Pallidotomy in Parkinson’s disease increases supplementary motor area and prefrontal activation during performance of volitional movements
An H$_2^15$O PET study


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Summary
Supplementary motor area and right dorsal prefrontal cortex activation in Parkinson’s disease is selectively impaired during volitional limb movements. Since posteroventral pallidotomy improves motor performance in Parkinson’s disease patients ‘off’ medication (i.e. off medication for 9–12 h), we hypothesized that it would also concomitantly increase supplementary motor area and dorsal prefrontal cortex activation. Six Parkinson’s disease patients with a median total motor Unified Parkinson’s Disease Rating Scale (UPDRS) of 52.5 (range 34–66) ‘off’ medication underwent unilateral right posteroventral pallidotomy. The patients had H$_2^15$O PET when ‘off’ medication before and 3–4 months after surgery. Each PET study comprised four to six measurements of regional cerebral blood flow either at rest or while performing regularly paced joystick movements in freely selected directions (forward, backward, left or right) using the left hand. Pre- and postoperative scans were performed in an identical manner and the associated levels of activation were compared using statistical parametric mapping. After pallidotomy, the median total motor UPDRS score ‘off’ medication decreased by 34.7 % (P = 0.03) and mean response times of joystick movements following the pacing tones improved by 13.8% (P = 0.08). Relative increases in activation of the supplementary motor area and right dorsal prefrontal cortex were observed during joystick movements (P < 0.001). Decreased activation was seen in the region of the right pallidum (P = 0.001). We conclude that pallidotomy reduces pallidal inhibition of thalamocortical circuits and reverses, at least partially, the impairment of supplementary motor area and dorsal prefrontal cortex activation associated with Parkinson’s disease.

Keywords: pallidotomy; Parkinson’s disease; PET activation; cortex

Abbreviations: rCBF = regional cerebral blood flow; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction
Over the last decade, there has been a renaissance of the use of posteroventral medial pallidotomy to treat Parkinson’s disease. Medial pallidotomy has been shown to improve bradykinesia, tremor, rigidity and gait disturbance, and to diminish the motor fluctuations and abnormal involuntary movements which occur as complications of chronic therapy with dopaminergic medication (Dogali et al., 1995; Lozano et al., 1995; Sutton et al., 1995).

Current models of basal ganglia connectivity suggest that the striatum projects to the medial portion of the globus
pallidus via two distinct pathways (Haber and Elde, 1981; Albin et al., 1989; Gerfen et al., 1990; Flaherty and Graybiel, 1994). A direct striato-pallidal pathway normally acts to inhibit the neurons of the medial globus pallidus. Indirect pathways comprise striatal projections to the medial globus pallidus via the lateral globus pallidus and the subthalamic nucleus. In Parkinson’s disease, loss of striatal dopamine is thought to lead to overactivity of the medial globus pallidus and subthalamic nucleus. The abnormal overactivity of the medial globus pallidus is further reinforced by the overactivity of the subthalamic nucleus since the subthalamic nucleus has an excitatory projection to the medial globus pallidus. Thus, the overall effect of striatal dopamine loss in Parkinson’s disease is inappropriate overactivity of the medial globus pallidus via both the direct and indirect pathways. Relative overactivity of medial globus pallidus neurons compared with lateral globus pallidus neurons has been documented in MPTP-treated primates (Filion and Tremblay, 1991) as well as in Parkinson’s disease patients during intra-operative single-cell recordings (Hutchinson et al., 1994; Sterio et al., 1994) from the basal ganglia.

The basal ganglia are postulated to influence specific cortical areas via distinct and parallel basal ganglia–thalamocortical circuits (Alexander et al., 1990). A ‘motor’ circuit comprises the supplementary motor area, the lateral premotor cortex, the primary motor cortex, dorsal putamen, ventral medial globus pallidus and the ventral lateral, ventral anterior and centromedian nuclei of the thalamus. A dorsolateral ‘prefrontal’ circuit encompasses the dorsal prefrontal cortex, dorsal caudate nucleus, dorsal medial globus pallidus and the ventral anterior nucleus of the thalamus. Other segregated circuits link the striatum and thalamus to the anterior cingulate cortex, the frontal eye fields and the orbitofrontal cortex. Within each segregated circuit, medial globus pallidus output neurons contain GABA (gamma-aminobutyric acid) and normally act to inhibit thalamic and cortical function tonically. Overactivity of medial globus pallidus neurons in Parkinson’s disease is thought to result in excessive inhibition of thalamic–cortical motor function and result in hypokinesia (Alexander et al., 1990; DeLong, 1990).

Studies comparing regional cerebral blood flow (rCBF) in bradykinetic Parkinson’s disease patients and normal volunteers have shown that Parkinson’s disease patients have relatively impaired activation of the supplementary motor area and right dorsal prefrontal cortex during performance of volitional movements (Playford et al., 1992; Jahanshahi et al., 1995). The impairment of function in these cortical association areas is postulated to be a consequence of the excessive inhibition of thalamocortical circuits by the overactive medial globus pallidus and to underlie the deficits of internally generated movements observed in patients with Parkinson’s disease (Dick et al., 1989; Marsden, 1989; Playford et al., 1992; Jahanshahi et al., 1995).

Single-cell electrophysiological recording from the medial globus pallidus in monkeys (DeLong et al., 1985; Kimura et al., 1990) and from patients with Parkinson’s disease (Hutchinson et al., 1994; Beric et al., 1996) during active and passive joint movements have revealed an organization in which the sensorimotor region lies caudally within the medial globus pallidus. The aim of functional neurosurgery in the treatment of Parkinson’s disease over the last decade has been to reduce the overactivity of the sensorimotor region of the medial globus pallidus. This has been achieved by ventral medial pallidotomy (Dogali et al., 1995; Lozano et al., 1995; Sutton et al., 1995) or high-frequency electrical stimulation of either the medial globus pallidus (Bacigalupo et al., 1996) or the subthalamic nucleus (Benabid et al., 1994) which leads to local inhibition of neuronal cell activity. If the medial globus pallidus output projections are inhibitory to the thalamic nuclei, reduction of the overactivity of the ventral medial globus pallidus in Parkinson’s disease would be expected to disinhibit the ventral thalamic nuclei and facilitate thalamic excitation of those cortical areas which receive projections from the thalamic nuclei.

We wished to test this hypothesis by measuring rCBF in Parkinson’s disease patients during performance of paced, freely selected joystick movements, pre- and post-medial pallidotomy. This paradigm involves the selection, preparation and execution of movements and has previously been shown to activate the prefrontal cortex, supplementary motor area and basal ganglia to a lesser extent in Parkinson’s disease compared with normal volunteers (Playford et al., 1992). We used $H_2^{15}O$ PET to investigate the pattern of activation associated with performance of this paradigm pre- and postoperatively in patients with Parkinson’s disease. We hypothesized that medial pallidotomy in patients with Parkinson’s disease would improve joystick-movement response-times and be accompanied by a relative increase in rCBF in those areas which show relative underactivity in Parkinson’s disease, namely the supplementary motor area and prefrontal cortex as well as the thalamus. Since the right medial globus pallidus was lesioned during the operations, we also expected the right medial globus pallidus to show less activation postoperatively compared with preoperatively.

**Material and methods**

**Subjects**

Six patients with medically intractable idiopathic Parkinson’s disease (four males and two females; mean age $52.2 \pm 9.5$ years, range $39–65$ years) were selected for stereotaxic right unilateral posteroverentral medial pallidotomy. The mean duration of Parkinson’s disease was $12.3 \pm 5.5$ years. The indications for pallidotomy were severe fluctuations in motor response to dopaminergic agents ($n = 6$) and severe levodopa-induced dyskinesias ($n = 5$; Patient 1 experienced no dyskinesia). All were responsive to levodopa. All had originally experienced onset of left-sided symptoms and the left limbs were more affected. Patients were assessed with the Unified Parkinson’s Disease Rating Scale (UPDRS) (Lang...
Pallidotomy in Parkinson's disease

Table 1 Preoperative clinical details of the patients undergoing right unilateral pallidotomy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of PD (years)</th>
<th>Total motor UPDRS 'off' medication</th>
<th>Total motor UPDRS 'on' medication</th>
<th>Maximum contralateral dyskinesia</th>
<th>Medication (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>9</td>
<td>34</td>
<td>8</td>
<td>0</td>
<td>Levodopa (1100); bromocriptine (35)</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>M</td>
<td>9</td>
<td>55</td>
<td>10</td>
<td>2</td>
<td>Levodopa (750); pergolide (3)</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>F</td>
<td>5</td>
<td>66</td>
<td>24</td>
<td>5</td>
<td>Levodopa (350)</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>15</td>
<td>54</td>
<td>14</td>
<td>4</td>
<td>Levodopa (1500); pergolide (6)</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>17</td>
<td>36</td>
<td>17</td>
<td>5</td>
<td>Levodopa (1450); selegiline (10)</td>
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<tr>
<td>6</td>
<td>52</td>
<td>F</td>
<td>19</td>
<td>51</td>
<td>18</td>
<td>7</td>
<td>Levodopa (1430) pergolide (6)</td>
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<tr>
<td>Median</td>
<td>(34–66)</td>
<td></td>
<td>(8–24)</td>
<td>(0–7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M = male; F = female; PD = Parkinson's disease.

Table 2 Pre- and post-pallidotomy UPDRS and dyskinesia subset scores

<table>
<thead>
<tr>
<th></th>
<th>Preoperative subset score</th>
<th>Postoperative subset score</th>
<th>Change (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total motor score ‘off’ medication</td>
<td>52.5 (34–66)</td>
<td>31.5 (23–43)</td>
<td>34.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Contralateral hemibody bradykinesia ‘off’ medication</td>
<td>13.5 (7–16)</td>
<td>6.0 (2–12)</td>
<td>43.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Contralateral wrist rigidity ‘off’ medication</td>
<td>3.0 (2–4)</td>
<td>0.5 (0–4)</td>
<td>87.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Maximum contralateral hemibody dyskinesia</td>
<td>4.0 (0–7)</td>
<td>1.0 (0–4)</td>
<td>60.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

and Fahn, 1989) in the ‘practically defined off’ and ‘on’ medication states (e.g. ‘off’ medication means off medication for 9–12 h) (Langston et al., 1992), both pre- and 3–4 months postoperatively. We also rated the severity of contralateral dyskinesias (maximum score = 8) induced by the administration of 250 mg of dispersible levodopa according to a standardized dyskinesia rating scale (Goetz et al., 1994). The clinical details of the patients, their preoperative total motor UPDRS scores ‘off’ and ‘on’ medication, and their maximum contralateral dyskinesia scores, are detailed in Table 1. Patient drug regimens were minimally, or not at all, modified postoperatively.

As we were particularly interested in the motor performance of the patients pre- and postoperatively, UPDRS subset scores for the following categories of motor performance were assigned: total motor scores ‘off’ medication (items 18–31 of the UPDRS examination, maximum score = 108), contralateral hemibody bradykinesia score ‘off’ medication (items 23–26, maximum = 16) and contralateral wrist rigidity score (items 22, maximum = 4).

Table 2 shows the pre- and postoperative UPDRS ‘off’ medication and maximum dyskinesia subset scores. For each patient we calculated the percentage change in their postoperative score compared with their postoperative score for each category. The median of the percentage changes was then calculated for each category. Pre- and postoperative scores were compared using paired Wilcoxon sign rank tests to assess significance of the changes detected.

All subjects gave informed consent prior to pallidotomy and scanning. The PET study was approved by the Ethics Committee of the Royal Postgraduate Medical School, Hammersmith Hospital. Permission to administer radioactive H215O pre- and postoperatively was obtained from the Administration of Radioactive Substances Advisory Committee of the Department of Health, UK.

Surgery

Four patients (1–4) were referred from Spain for medial pallidotomy at Emory University, Atlanta, Georgia, USA. Two patients (5 and 6) were from the UK and underwent medial pallidotomy at the National Hospital for Neurology and Neurosurgery, London, UK. The operations were performed in a similar manner. The intended target was located in the posterior and ventral portion of the right medial pallidum. Anatomical target selection for all patients was by stereotactic CT guidance. The lesion coordinates were defined intra-operatively by recording single-cell, high frequency (>50 Hz) tonic discharges from the target area during passive movements of the contralateral limbs, and from the optic tract during photic stimulation. Electrical stimulation (300 Hz; 0.2-ms pulses; intensity 0.1–1.5 mA) of the target area was performed prior to making a permanent lesion to ensure photopsia and motor deficits were absent. If the patient experienced these phenomena on electrical stimulation of the target, the lesioning electrode was repositioned. The permanent lesions were made by thermo-coagulation (70–75°C for 60–90 s).
Five patients underwent MRI scans (1.0 Tesla Picker HPQ scanner, TR 24 ms, TE 6 ms, voxel size 1.0 × 1.0 × 1.3 mm) 3–4 months postoperatively at the Hammersmith Hospital in order to assess lesion size and location. Calculations were performed using the ‘Analyze’ image display software version 7.0 (BRU, Mayo Foundation). The characteristics of the lesion in Patient 3 were obtained from his surgical scans.

PET activation paradigm
The paradigm performed during PET consisted of moving a joystick at regular intervals, with the left hand in freely selected directions and has been described previously (Playford et al., 1992). The joystick was placed in a similar position relative to the patient during the pre- and postoperative scans in order to ensure that similar limb movements were made, and it was linked to an IBM personal computer which generated pacing tones. Depending on the patient’s degree of bradykinesia, the pacing frequency for individual patients was set prior to commencement of scanning at the fastest rate at which the patient was able to perform brisk and complete movements without omissions. For Patients 1 and 2, the pacing frequency was set to 1 tone every 3 s, for Patients 3 and 4 the pacing tone was set to 1 tone every 7 s and for Patients 5 and 6 the pacing tone was set to 1 tone every 6 s.

There were two tasks in this paradigm: ‘rest’ and ‘movement’. The order of the tasks was balanced in order to eliminate the effects of time and habituation. The baseline condition was ‘rest’. This involved the patients holding the joystick loosely with the left hand. They were instructed not to move, to ignore the pacing tones, to close their eyes and to clear their minds as much as possible. During the ‘movement’ task, they were instructed to move the joystick in one of four directions: left, right, forward or backward. They were instructed to make one joystick movement for each pacing tone and to choose a different direction of movement on each occasion. They were instructed to move the joystick as soon as possible after each tone and to avoid performing repetitive sequences of movements. Prior to PET, all subjects practised the movement task to ensure that they understood and performed it correctly. During PET, subjects were viewed on a video screen to ensure that they were performing the tasks correctly and that no unwanted head movement occurred during scanning.

Task performance
The response times for each movement were recorded by the personal computer. The response time denoted the time from the pacing tone to the registration of the completed joystick movement by the computer. We computed the mean response time for the preoperative and postoperative movement tasks during the scans and compared them by using a paired two-tailed Student’s t test.

The order of responses was also recorded in order to assess any stereotypic or perseverative movements made by the patients. If the directions of the joystick movements were chosen randomly, then all possible generated combinations of single (4), double (16), triple (64) and quadruple sequences (256) should occur with the same frequency. The frequency of the generated single, double, triple and quadruple sequences was compared with the number of potential sequences and an ‘information’ statistic calculated for each sequence of responses for each patient. The ‘information’ statistic had a value between 0 and 2; 2 indicated a fully random sequence (Frith and Done, 1983). We compared the median ‘information’ statistic for each set of responses preoperatively with the ‘information’ statistic obtained postoperatively by using Wilcoxon sign rank tests.

PET scanning
Initially, all patients underwent H215O PET activation scans 1–3 months preoperatively at the MRC Cyclotron Unit, Hammersmith Hospital, London, UK. Measurements of rCBF were performed using a CTI 953B PET camera (CTI/ Siemens, Knoxville, Tenn., USA) with the interplane septa retracted to acquire the data in 3D mode (Spinks et al., 1992). The camera enabled the acquisition of data simultaneously from 31 consecutive axial planes. Each patient’s head was placed in the scanner, supported in a vacuum-operated polystyrene support, with line markings drawn on the patient’s orbito-meatal lines and centrally on the forehead. The gantry of the scanner was tilted to lie parallel to these lines. Correct alignment of the head within the aperture was maintained by aligning these lines with two perpendicular laser lines located on the gantry on the camera. Initially, a 5-min transmission scan was obtained to ensure correct axial head positioning within the camera’s field of view (10.65 cm) and adjustments to head position could be made at this stage to ensure that the top of the head was included in the field of view. Following backprojection and filtering (Hanning filter, cut-off frequency 0.5 cycles/pixel) image resolution was 8.5 × 8.5 × 4.3 mm full-width at half-maximum. Each reconstructed image was displayed in a matrix of 128 × 128 × 31 voxel format, each voxel measuring 2.09 × 2.09 × 3.43 mm. Prior to the acquisition of the emission data, a 20-min transmission scan was recorded by exposing the camera’s three retractable rotating 68Ge/68Ga rods. This transmission scan enabled a measured correction of tissue attenuation to be performed on the emission data.

All subjects were scanned lying supine, in a darkened room. Preoperatively and postoperatively, patients were scanned after an overnight withdrawal (9–12 h) of anti-parkinsonian drugs. Since all patients were ‘off’ medication, none of them experienced dyskinesias during scanning. Twelve measurements of rCBF were recorded for Patients 1–4 preoperatively, six measurements for each task. Patient 3 moved unacceptably during the second preoperative measurement of his rCBF and so we were only able to utilize
five measurements of each task for his analysis. Patients 5 and 6 underwent four measurements of rCBF for each task preoperatively. Each measurement of rCBF was started with a background scan of 30 s. After a delay of 30 s, a preloaded bolus of 3 ml of normal saline containing 11.5 mCi of H$_2^{15}$O was flushed over a 20-s period into an antecubital vein of the patient’s right arm. Scanning commenced 30 s after the start of the infusion, ~5 s before the onset of the rise of the background counts. The patients commenced the tasks 10 s before PET to ensure that the rise in counts coincided with performance of the tasks. Peak counts were recorded at 30–40 s after the bolus was infused. Scanning was continued for 90 s to measure tracer washout. A 10-min interval was allowed between successive measurements of rCBF to allow for radioactive decay (the half-life of $^{15}$O is 2.05 min). The position of the patients’ head was checked before and after each recording.

Each patient returned to the MRC Cyclotron Unit at the Hammersmith Hospital 3–4 months postoperatively to undergo the postoperative measurements of rCBF. Each patient performed the postoperative tasks at the same pacing frequency as they had preoperatively and underwent the same number of rCBF measurements as they had preoperatively. Thus, each patient’s postoperative scan was performed in an identical manner to his/her preoperative scan.

**Image transformation**

All calculations and image transformations were performed on a Sun SPARC 5 workstation (Sun Computers Europe Inc., Surrey, UK) using Analyze version 7.0 image display software (BRU, Mayo Foundation). Data were analysed using statistical parametric mapping software (SPM 95, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc, Sherborn, Mass., USA). Initially, each patient’s preoperative rCBF images were realigned using an automated realignment program based on a six parameter rigid-body transformation using a least squares technique on a voxel-by-voxel basis (Friston et al., 1995a). This generated an aligned set of preoperative images and a mean image (each of 31 planes) for each patient. For each patient, the mean image having most anatomical detail was transformed into standard stereotactic space using linear, quadratic and non-linear 3D transformations on a slice-by-slice basis (Friston et al., 1995a). The same transformations were then applied to each of the patient’s realigned images to put all the images into the standard stereotactic space corresponding to the atlas of Talairach and Tournoux (1988). Each preoperative scan now comprised 26 planes with each voxel having dimensions of $2 \times 2 \times 4$ mm. The stereotactic normalization of each scan places homologous brain regions into standard anatomical space and therefore enables inter-subject averaging to be performed across patients. All preoperative scans were smoothed using an isotropic Gaussian kernel of 12 mm to increase the signal-to-noise ratio and to compensate for the differences in gyral anatomy between individuals.

Each patient’s postoperative scans were realigned, normalized and smoothed in an analogous manner to their preoperative scans.

**Data analysis**

The technique of statistical parametric mapping was used (Friston et al., 1995b). Global blood flow was normalized by proportional scaling across the entire data set to a mean of 50 ml/100 ml/min. The normalization process adjusted the rCBF values for each voxel to take into account variations in global activity across subjects, pre- and postoperatively. The adjusted rCBF voxel values were used for the statistical analyses.

The pattern of cerebral activation associated with joystick movements preoperatively was determined by comparing the adjusted mean rCBF value of the preoperative ‘movement’ task with the adjusted mean rCBF value of the preoperative ‘rest’ task (Comparison 1). Similarly, the activation associated with joystick movements postoperatively was determined by comparing the adjusted mean rCBF value of the postoperative ‘movement’ task with the adjusted mean rCBF value of the postoperative ‘rest’ task (Comparison 2). We were also particularly interested to investigate the effect of medial pallidotomy on movement-associated activation. For these comparisons, we conservatively considered the preoperative scans and postoperative scans as originating from two separate patient groups. We tested for postoperative relative increases (Comparison 3) and decreases (Comparison 4) in activation by comparing the postoperative movement-associated rCBF increases (i.e. postoperative ‘movement’ versus postoperative ‘rest’) with the preoperative movement-associated rCBF decreases (i.e. preoperative ‘movement’ versus preoperative ‘rest’).

All comparisons were specified by appropriately weighted categorical contrasts and performed on a voxel-by-voxel basis using an ANOVA (analysis of variance). This generated SPM($t$) maps for the activations associated with each comparison. The SPM($t$) maps were subsequently transformed into SPM($Z$) maps and the level of significance of areas of activation was assessed by the peak height of their foci using estimations based on the Theory of Random Gaussian Fields (Friston et al., 1994). Significance was accepted if voxels survived an uncorrected threshold of $P < 0.001$. In phantom experiments, this value of significance has previously been shown to be sufficiently conservative to protect against false positive results (Bailey et al., 1991).

**Results**

**Surgical lesions**

All lesions were located in the right ventral medial pallidum. Lesion size ranged from 60–150 mm$^3$ in
Fig. 1 Percentage improvement postoperatively in categories of motor performance in individual patients. Each column represents an individual patient. * = no pre- or postoperative dyskinesia.

Clinical response to pallidotomy

Motor performance for each patient improved postoperatively (Fig. 1). The group median preoperative and postoperative subset scores, percentage changes and levels of significance of the group changes are detailed in Table 2. Postoperatively, there was an overall significant 40% improvement in the contralateral UPDRS score ‘off’ medication and 60% improvement in the dyskinesia subset score when compared with the preoperative scores.

Task performance

The mean preoperative response time for joystick movements was $1.10 \pm 0.52 \text{s}$. The mean response time for postoperative joystick movements was $0.95 \pm 0.51 \text{s}$. Postoperatively, the patients’ mean response time improved by $13.8\%$ ($P = 0.08$). When we inspected the individual joystick times for each patient, we noted faster postoperative response times for five of the six patients but a longer postoperative response time for Patient 6. When we calculated mean response times using only the five patients who showed faster postoperative joystick response-times, we detected a significant improvement of $18\%$ ($P = 0.03$).

We detected no evidence of perseveration in movement selection pre- or postoperatively. The median ‘information’ statistics for single movements was $1.96$ (range $1.89–1.99$) preoperatively and $1.95$ (range $1.88–2.00$) postoperatively. There were no significant differences between the median postoperative and preoperative ‘information’ statistics for any sequence of directions.

Regional cerebral blood flow

Comparison 1 (preoperative activation): paced, freely selected joystick movements compared with rest

When mean preoperative rCBF values associated with joystick movements of the left hand were compared with mean rCBF values at rest, significant foci of activation ($P < 0.001$ uncorrected) were found in the right primary sensorimotor cortex, as well as bilaterally in the lateral premotor cortex, caudal supplementary motor area and right parietal association cortex (Brodmann area 40). These regions formed a contiguous cluster containing 2284 voxels. Foci of activation were also present in the left ventrolateral premotor area/Brodmann area 44 and left parietal association cortex (area 40). Additionally, we found significant activation subcortically in the striatum and thalamus. Neither at this threshold, nor at a more lenient threshold of $P < 0.01$ was there a focus of significant activation detected in prefrontal cortex.

Comparison 2 (postoperative activation): paced, freely selected joystick movements compared with rest

When mean postoperative rCBF values of the joystick movements of the left hand were compared with the mean rCBF values at rest, significant foci of activation ($P < 0.001$ uncorrected) were present in a pattern which was similar in distribution to the preoperative movement activation pattern. A large volume of activation was found (2710 voxels) which

volume. The locations of the centres of the lesions ranged from 16–23 mm lateral to the midline and 2–6 mm anterior to the mid-commissural point, with the most ventral points of the lesions lying 3–7 mm below the commissural plane.
Table 3 Locations and peak Z-scores of areas of activation during joystick movements

<table>
<thead>
<tr>
<th>Area of activation</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x, y, z Z-score</td>
<td>x, y, z Z-score</td>
</tr>
<tr>
<td>Right SMC</td>
<td>32, –32, 56 8.31</td>
<td>32, –20, 56 7.65</td>
</tr>
<tr>
<td>Right PMC</td>
<td>24, –4, 56 5.18</td>
<td>24, –12, 60 7.15</td>
</tr>
<tr>
<td>Left PMC</td>
<td>–22, –12, 56 6.36</td>
<td>–20, –14, 56 6.66</td>
</tr>
<tr>
<td>Right SMA</td>
<td>10, –6, 52 5.46</td>
<td>4, –2, 60 6.02</td>
</tr>
<tr>
<td>Left SMA</td>
<td>–4, –8, 60 4.58</td>
<td>–6, –6, 60 6.95</td>
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<tr>
<td>Right parietal cortex (area 40)</td>
<td>40, –34, 48 7.18</td>
<td>40, –34, 48 6.38</td>
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<tr>
<td>Left parietal cortex (area 40)</td>
<td>–46, –36, 32 7.02</td>
<td>–46, –40, 32 6.07</td>
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<td>Right SMA</td>
<td>10, 6, 52 5.46</td>
<td>4, 2, 60 4.69</td>
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<td>–4, –8, 60 4.58</td>
<td>–6, –6, 60 6.95</td>
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<td>Right parietal cortex (area 40)</td>
<td>40, –34, 48 7.18</td>
<td>40, –34, 48 6.38</td>
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<td>Left parietal cortex (area 40)</td>
<td>–46, –36, 32 7.02</td>
<td>–46, –40, 32 6.07</td>
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<td>Left ventral PMC/area 44</td>
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<td>–26, –4, 4 3.98</td>
</tr>
</tbody>
</table>

Locations given by Talairach and Tournoux coordinates. SMC = sensorimotor cortex; PMC = premotor cortex; SMA = supplementary motor area; PFC = prefrontal cortex.

contained local maxima in the right sensorimotor cortex, right parietal cortex, supplementary motor area bilaterally and lateral premotor cortex bilaterally as well as separate foci of activation in the left ventrolateral premotor area/ Brodmann area 44 and left parietal association cortex (area 40). However, a focus of significant activation comprising 10 voxels was now present in the right dorsal prefrontal cortex (P < 0.001 uncorrected).

The location and associated peak Z-scores of the foci of the activations associated with the performance of the joystick movements pre- and postoperatively are presented in Table 3. The extent of these activations is displayed in Fig. 2 as SPM{Z} maximum intensity projections maps in three orthogonal views. Reference to each view is necessary to localize an area of activation. This figure is thresholded to show all voxels which survived a threshold of P < 0.001, without a correction for multiple non-independent comparisons.

Comparison 3 (effect of pallidotomy on movement-associated activation): areas of relatively increased activation postoperatively compared with preoperatively

We tested for areas of relative increases in movement-associated activation post-pallidotomy compared with pre-pallidotomy. We detected a significantly greater increase in rCBF in the rostral supplementary motor area (P = 0.001) and in the right dorsal prefrontal cortex (P < 0.001) during postoperative joystick movements compared with preoperative joystick movements. We also found relative increases in rCBF in the right visual association area (P < 0.001) and in the left anterior insula (P < 0.01). The locations and peak Z-scores of these areas are shown in Table 4.

The extents of the areas of relatively increased activation in the rostral supplementary motor area and right dorsal prefrontal cortex were demonstrated by rendering all activated PET voxels (P < 0.01) on to orthogonal, spatially normalized T1-weighted MRI sections available within the SPM 95 software. These areas are displayed in Fig. 3A and B.

Comparison 4 (effect of pallidotomy on movement-associated activation): areas of relatively decreased activation postoperatively compared with preoperatively

We also detected a significant relative decrease in rCBF in an area which has Talairach and Tournoux coordinates of (20, –14, –8 mm), (Z-score = 3.03, P = 0.001 uncorrected). This area lies immediately ventral to the right medial globus pallidus.

We used the adjusted rCBF values of the voxels with the peak Z-scores in the supplementary motor area, dorsal prefrontal cortex, insula, visual association area and right medial globus pallidus to calculate the per cent change in rCBF at these coordinates pre- and postoperatively compared with rest. Levels of rCBF in the supplementary motor area rose by 1.2% preoperatively and by 4.4% postoperatively when joystick movements were compared with rest. In the right dorsal prefrontal cortex, there was no significant activation preoperatively but rCBF increased by 2.4% during performance of joystick movements postoperatively. We also documented a relative postoperative decrease in movement-induced rCBF change in the region of the lesioned medial globus pallidus. These results are shown in Fig. 4.
Fig. 2 SPM\{Z\} maximum intensity projection maps showing areas of activation associated with freely selected joystick movements in patients with Parkinson’s disease before (A) and after (B) medial pallidotomy. Threshold $P < 0.001$. PC = parietal cortex; SMC = sensorimotor cortex; SMA = supplementary motor area; PMC = lateral premotor cortex; BG/T = basal ganglia/thalamus; DPFC = dorsal prefrontal cortex; VAC represents anterior commissural line; VPC represents posterior commissural line; 0 represents anterior–posterior commissural plane.

Table 4 Locations and peak Z-scores of areas in which rCBF during joystick movements was significantly greater postoperatively than preoperatively

<table>
<thead>
<tr>
<th>Area of increased activation</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesial SMA</td>
<td>−4</td>
<td>0</td>
<td>52</td>
<td>3.21</td>
</tr>
<tr>
<td>R dorsolateral PFC</td>
<td>24</td>
<td>40</td>
<td>32</td>
<td>3.33</td>
</tr>
<tr>
<td>R visual association area</td>
<td>16</td>
<td>−64</td>
<td>−4</td>
<td>3.30</td>
</tr>
<tr>
<td>Left anterior insula</td>
<td>−44</td>
<td>16</td>
<td>0</td>
<td>2.89</td>
</tr>
</tbody>
</table>

Locations given by Talairach and Tournoux coordinates. R = right; SMC = supplementary motor cortex; PFC = prefrontal cortex.

Discussion

We have shown that after unilateral right pallidotomy, the contralateral bradykinesia score ‘off’ medication improved significantly by 44% in our group of patients, as measured with the UPDRS, but only by 14% (non-significantly) as reflected by the motor response-times obtained during PET scanning. This apparent difference arose because one patient (Patient 6) showed slower (10%) joystick response-times postoperatively. Additionally, UPDRS subset scores include measures of leg bradykinesia and were performed outside the scanner with the patients sitting with eyes open while the joystick response-times were measured for the performing arm only with the patients lying supine in the PET camera with eyes closed. Nonetheless, both parameters indicated that bradykinesia scores improved post-pallidotomy as compared with preoperatively. Indeed, more detailed neurophysiological analysis of arm movements in four of these patients showed a marked effect of pallidotomy on bradykinesia scores (Obeso et al., 1996). These results, along with the improvement in total motor UPDRS scores ‘off’ medication, rigidity scores and the diminution of the contralateral levodopa-induced dyskinesias, are in agreement with previous reports on the effects of medial pallidotomy on motor performance (Dogali et al., 1995; Lozano et al., 1995; Sutton et al., 1995).

Postoperatively, the improvement in motor response-times in our patients was accompanied by a significant increase in relative levels of rostral supplementary motor area and right dorsal prefrontal cortex activation. These findings add support to the hypothesis that medial globus pallidus overactivity in Parkinson’s disease patients leads to underactivity of the supplementary motor area and right dorsal prefrontal cortex during performance of volitional motor tasks.

Studies with normal volunteers and primates have implicated the rostral supplementary motor area and right dorsal prefrontal cortex in motor programming rather than execution. Previous rCBF studies have shown that the rostral supplementary motor area is relatively more activated during performance of internally generated movements than during cued movements (Roland et al., 1980; Deiber et al., 1991; Playford et al., 1992; Jahanshahi et al., 1995), while activation of the right dorsal prefrontal cortex is only detected when normal volunteers freely selected the timing (Jahanshahi et al., 1995) or the direction (Playford et al., 1992) of
Fig. 3 Areas of increased movement-associated activation post-pallidotomy compared with pre-pallidotomy in Parkinson’s disease. Activated regions (threshold $P < 0.01$) have been rendered on to a normalized $T_1$-weighted MRI scan. SMA = supplementary motor area; PFC = prefrontal cortex; R = right.

movements. Electrophysiological studies in monkeys have also shown that a subset of supplementary motor area cells respond exclusively to volitional performance of pre-learned sequences of movements but not when the movements were instructed by visual cues (Mushiake et al., 1990; Tanji and Shima, 1994). Furthermore, supplementary motor area lesions in monkeys result in impaired performance of learned sequences of movement in the absence of limb weakness.
Improvements in motor execution, but we feel that this is visually cued arm movements pre- and post-pallidotomy in relation to motor preparation, planning and selection. This suggests changes, may have prevented resolution of focal changes in our patients underwent right pallidotomy, and that perhaps disease patients. No relative increase in resting supplementary motor area; SMA = supplementary motor area; DPFC = dorsal prefrontal cortex; GPM = medial globus pallidus.

Increased activation in the dorsal prefrontal cortex postoperatively compared with preoperatively would not be a predicted finding if the functional effects of medial pallidotomy were limited to the ‘motor’ circuit. However, the trajectories of the recording and lesioning electrodes pass through dorsal pallidum to reach ventral pallidum. Additionally, the multiple lesions which ablated the dorsal to ventral extent of the sensorimotor medial globus pallidus are likely to include some of the output projections of the dorsal medial globus pallidus which form part of the ‘prefrontal’ circuit. In previous PET studies comparing movement-associated activation in Parkinson’s disease patients with that in normal volunteers, where the subjects had to choose either the direction of the movements (Playford et al., 1996) or the timing of movements (Jahanshahi et al., 1995), impaired activation in the right dorsal prefrontal cortex was found in the Parkinson’s disease group. We found a significant increase in activation of the right dorsal prefrontal cortex postoperatively compared with preoperatively. These results are in keeping with the notion that the right rather than the left prefrontal cortex has a specialist role in motor planning, possibly because of the spatial component involved. In contrast, free selection of words leads to predominantly left prefrontal cortex activation (Friston et al., 1991; Warburton et al., 1996). An alternative explanation for the lateralized dorsal prefrontal cortex result would be that all of our patients underwent right pallidotomy, and that perhaps an increase in activation in the left dorsal prefrontal cortex would be observed if a similar study were conducted on patients undergoing left pallidotomy.

Since the general health of our patients improved postoperatively, it is possible that the patients were better able to attend the task compared with preoperatively. This may have contributed to the relatively enhanced activation observed in the dorsal prefrontal cortex postoperatively. However, the pre- and postoperative scans for each of our patients were performed in an identical manner and demanded the same attentional loads. We anticipate the results of ongoing PET studies on patients undergoing high-frequency deep brain stimulation of the medial globus pallidus, in which the pre- and post-lesion data can be collected during one scanning session.

Although we found significant bilateral thalamic activation during joystick movement, both pre- and postoperatively, we were unable to detect a relative change in thalamic activation comparing the postoperative with the preoperative measurements. This may have been because the smoothing applied to the data, in order to reveal the cortical activation changes, may have prevented resolution of focal changes in the ventral thalamic signal.

Our results are in reasonable agreement with a previous PET study measuring rCBF during the performance of visually cued arm movements pre- and post-pallidotomy in patients with Parkinson’s disease (Grafton et al., 1995). Levels of postoperative supplementary motor area activation were significantly increased in this study, although there was no significant clinical improvement. No free selection of movement timing or direction was involved in this task and as a consequence, activation of the dorsal prefrontal cortex was not evident. Grafton et al. (1995) also found that right lateral premotor activation was increased along with supplementary motor area activation following pallidotomy. A reason for the different findings in Grafton’s and our studies may be that in Grafton’s study the task was performed under visual guidance while our study was performed with the eyes closed and involved internal selection of movement directions. The lateral premotor cortex is most concerned with motor responses to external stimuli and has previously been shown to have normal or raised levels of activation in Parkinson’s disease patients (Playford et al., 1992; Samuel et al., 1996).

Recently, a 18-fluorodeoxyglucose PET study has examined changes in regional patterns of covariance of resting glucose metabolism in Parkinson’s disease patients following pallidotomy (Eidelberg et al., 1996). This demonstrated significant relative increases in resting metabolism in the ipsilateral dorsal prefrontal cortex, primary motor cortex and lateral premotor cortex, and significant decreases in thalamic and lentiform nucleus resting metabolism following pallidotomy. These results add further support to the notion that basal ganglia–thalamo-cortical circuits are disinhibited by medial pallidotomy in Parkinson’s disease patients. No relative increase in resting supplementary motor area metabolism was detected. This is in contrast to...
activation studies that directly examine the functional capacity of brain regions.

In agreement with the arm-reaching PET activation study of Grafton et al. (1995), we found a relative increase in activation in the left anterior insula during joystick movements postoperatively compared with preoperatively ($P < 0.01$). We also noted a significant relative increase in activation in the right visual association cortex (Brodmann's area 19). By comparing the relative activity of the voxel with the peak $Z$-score in these regions during the four conditions in our study, we observed that these areas were, in fact, less deactivated postoperatively than preoperatively and this manifested as relative increases in rCBF postoperatively. These regions lie outside the postulated basal ganglia–thalamo-cortical circuits and we speculate that postoperatively the patients have less requirement to deactivate redundant brain regions, since they are better able to activate the areas necessary for performance of the task.

We did not compare pre- and postoperative levels of activation in Parkinson’s disease with normal volunteers, but thought it reasonable to assume that the baseline activations in the supplementary motor area and dorsal prefrontal cortex in our patients were abnormal, based on the results of a previous PET study in normal volunteers and patients with Parkinson’s disease using this same paradigm (Playford et al., 1992). We were primarily interested in the changes in activation which result from the pallidotomy, rather than the differences in activation between Parkinson’s disease and normal volunteers. A study of this type would, however, be valuable in determining whether pallidotomy can restore rCBF in the supplementary motor area and dorsal prefrontal cortex activation to normal levels.

While alleviation of inhibition of ‘motor’ and ‘prefrontal’ circuits by medial pallidotomy may explain the improvement of bradykinesia scores in Parkinson’s disease, it does not clearly explain the marked effect of pallidotomy in diminishing levodopa-induced dyskinesias. In fact, one would predict from current models of basal ganglia connectivity that medial pallidotomy, by releasing cortical and thalamic metabolic activity, might increase the propensity for involuntary movements. We have shown that the significant increases in activation post-pallidotomy occur in cortical association areas thought to be more involved with the planning and preparation of movements. This would enable the patient to have more, rather than less, control over their movements. The diminution of involuntary movements may, therefore, reflect a state of improved motor control postoperatively. However, the PET changes were measured ‘off’ medication during activation while involuntary movements occur ‘on’ medication mainly at rest. Since our patients’ dyskinesia was marked preoperatively, it was practically impossible to record PET data during episodes of dyskinesia and so we cannot compare the dyskinetic and non-dyskinetic states. The current study has, therefore, addressed only one aspect of the adaptation of the basal ganglia–thalamo-cortical circuits which occurs post-pallidotomy. The effects of pallidotomy on other dysfunctional nuclei (such as the lateral globus pallidus, the deafferented striatum and the substantia nigra pars reticularis) have yet to be addressed in order to disentangle the beneficial effects of pallidotomy on bradykinesia from those on dyskinesia.

In conclusion, our study has revealed significant increases in supplementary motor area and right dorsal prefrontal cortex activation in Parkinson’s disease after unilateral pallidotomy, associated with improved response times during performance of arm movements in freely selected directions. No accompanying increase in primary motor cortex or lateral prefrontal cortex activation was seen. This supports the concept that pallidotomy improves function in Parkinson’s disease by increasing activity in cortical areas that are principally involved in motor planning and that receive projections from the basal ganglia.

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