 3.75 mm thick slices.

PET image transformation

The data were analysed using SMP2 software (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB, Version 7 (Mathworks Inc., Sherborn, MA). Statistical parametric maps are spatially extended statistical processes that are used to characterize specific regional effects in imaging data. It combines the general linear model (to create the statistical map) with Gaussian field theory in order to draw statistical inferences about regional effects (Friston *et al.*, 1995).

All the subjects' images were first realigned and spatially normalized into standard stereotactic space according to Talairach and Tournoux's atlas (Talairach and Tournoux, 1988). This normalizing spatial transformation matched each scan to our own specially created ^{18}F-FDG template image, which already conformed to the standard space. In effect, in order to optimize

the statistical analysis using SPM2, instead of using the ^{15}O-H2O template provided in the statistical parametric mapping (SPM) software package, in line with Gispert *et al.* (2003), we created our own ^{18}F-FDG template, using the images of 15 control subjects acquired in the same injection, acquisition and reconstruction conditions. We were able to use this template because our Parkinson's disease patients did not present any atrophy, as attested by the preoperative MRI.

An affine transformation was performed to determine the 12 optimum parameters for registering the brain images on the template and the subtle differences between the transformed image and the template were then removed using a non-linear registration method. Finally, spatially normalized images were smoothed using an isotropic 12 mm full width at half-maximum isotropic Gaussian kernel to compensate for inter-individual anatomical variability and render the imaging data more normally distributed.

Statistical analysis

Neuropsychological and emotional data. Because of the small number of subjects and the considerable variance within the patient group, non-parametric analyses were carried out.

For the inter-group comparisons, paired comparisons were performed using the non-parametric Mann–Whitney U-test for two independent groups.

For the intra-group comparisons, Wilcoxon's test for paired groups was used to evaluate the effect of the experimental condition (before versus after surgery). P-values <0.05 were considered to be significant.

Correlation studies. (i) *First step:* The effects of global metabolism were removed by normalizing the count of each voxel to the total brain count (proportional scaling in SPM). Then significant changes of regional cerebral metabolism in the 13 Parkinson's disease patients were estimated by comparing their PET images in pre- and post-operative on-stimulation conditions using a *t*-test at every voxel. Clusters of a minimum of 100 contiguous voxels, with a threshold of two-tailed $P < 0.005$ (corrected for multiple comparison), were considered to be significantly different.

(ii) *Second step:* The SPM software established correlations between post- versus pre-operative changes in the fear RFE score and post- versus pre-operative changes in brain glucose metabolism. To identify, which regions correlated significantly with impaired fear recognition, a general linear 'single subject, covariates only' model was tested at each voxel, with the fear RFE score as a covariant. This yielded a regression coefficient, which was then transformed into a *t*-value.

Two *t*-tests were performed: there was a positive correlation when decreased fear RFE scores (poor performances) were associated with decreased voxel values, and a negative correlation when decreased fear RFE scores (poor performances) were associated with increased voxel values.

T-statistics SPMs were then calculated and thresholded at $P < 0.005$, with multiple comparison correction ($k > 100$).

All coordinates reported here are based on the Talairach atlas and were transformed by applying procedures developed by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging).

Results
Clinical and motor results

A significant motor improvement was observed 3 months after surgery, as shown by the changes in the motor UPDRS, the Hoehn and Yahr and the Schwab and England scores. Table 2 shows the effects of surgery on the motor symptoms.

Neuropsychological and RFE results

Neuropsychological background and Benton Facial Recognition Test

The neuropsychological backgrounds of all subjects and their Benton Facial Recognition Test data are presented in Table 3.

Inter-group comparisons. In the preoperative condition, no significant difference was found between the neuropsychological backgrounds of the STN and HC groups (all measures $P > 0.2$), except for the number of errors and perseverations on the Modified Wisconsin Card Sorting Test ($P = 0.01$ and $P = 0.01$, respectively).

In the postoperative condition, no significant difference was found between the neuropsychological backgrounds of the STN and HC groups (all measures $P > 0.1$), except for the Interference score on the Stroop test ($P = 0.003$).

Intra-group comparisons. In Parkinson's disease patient group, no significant difference was found between the pre- and post-operative conditions for the neuropsychological background tests. It should be noted that analyses revealed a trend towards significance ($P = 0.07$) between the pre- and

Table 2 Motor scores (mean ± SD) before (preoperative condition, baseline) and after (postoperative condition, M+3) STN DBS in Parkinson's disease patients

	Off-dopa period score		On-dopa period score	
	Preoperative (baseline) Mean ± SD	Postoperative (M+3) Mean ± SD	Preoperative (baseline) Mean ± SD	Postoperative (M+3) Mean ± SD
UPDRS III	28.8 ± 9.1	18.2 ± 8.3*	7.1 ± 3.8	7.5 ± 4.7
Schwab and England (%)	65 ± 21.5	76.1 ± 11.2	90 ± 6	88.4 ± 10.7
Hoehn and Yahr	2.3 ± 1.0	2.2 ± 0.8	1 ± 0.6	1.1 ± 1

Differential effects between the two conditions are reported (Wilcoxon's test for paired comparisons).
*$P < 0.05$. UPDRS = united PD rating scale; SD = standard deviation.

Table 3 Neuropsychological background data (mean ± SD) before (preoperative condition, baseline) and after (postoperative condition, M+3) STN DBS in Parkinson's disease patients

	Preoperative condition (baseline) Mean ± SD	Postoperative condition (M+3) Mean ± SD	HC group Mean ± SD
Benton (/54)	46.4 ± 3.7	47 ± 4	46.5 ± 4.6
Mattis (/144)	139.8 ± 2.4	138.9 ± 3.4	140.7 ± 1.6
Stroop test interference	2.6 ± 7.3	−2.4* ± 6.5	3.1 ± 4.8
TMT (s) B−A	77.6 ± 57.8	64.3 ± 42.3	70.5 ± 29.3
Verbal fluency			
Categorical	23.2 ± 9.9	21.7 ± 8.6	26.4 ± 8.9
Phonemic	20.8 ± 8.9	21.6 ± 11.6	19.7 ± 6.4
MCST			
Number of categories	5.6 ± 0.4	5.5 ± 0.9	5.8 ± 0.3
Number of errors	6.6* ± 3.9	5.3 ± 5	2.7 ± 2.9
Number of perseverations	1.9* ± 1.4	1.6 ± 2.2	0.6 ± 1
MADRS	4.1 ± 6.3	4.2 ± 5.3	–

*$P < 0.01$ when compared with HC group (Mann-Whitney test). TMT = Trail Making Test; MCST = Modified Wisconsin Card Sorting Test; MADRS = Montgomery-Asberg Depression Scale; SD = standard deviation.

post-operative conditions for the Interference score of the Stroop test.

RFE

Inter-group comparisons. No significant difference was found in the pre- and post-operative conditions between the STN and HC groups for RFE ($P > 0.1$), either for each of the six emotions or for the overall score.

Intra-group comparisons. Total RFE was significantly impaired following STN DBS, compared with the pre-operative assessment ($P = 0.008$). This was due to a significant selective reduction in RFE for fear ($P < 0.05$).

The RFE data for the Parkinson's disease patient group and the HC group are presented in Table 4.

Cerebral metabolic results

First step: differences between pre- versus post-operative on-stimulation conditions

Areas of significant differences found by comparing the patients in pre- and post-operative on-stimulation conditions are shown in Fig. 1.

In our analysis of postoperative decreases in metabolism, four clusters were significant at level $P < 0.005$ with correction for multiple comparison. Hypometabolism was observed in the bilateral limbic lobe, cingulate gyrus [Brodmann areas (BA) 24, BA 33)], right superior frontal gyrus (BA 8 and 9), right pre-central gyrus (BA 6),

Table 4 Percentage of correct RFE (mean ± SD) before (preoperative condition, M-3) and after (postoperative condition, M+3) STN DBS in Parkinson's disease patients, and HC participants

	Preoperative condition (baseline) Mean ± SD (%)	Postoperative condition (M+3) Mean ± SD (%)	HC group Mean ± SD (%)
Happiness	97.6 ± 5.9	95.1 ± 6.8	95 ± 8.2
Sadness	64.2 ± 25.1	59.6 ± 25	55.6 ± 24.6
Fear	54.1 ± 22.2	38.1 ± 31.9#	51.3 ± 22.9
Surprise	85.8 ± 24	87.9 ± 19.2	89 ± 18.6
Disgust	94.6 ± 7	87.4 ± 14.8	89 ± 11.7
Anger	67 ± 25.7	58 ± 25.9	67.5 ± 25.4
No emotion	80.2 ± 24.4	81.3 ± 24.3	85.7 ± 19.4
Total score	83.6 ± 21.6	75.6 ± 10.3##	76.1 ± 11.4

#$P < 0.05$ and ##$P < 0.01$ when compared with preoperative condition (Wilcoxon's test for paired samples).

right middle frontal gyrus (BA 46) and right superior temporal gyrus (BA 42).

When we studied postoperative increases in metabolism, two clusters were significant at level $P < 0.005$, with multiple comparison correction.

Hypermetabolism was observed in the bilateral cerebellum and right fusiform gyrus (BA 19).

Second step: correlations studies

Positive correlation between changes of glucose metabolism and impairment of fear recognition. All significant findings obtained by positively correlating changes in glucose metabolism with modified cognitive performances are summarized in Table 5, together with their Talairach coordinates.

Positive correlations were observed in two significant clusters ($P < 0.005$, multiple comparison correction). The first cluster concerned the bilateral frontal lobe, orbital gyrus (right BA 10 and right and left BA 11), predominantly in the right side. The second cluster included the middle and inferior frontal gyri (right and left BA 47, left BA 46, left 45) (Figs 2 and 3).

Negative correlation between changes in glucose metabolism and impairment of fear recognition. All significant findings obtained by negatively correlating changes in glucose metabolism with modified cognitive performances are summarized in Table 6.

Negative correlations were observed in two significant clusters ($P < 0.005$, corrected for multiple comparison), in the right posterior cerebellum and right temporal lobe (BA 22, 39, 40). The amygdala were seen as a small significantly negatively correlated cluster ($k = 40$) ($P < 0.005$ corrected for multiple comparison) (Fig. 4).

Discussion

The aim of this article was to correlate RFE abilities, especially fear recognition, with modifications in cerebral
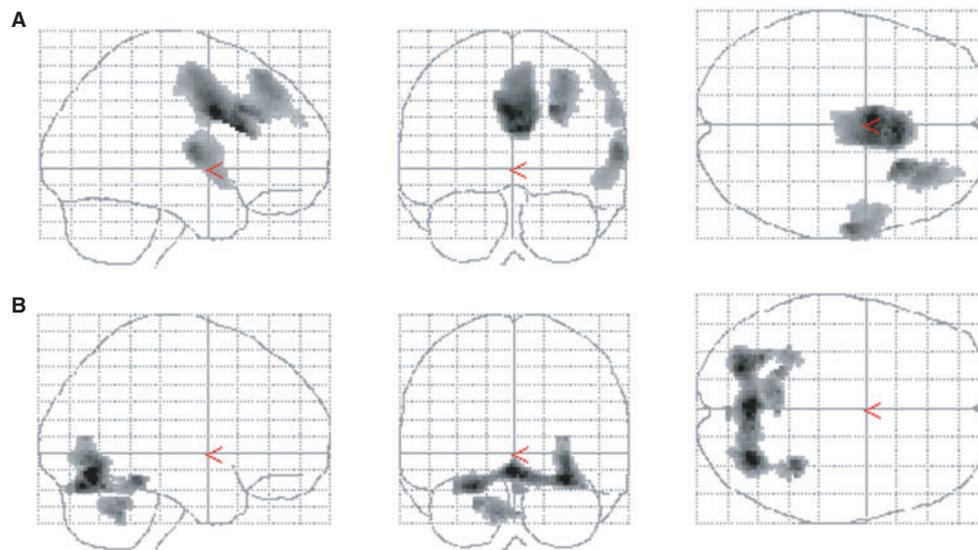
Fig. 1 Statistical parametric maps displaying differences between cerebral glucose metabolism of patients with STN DBS in pre- versus post-operative on-stimulation conditions. Significant differences (two-tailed $P < 0.005$, $k > 100$) are shown on three orthogonal views. (**A**) areas with decrease glucose metabolism in postoperative on-stimulation conditions; (**B**) areas with increase glucose metabolism in postoperative on-stimulation conditions.

Table 5 Regions of positive correlation between fear RFE and changes in glucose metabolism ($P < 0.005$, corrected for multiple comparison, $k > 100$)

Regions	BA	Talairach coordinates			*T*-value	Cluster size
		X	Y	Z		
Right frontal lobe, orbital gyrus	BA 11	9	37	−27	5.17	1751
Left frontal lobe, orbital gyrus	BA 11	−4	36	−27	4.64	1751
Right frontal lobe, orbital gyrus	BA 47	16	32	−25	4.97	1751
Left frontal lobe, middle frontal gyrus	BA 46	−46	47	7	3.68	1086
Left frontal lobe, inferior frontal gyrus	BA 47	−36	31	−5	4.04	1086
Left frontal lobe, inferior frontal gyrus	BA 45	−57	25	2	3.64	1086
Right frontal lobe, orbital gyrus	BA 10	10	52	−9	3.15	1751

BA = Brodmann area.

glucose metabolism in Parkinson's disease patients following STN DBS.

Our group had already reported a specific impairment of fear recognition after STN DBS in Parkinson's disease patients (Biseul *et al.*, 2005). We suggested at the time that this impairment might be a marker of a general associative or limbic dysfunction following STN DBS, especially in the OFC. In the present study, we confirmed these previous results with a different group of patients and provided a preliminary demonstration in thirteen Parkinson's disease patients of a positive correlation between decreased glucose metabolism, mainly in the right OFC (BA: 10, 11, 47), and impaired RFE for fear.

The postoperative PET scans were performed 3 months after surgery, so that we could exclude the microlesional effects due to STN implantation related in Hilker *et al.*'s study (Hilker *et al.*, 2004) where no clusters with significant differences were found between FDG-pre- versus post-operative-STN DBS off 3.8 ± 1.8 months after implantation.

The metabolic cortical modifications following STN DBS found in our study suggest that the STN region influences widespread cortical projection areas. The STN is described as occupying a central position in each of the five corticobasal ganglia-thalamocortical circuits, which have specific motor, occulomotor, associative or limbic functions (Alexander *et al.*, 1990). Animal neuroanatomical studies have demonstrated that the STN can be functionally divided into sensorimotor (dorsolateral), limbic (medial) and cognitive-associative (ventromedial) areas (Parent and Hazrati, 1995; Joel and Weiner, 1997). Several clinical studies (for a review, see Temel *et al.*, 2006) have shown that modulating neuronal activity in the STN results in substantial improvements in pathological motor behaviour, but may be accompanied by behavioural changes. Different aspects of behaviour have
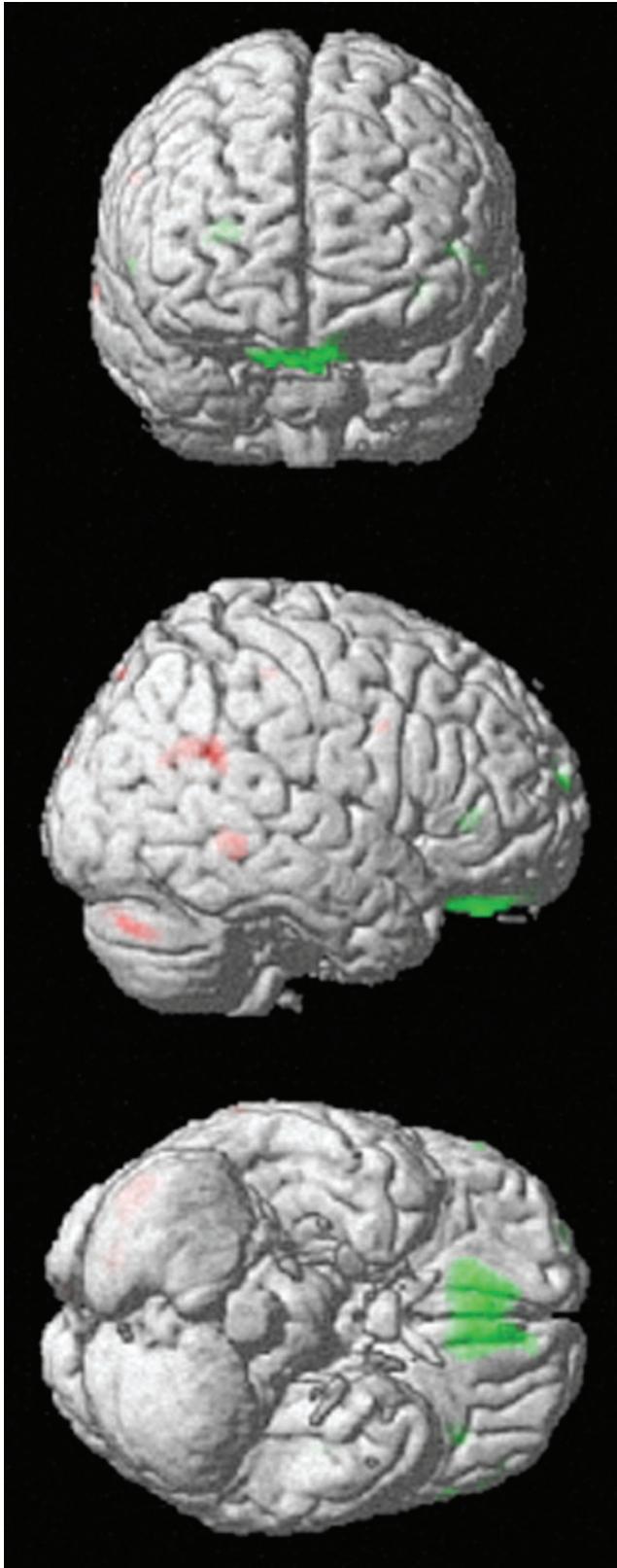
Fig. 2 Regions with significantly positive correlations (green) and negative correlations (red) between changes in glucose metabolism and fear RFE following STN DBS, as measured with SPM2 (*P* < 0.005 on cluster level). Three dimensional surface projection.
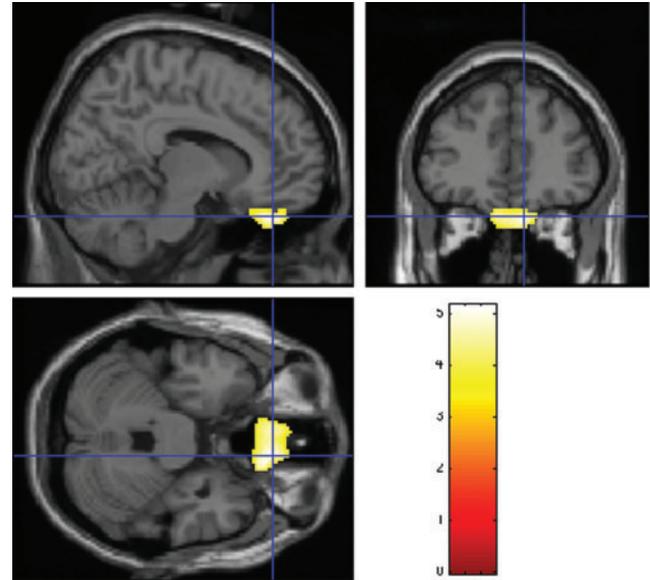

Fig. 3 Significantly positive correlations between changes in the glucose metabolism of the OFC and changes in fear RFE following STN DBS (*P* < 0.005 on cluster level corrected for multiple comparisons, colour bar represents *t*-values). Transversal, sagittal and coronal views in projection into brain slices of a standard MRI (*x/y/z* Talairach coordinates).

been found to be impaired in patients, with specific cognitive functions being affected. All the data presented in these studies underline the potent regulatory function of the STN in processing associative and limbic information sent to cortical and subcortical regions. Although the motor neurones (dorsolateral territory) are the target of functional surgery, these data indicate that other territories are also affected. The very small size of the STN (10 mm in the mediolateral axis, 8 mm in the anteroposterior axis and 6 mm in the ventrodorsal axis) could account for current diffusion and for the active effects of stimulation on territories other than the motor one (Dujardin *et al.*, 2004*b*).

This hypothesis has also been confirmed by neuroimaging studies. In a ^{15}O-H$_2$O-PET study, impaired task performances (Stroop task) were associated with decreased activation in both the right anterior cingulate cortex and the right ventral striatum during STN stimulation, this decreased activation providing direct evidence of STN modulation of non-motor basal ganglia-thalamocortical circuitry (Schroeder *et al.*, 2002). Similarly, decreased frontal activity during STN stimulation was found to be associated with poor performances on the fluency task (Schroeder *et al.*, 2003). In a ^{18}F-FDG-PET study, in the STN DBS on-condition, clusters of significantly increased glucose metabolism were found in the right frontal lobe, corresponding to the dorsolateral pre-frontal cortex (BA 9) and the OFC (BA 47), the right middle temporal gyrus (BA 21), the right posterior cingulate (BA 31) and the left anterior cingulate (BA 32). In the subcortical regions, bilateral clusters of significantly increased glucose metabolism comprised both lower

Table 6 Regions of negative correlation between fear RFE and changes in glucose metabolism

Regions	BA	Talairach coordinates			T-value	Cluster size
		X	Y	Z		
Right posterior cerebellum		46	−73	−25	4.15	567
Left parahippocampal gyrus, amygdala		−22	0	−12	3.01	40*
Right temporal lobe, superior temporal gyrus	BA 39	44	−55	27	4.34	886
Right temporal lobe, fusiform gyrus	BA 40	67	−49	23	3.42	886
Right temporal lobe, superior gyrus	BA 22	67	−56	14	3.03	886

$P < 0.005$ corrected for multiple comparison, $k > 100$, *$P < 0.005$ corrected for multiple comparison, $k > 30$.
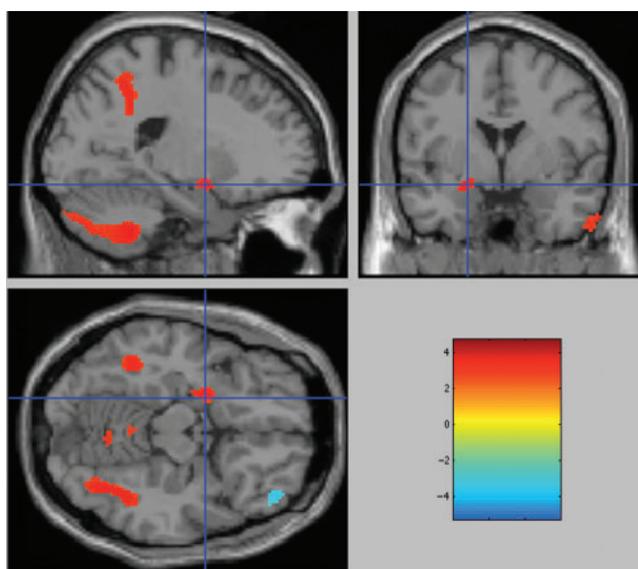BA = Brodmann area.

Fig. 4 Significantly negative correlation between changes in the glucose metabolism of the amygdala and changes of fear RFE following STN DBS ($P < 0.005$ on cluster level corrected for multiple comparisons, colour bar represents *t*-values). Transversal, sagittal and coronal views in projection into brain slices of a standard MRI (*x/y/z* coordinates according to Talairach atlas).

ventrolateral thalami. These data confirm the central role played by the STN in associative and limbic basal ganglia circuits (Hilker *et al.*, 2003).

Our previous neuropsychological results showed that fear recognition was selectively impaired, although both Dujardin *et al.* (2004*b*) and Schroeder *et al.* (2004) reported a much broader decoding deficit, covering sadness and anger as well. Using functional resonance magnetic imaging (fMRI), Sprengelmeyer *et al.* (1998) demonstrated that RFE of disgust, fear and anger is based on separate neural systems. Previous neuroimaging and neuropsychological studies have investigated the neural substrates that mediate responses to fearful expressions. The right hemisphere plays a role in emotional and social processing, encompassing perception as well as recognition. In patients with right hemisphere lesions, Adolphs *et al.* (1996) found that recognition of all emotional expressions was impaired, but that recognition of fear was the most impaired of all. This specialization of the right

hemisphere for mood and behavioural regulation was subsequently described by (Adolphs, 2002*a*). A large number of different structures are involved in recognizing facially expressed emotion. The OFC also seems to be a key structure when it comes to processing this emotion (Adolphs, 2002*a*). Damage to the OFC, especially the right side, can result in impaired recognition of facial expressions, especially expressions of fear (Adolphs, 2002*b*). A study by Hornak *et al.* (1996) was the first to explicitly demonstrate impaired recognition of facial expressions following damage to the OFC. Their patients had unilateral and bilateral damage to medial and lateral aspects of the orbital cortex, and right unilateral damage was much more frequently associated with impaired emotion recognition. Marinkovic *et al.* (2000) found that surgically removing the right anterior inferior pre-frontal cortex for intractable epilepsy produced a profound deficit in recognizing the facial expression of fear, although the recognition of other facial expressions appeared to be intact. This type of deficit is also seen in patients with right pre-frontal lesions (Adolphs *et al.*, 1996). These results suggest that STN DBS brings about modifications to the orbitofrontal circuit, and we took this as our 'a priori' hypothesis for our statistical analysis. This confirmed that changes in glucose metabolism correlated with cognitive impairment mainly occur in the right hemisphere and the right OFC. Nevertheless, the fact that we studied Parkinsonian brains means that we can make only limited speculations about the role of the STN and OFC in RFE in normal brains, although it is worth noting that our Parkinson's disease patients had a satisfactory neuropsychological status and their preoperative MRI scans were normal (Welter *et al.*, 2002). Moreover, the presence of emotional disturbances in Parkinson's disease is still a matter for debate (Adolphs *et al.*, 1998; Dujardin *et al.*, 2004*a*).

In the present study, modifications in glucose metabolism were observed in brain areas other than the OFC, in particular the amygdala with negative correlation between changes in glucose metabolism and changes in RFE. Recent studies have suggested abnormal functioning of the amygdala in Parkinson's disease using an RFE paradigm (Yoshimura *et al.*, 2005). Several studies have described the amygdala as a structure involved in the rapid, coarse perceptual processing of facial expressions (Blair and Curran, 1999; Adolphs *et al.*, 2002). Blair and Curran (1999) showed that the amygdala

responds to sad and fearful expressions. Our results suggest that the STN may modify amygdala activity, although direct interconnections between these two structures have never been proven, either in animals or in humans. For the first time, therefore, we have been able to demonstrate the existence of interconnections between the amygdala and the STN, albeit probably indirect ones, passing through the OFC, as recently suggested by Ghashghaei *et al.* (2007). In addition, on the basis of recent findings (Grandjean *et al.*, 2007) suggesting a functional synchrony between the OFC and the amygdala, we can speculate that STN DBS is responsible for a desynchronization of these two structures.

To conclude, our results, demonstrating a correlation between reduced RFE for fear and changes in the glucose metabolism of Parkinson's disease patients under bilateral STN DBS, confirm—in humans—the role of the STN as a key basal ganglia structure in associative and limbic circuitry.

Acknowledgements

References

Adolphs R. Neural systems for recognizing emotion. Curr Opin Neurobiol 2002a; 12: 169–77.

Adolphs R. Recognizing emotion from facial expressions: psychological and neurological mechanisms. Behav Cogn Neurosci Rev 2002b; 1: 21–62.

Adolphs R, Damasio H, Tranel D. Neural systems for recognition of emotional prosody: a 3-D lesion study. Emotion 2002; 2: 23–51.

Adolphs R, Damasio H, Tranel D, Damasio AR. Cortical systems for the recognition of emotion in facial expressions. J Neurosci 1996; 16: 7678–87.

Adolphs R, Schul R, Tranel D. Intact recognition of facial emotion in Parkinson's disease. Neuropsychology 1998; 12: 253–8.

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, ''prefrontal'' and ''limbic'' functions. Prog Brain Res 1990; 85: 119–46.

Bejjani BP, Houeto JL, Hariz M, Yelnik J, Mesnage V, Bonnet AM, et al. Aggressive behavior induced by intraoperative stimulation in the triangle of Sano. Neurology 2002; 59: 1425–7.

Benabid AL, Krack PP, Benazzouz A, Limousin P, Koudsie A, Pollak P. Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: methodologic aspects and clinical criteria. Neurology 2000; 55: S40–4.

Benton AL, Hamsher KS, Varney N, Spreen O. Contributions to neuropsychological assessments: a clinical manual. Oxford: Oxford University Press; 1983.

Biseul I, Sauleau P, Haegelen C, Trebon P, Drapier D, Raoul S, et al. Fear recognition is impaired by subthalamic nucleus stimulation in Parkinson's disease. Neuropsychologia 2005; 43: 1054–9.

Blair RJ, Curran HV. Selective impairment in the recognition of anger induced by diazepam. Psychopharmacology (Berl) 1999; 147: 335–8.

Canteras NS, Shammah-Lagnado SJ, Silva BA, Ricardo JA. Afferent connections of the subthalamic nucleus: a combined retrograde and anterograde horseradish peroxidase study in the rat. Brain Res 1990; 513: 43–59.

Cardebat D, Doyon B, Puel M, Goulet P, Joanette Y. Evocation lexicale formelle et sémantique chez des sujets normaux: performances et dynamiques de production en fonction du sexe, de l'âge et du niveau d'étude. Acta Neurologica Belgica 1990; 90: 207–17.

Dérouesné C. Echelles et classifications: le mini-mental state examination, version française consensuelle du GRECO. Revue Neurologique 2001; 157: 567–71.

Drapier D, Drapier S, Sauleau P, Haegelen C, Raoul S, Biseul I, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? J Neurol 2006; 253: 1083–91.

Dujardin K, Blairy S, Defebvre L, Duhem S, Noel Y, Hess U, et al. Deficits in decoding emotional facial expressions in Parkinson's disease. Neuropsychologia 2004a; 42: 239–50.

Dujardin K, Blairy S, Defebvre L, Krystkowiak P, Hess U, Blond S, et al. Subthalamic nucleus stimulation induces deficits in decoding emotional facial expressions in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004b; 75: 202–8.

Ekman P, Friesen WV. Pictures of facial affect. Palo Alto: Consulting Psychologist Press; 1976.

Fahn S, Elton R. UPDRS development committee. Unified Parkinson's disease Rating Scale. Recent Dev Park Dis 1987; 2: 153–63.

Friston K, Holmes A, Worsly K, Poline J, Frith C, Frackowiak RS. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995; 2: 189–210.

Ghashghaei HT, Hilgetag CC, Barbas H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. Neuroimage 2007; 34: 905–23.

Gispert JD, Pascau J, Reig S, Martinez-Lazaro R, Molina V, Garcia-Barreno P, et al. Influence of the normalization template on the outcome of statistical parametric mapping of PET scans. Neuroimage 2003; 19: 601–12.

Grandjean D, Pourtois G, Sander D, Tamari L, Schwartz S, Vuillemier P, et al. The emotional voices: human amygdala and orbito-frontal responses to emotional prosody: human intra-cranial recordings. J Cogn Neurosci 2007 (Suppl): 203–4.

Hilker R, Voges J, Ghaemi M, Lehrke R, Rudolf J, Koulousakis A, et al. Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. Mov Disord 2003; 18: 41–8.

Hilker R, Voges J, Weisenbach S, Kalbe E, Burghaus L, Ghaemi M, et al. Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum: evidence from a FDG-PET study in advanced Parkinson's disease. J Cereb Blood Flow Metab 2004; 24: 7–16.

Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967; 17: 427–42.

Hornak J, Rolls ET, Wade D. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 1996; 34: 247–61.

Houeto JL, Mesnage V, Mallet L, Pillon B, Gargiulo M, du Moncel ST, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002; 72: 701–7.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181–4.

Joel D, Weiner I. The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. Brain Res Brain Res Rev 1997; 23: 62–78.

Krack P, Fraix V, Mendes A, Benabid AL, Pollak P. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 2002; 17 (Suppl 3): S188–97.

Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, et al. Core assessment program for intracerebral transplantations (CAPIT). Mov Disord 1992; 7: 2–13.

Limousin-Dowsey P, Pollak P, Van Blercom N, Krack P, Benazzouz A, Benabid A. Thalamic, subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. J Neurol 1999; 246 (Suppl 2): II42–5.

Lozano AM, Lang AE, Galvez-Jimenez N, Miyasaki J, Duff J, Hutchinson WD, et al. Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 1995; 25: 1383–7.

Marinkovic K, Trebon P, Chauvel P, Halgren E. Localised face processing by the human prefrontal cortex: face selective intra cerebral potentials and post-lesions deficits. Cogn Neuropsychol 2000; 17: 187–99.

Mattis S. Dementia Rating Scale. Ressources Inc Odessa, FL: Psychological Assessment; 1988.

Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134: 382–9.

Nelson H. A modified card sorting test sensitive to frontal lobe defects. Cortex 1976; 12: 313–24.

Oldfield RC. The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia 1971; 9: 97–113.

Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev 1995; 20: 128–54.

Pillon B, Ardouin C, Damier P, Krack P, Houeto JL, Klinger H, et al. Neuropsychological changes between ''off'' and ''on'' STN or GPi stimulation in Parkinson's disease. Neurology 2000; 55: 411–8.

Reitan R. Validity of the trail making test as an indication of organic brain damage. Percept Mot Skills 1958; 8: 271–6.

Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 2000; 123 (Pt 10): 2091–108.

Schroeder U, Kuehler A, Haslinger B, Erhard P, Fogel W, Tronnier VM, et al. Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: a PET study. Brain 2002; 125: 1995–2004.

Schroeder U, Kuehler A, Hennenlotter A, Haslinger B, Tronnier VM, Krause M, et al. Facial expression recognition and subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry 2004; 75: 648–50.

Schroeder U, Kuehler A, Lange KW, Haslinger B, Tronnier VM, Krause M, et al. Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. Ann Neurol 2003; 54: 445–50.

Schwab R, England A. Projection techniques for evaluating surgery in Parkinson's disease. Third Symposium on Parkinson's disease, May 20–22, 1968. Royal College of Surgeons in Edinburgh: E. & S. Livingstone Ltd; 1969. p. 152–7.

Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci 1998; 265: 1927–31.

Stroop J. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18: 643–62.

Talairach J, Tournoux P. Co-planar steretoxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. New York: Theme Medical; 1988.

Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. Parkinsonism Relat Disord 2006; 12: 265–72.

Trepanier LL, Kumar R, Lozano AM, Lang AE, Saint-Cyr JA. Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease. Brain Cogn 2000; 42: 324–47.

Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 2002; 125: 575–83.

Yoshimura N, Kawamura M, Masaoka Y, Homma I. The amygdala of patients with Parkinson's disease is silent in response to fearful facial expressions. Neuroscience 2005; 131: 523–34.