Evidence for lateral premotor and parietal overactivity in Parkinson’s disease during sequential and bimanual movements

A PET study


Summary

Patients with Parkinson’s disease have great difficulty in performing sequential and bimanual movements. We used $H_2^{15}$O PET to study the regional cerebral blood flow associated with performance of sequential finger movements made unimanually and bimanually in a group of Parkinson’s disease patients and a group of control volunteers. In controls, sequential finger movements led to activation of the contralateral motor cortex and inferior parietal cortex (Brodmann area 40), the lateral premotor cortex and bilateral supplementary motor area. No prefrontal activation was seen.

Keywords: premotor; parietal; Parkinson’s disease; PET

Abbreviations: ANCOVA = analysis of covariance; BA = Brodmann area; MRP = movement related potential; rCBF = regional cerebral blood flow; SPM = statistical parametric mapping

Introduction

Idiopathic Parkinson’s disease is characterized by bradykinesia, tremor and rigidity. Repetitive, sequential and bimanual movements are especially difficult for Parkinson’s disease patients, particularly when volitional (Benecke et al., 1986; Benecke et al., 1987; Fleminger, 1992; Georgiou et al., 1994). Parkinson’s disease patients may compensate for some of their motor deficits by the use of sensory guidance (Martin, 1967; Brown and Marsden, 1988; Dietz et al., 1990; Georgiou et al., 1994). The parkinsonian brain may, therefore, be capable of reorganization, in order to facilitate performance of volitional movements.

In Parkinson’s disease there is degeneration of the dopaminergic nigrostriatal pathway. The deafferentiated striatal output is relayed to the cortex via the internal segment of the globus pallidus and the ventral anterior, ventral lateral and centromedian nuclei of the thalamus. The thalamic nuclei are postulated to influence specific cortical areas via segregated, parallel loops which project to the dorsolateral prefrontal cortex, supplementary motor area, the anterior cingulate gyrus, the orbitofrontal cortex and the frontal eye fields (Alexander et al., 1990). Disruption of nigrostriatal function is manifested as increased firing of the globus pallidus pars interna (Hutchinson et al., 1994; Sterio et al., 1994). Current models of brain connectivity suggest that this
results in excessive inhibition of thalamic and frontal function. Previous electrophysiological (Dick et al., 1989) and regional cerebral blood flow (rCBF) studies (Playford et al., 1992; Jahanshani et al., 1995) have shown that single ballistic movements in Parkinson’s disease are associated with significantly impaired activation of mesial frontal and dorsal prefrontal association areas but not of lateral premotor cortex or primary motor cortex.

Microelectrode recording studies of supplementary motor area in monkeys (Mushiake et al., 1990; Tanji and Shima, 1994) have demonstrated that a proportion of supplementary motor area cells increase their activity specifically in relation to internally generated learned patterns of sequential movements, whereas microelectrode recording of cells in the lateral premotor cortex of the monkey (Godschalk et al., 1981; Halsband et al., 1994) reveal that approximately half of the premotor cortex neurons increase their activity preferentially or exclusively in relation to movements which are guided by visual cues. These data, along with lesion studies of monkey mesial frontal cortex (Brinkman, 1984; Chen et al., 1995) and lateral premotor cortex (Petrides, 1982; Passingham, 1985) suggest that the supplementary motor area is involved more with generation of volitional movement, particularly sequential patterns, whereas the lateral premotor cortex is involved more with externally guided movements (Roland, 1984; Passingham, 1988).

The lateral premotor cortex receives input from the deep cerebellar nuclei (Schell and Strick, 1984) and the inferior and superior parietal association areas, which in turn project back to the cerebellum via the pontine nuclei (Schmahmann and Pandya, 1989). While the parietal association cortex has reciprocal connections with the supplementary motor area, premotor cortex and prefrontal cortex (Pandya and Yeterian, 1985), it receives no input from the basal ganglia. It is, therefore, reasonable that parietal and lateral premotor function is preserved in Parkinson’s disease, as has previously been demonstrated in Parkinson’s disease patients performing paced joystick movements in freely-selected directions (Playford et al., 1992). Recently, ipsilateral cerebellar overactivity during performance of finger opposition movements has been reported in Parkinson’s disease patients compared with control volunteers using $^{133}$Xe-SPECT (single photon emission computed tomography) to measure rCBF (Sabatini et al., 1996). As the cerebellum is connected with parietal and lateral premotor cortex, overactivity of this circuit may, therefore, provide an adaptive mechanism by which Parkinson’s disease patients can use sensory guidance to help overcome the impairment of their movement which arises from the dysfunctional basal ganglia-mesial frontal projections.

We tested this hypothesis by using $^{15}$O PET to measure rCBF of brain regions in patients with Parkinson’s disease and normal volunteers during performance of dominant unimanual and bimanual automatic sequential finger movements. A previous study from our unit involving ballistic joystick movements demonstrated impaired activation of the mesial frontal cortex and prefrontal cortex in Parkinson’s disease patients (Playford et al., 1992) but failed to detect significant lateral premotor-parietal overactivity (Playford, 1993). Our new tasks were predicted to require greater cortical activation because of their sequential and bimanual nature. We predicted that both tasks would be associated with activation of the motor cortex, mesial frontal cortex, lateral premotor cortex and parietal cortex. Additionally, we postulated that our tasks, requiring greater finger spatial orientation than single ballistic movements, would be more likely to lead to a switch to the use of lateral premotor cortex and parietal circuits in Parkinson’s disease patients. We, therefore, tested for relative increases in the lateral premotor cortex and parietal cortex in the Parkinson’s disease patients compared with a control group, along with the predicted impairment of mesial frontal and striatal activation.

**Material and methods**

**Subjects**

Six right-handed patients with Parkinson’s disease were studied (four males and two females; mean age ± SD, 70.2 ± 4.6 years; range, 65–78 years). Handedness was determined by simple enquiry. The patients fulfilled the UK Parkinson’s Disease Brain Bank criteria for idiopathic Parkinson’s disease (Gibb and Lees, 1988). All had experienced the original onset of their symptoms on the right and the right hand was still worse affected. Five were l-dopa responsive and were studied after overnight withdrawal of medication. Patient 2 was not taking medication at the time of the study, but was commenced on Sinemet CR 1 month after his scan with an excellent response. Prior to scanning, patients were assessed in the ‘OFF’ state, off medication, and normal volunteers during performance of dominant unimanual and bimanual automatic sequential finger movements, whereas microelectrode recording of cells in the lateral premotor cortex of the monkey (Godschalk et al., 1981; Halsband et al., 1994) reveal that approximately half of the premotor cortex neurons increase their activity preferentially or exclusively in relation to movements which are guided by visual cues. These data, along with lesion studies of monkey mesial frontal cortex (Brinkman, 1984; Chen et al., 1995) and lateral premotor cortex (Petrides, 1982; Passingham, 1985) suggest that the supplementary motor area is involved more with generation of volitional movement, particularly sequential patterns, whereas the lateral premotor cortex is involved more with externally guided movements (Roland, 1984; Passingham, 1988).

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Each keypad had four keys, one key allocated for each finger. The keypads were linked to an Amiga 2000 computer which generated one pacing tone every 3 s. There were three tasks, each one repeated three times. The tasks were performed in random order in order to avoid the effects of habituation. Each subject, therefore, underwent nine measurements of rCBF. The baseline condition was ‘rest’. This involved the subjects resting the fingers of both hands on the buttons allocated to each finger on each pad. They were instructed not to move, to ignore the pacing tones, to close their eyes, and clear their minds as much as possible. During the right (dominant) finger-sequencing task, they were instructed to press and release the keys using the right hand only, while they rested the fingers of the left hand on the appropriate keys. For each pacing tone, they made one finger press in the order of index, middle, ring and little fingers, and continued in that sequence for the duration of that scan. During the bimanual finger-sequencing task, they were asked to make finger presses with the two corresponding fingers of both hands simultaneously. Thus, they performed externally paced simultaneous, bimanual, symmetrical, sequential finger movements.

During the finger-sequencing tasks, subjects were instructed to only make movements in the specified order of index, middle, ring and little finger. If they made an error they were instructed to start the sequence again from the index finger. Prior to the scans, all subjects practised the sequential finger movements until they were able to perform the movements automatically.

**Task performance**

The response times of each individual finger press were recorded by the Amiga 2000 computer which generated the pacing tones. The response time denoted the time from the pacing tone and the registration of the finger press by the computer. For each subject, the Amiga computer recorded response times for right-hand right finger movements during both unimanual and bimanual sequencing.

We compared the mean response times for movements of right fingers during unimanual and bimanual sequencing within groups, and unimanual and bimanual mean response times between groups. Significant differences in performance were tested within and between groups using a paired Student’s $t$ test. Individual response times of each of the Parkinson’s disease patients for each task were compared with the mean control response times by an unpaired Student’s $t$ test.

The order of responses was also recorded in order to assess the number of errors in the sequences which were made. The number of recorded errors made during the performance of each sequence was converted to a percentage score of the total number of responses made for that sequence. The median percentage error was then calculated for each task, and within- and between-group comparisons were made using paired Wilcoxon sign rank tests. Individual patients’ error scores were compared with the median control error score for each task by an unpaired Wilcoxon sign rank test.

**PET scanning**

Measurements of rCBF were performed using a CTI 953B PET camera (CTI/Siemens, Knoxville, Tenn., USA). The interplane septa were retracted to acquire data in 3D mode (Spinks et al., 1992). The camera had a field of view was 10.65 cm and acquired data simultaneously from 31 consecutive axial planes. As we were interested in the supplementary motor area, we were unable to include the entire cerebellum in this study. Following back-projection and filtering (Hanning filter, cut-off frequency 0.5 cycles per pixel) image resolution was $8.5 \times 8.5 \times 4.3$ mm full-width at half-maximum. Each reconstructed image was displayed in a matrix of $128 \times 128 \times 31$ voxel format, each voxel measuring $2.09 \times 2.09 \times 3.43$ mm.

The subject’s head was placed in the scanner supported in a vacuum-operated polystyrene support, with line markings drawn on the subject’s orbito-meatal lines and centrally on the forehead. 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. The gantry of the scanner was tilted to lie parallel to these lines. Initially, a 5-min transmission scan was obtained to

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**Table 1 Clinical details of Parkinson’s disease patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>UPDRS motor score ‘OFF’ medication</th>
<th>Hoehn and Yahr</th>
<th>Folstein’s mental score (/30)</th>
<th>Dose of l-dopa (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M)</td>
<td>70</td>
<td>3</td>
<td>21</td>
<td>III</td>
<td>29</td>
<td>600</td>
</tr>
<tr>
<td>2 (M)</td>
<td>66</td>
<td>1</td>
<td>22</td>
<td>II.5</td>
<td>30</td>
<td>None</td>
</tr>
<tr>
<td>3 (F)</td>
<td>65</td>
<td>4</td>
<td>9</td>
<td>II</td>
<td>27</td>
<td>200*</td>
</tr>
<tr>
<td>4 (M)</td>
<td>71</td>
<td>2</td>
<td>12</td>
<td>II</td>
<td>28</td>
<td>300†</td>
</tr>
<tr>
<td>5 (M)</td>
<td>71</td>
<td>4</td>
<td>36</td>
<td>II.5</td>
<td>28</td>
<td>300†</td>
</tr>
<tr>
<td>6 (F)</td>
<td>78</td>
<td>2</td>
<td>6</td>
<td>I</td>
<td>30</td>
<td>150</td>
</tr>
</tbody>
</table>

Mean ± SD: 70.2 ± 4.6, 2.3 ± 1.0, 17.7 ± 11.0, 2.1 ± 0.6, 28.7 ± 1.2

None = not taking anti-parkinsonian medication at time of study; UPDRS = Unified Parkinson’s Disease Rating Scale. *Plus pergolide 1050 mg/day. †Plus deprenyl 10 mg/day.
ensure correct axial head positioning within the camera’s field of view, and adjustments to head position could be made at this stage. Prior to the acquisition of the emission data, a 20-min transmission scan was recorded. This transmission scan enabled a measured correction of tissue attenuation to be performed on the emission data. Both transmission scans were recorded by exposing the camera’s three retractable rotating $^{68}$Ge/$^{68}$Ga rods.

All subjects were scanned lying supine, in a darkened room. Each measurement was started with a background scan of 30 s. After a further 30 s a preloaded bolus of 11.5 mCi of $^{15}$O in 3 ml of normal saline was automatically flushed over 20 s into the subject’s antecubital vein. Scanning commenced ~25 s after the start of the infusion, 5 s before the onset of rise of the background head counts. The subjects commenced the tasks 10 s before scanning commenced. Scanning was maintained for 90 s after the slow bolus was infused to measure peak head counts (at 30–40 s) and 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 subject’s head was checked before and after each recording and minor adjustments to head position were made between PET measurements. All patients were viewed on a video screen while performing the task during scanning to ensure that no unwanted additional movements occurred.

**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 (SPM) software (SPM 95; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, Mass., USA). Initially, the nine scans of each individual were realigned to his/her first scan on a voxel-by-voxel basis using an automated realignment program based on a six-parameter rigid-body transformations using a least squares technique (Friston et al., 1995a). This generated nine aligned scans, their mean scan (each of 31 axial planes) and values for the magnitude of head displacement which occurred between PET measurements for each subject (translation in laterality, anterior–posterior direction, superior–inferior directions and rotations in pitch, yaw and roll). Inspection of the parameters of movement revealed that the maximum displacement for any subject was 5 mm in translation and 3° of rotation. There was no evidence of systemic head movement across subjects.

The mean scan, having the most anatomical detail, was then transformed into standard stereotactic space, using a 12 parameter linear transformation, as well as a six-parameter quadratic deformation and a non-linear 3D deformation on a slice-by-slice basis (Friston et al., 1995a). The same transformations were then applied to each of the realigned scans to put all the subject’s scans into the standard stereotactic space, to allow inter-subject averaging. The stereotactically normalized scans contain 26 planes, with a voxel size of 2 $\times$ 2 $\times$ 4 mm, corresponding to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). Smoothing was performed on all scans using an isotropic Gaussian kernel of 12 mm to increase the signal-to-noise ratio and to allow for the differences in gyral anatomy between individuals. The final resolution of the PET data was 17 $\times$ 17 $\times$ 20 mm.

**Data analysis**

The technique of SPM was used (Friston et al., 1995b). The effect of variance due to global blood flow was removed by using a voxel-by-voxel analysis of covariance (ANCOVA) with global flow as the confounding variable (Friston et al., 1990). Global blood flow was normalized to 50 ml/100 ml/min. This generated normalized mean rCBF values on a voxel-by-voxel basis for each task in this experiment. Significant changes in rCBF in different brain region associated with performance of each of the movement tasks were identified by comparing the task-specific levels of adjusted mean rCBF with the rest level on a voxel-by-voxel basis with $t$ statistics. All comparisons were specified by the use of appropriately weighted categorical contrasts. These analyses generated (SPM($t$)) maps which were subsequently transformed to SPM($Z$) maps (Friston et al., 1995b). The exact level of significance of volumes of activation was characterized by peak amplitude (Friston et al., 1995b). Clusters of voxels which had a peak Z-score of $>3.09$ (threshold $P < 0.001$) were considered to show significant activation while a peak Z-score of $>2.33$ (threshold $P < 0.01$) was considered to be a trend towards activation.

**Within-group comparisons**

The pattern of cerebral activation associated with performance of unimanual and bimanual tasks compared with rest was determined for the normal and the Parkinson’s disease groups. The local maxima and peak Z-scores of areas of significant increase in rCBF were identified and are detailed in Table 4. Results are also displayed as SPM($Z$) maximum intensity projection maps in three orthogonal planes. In order to identify the position of each voxel, reference to each of the three projections is necessary.

**Between-group comparisons**

In order to test for relative differences in the pattern of resting rCBF between controls and patients, we used the three resting scans from each subject to generate an average resting image for that subject. We subsequently compared the six averaged resting scans of the patients with the six averaged resting scans of the controls and significant differences were accepted at a threshold of $P < 0.001$.

Based on previous work, we predicted that the supplementary motor area/anterior cingulate and striatal activation
would be impaired in Parkinson’s disease during performance of unimanual sequential and bimanual sequential finger movements. We also hypothesized that relative increases in levels of lateral premotor cortex and parietal cortex activation would be present in the Parkinson’s disease group during performance of these tasks. Activation differences at these sites were considered significant at $P < 0.001$ whereas differences at $P < 0.01$ were considered to represent trends. The locations and peak Z-scores of volumes showing relative under and overactivity in the Parkinson’s disease group compared with controls were identified. The locations of activated volumes were displayed by rendering them on to axial sections of a spatially normalized high-resolution T$_1$-weighted MRI brain scan, provided by the SPM95 software. For display purposes only, a threshold of $P < 0.01$ was used.

The between-group comparisons demonstrated the locations of relative activation differences between the Parkinson’s disease and control groups. We subsequently used the ANCOVA-adjusted rCBF values to interrogate the direction, magnitude and significance of the activation changes associated with task performance compared with rest at these locations for the Parkinson’s disease and control groups separately.

**Results**

**Task performance: response times**

Mean response times for finger movements of the right hand by the control and Parkinson’s disease groups during performance of the unilateral and bimanual tasks are shown in Table 2. The control group performed the bimanual task more slowly (9.2%) than the unimanual task ($P = 0.04$). The Parkinson’s disease group also performed the bimanual task more slowly (14.0%) than the unimanual task but this impairment did not reach statistical significance ($P = 0.30$).

Sequential unimanual movements were performed 6.7% slower and bimanual movements 11.4% slower by the Parkinson’s disease group compared with the control group. These differences, however, did not reach statistical significance (control unimanual versus Parkinson’s disease unimanual $P = 0.54$, control bimanual versus Parkinson’s disease bimanual $P = 0.53$).

When the response times for individual Parkinson’s disease patients were compared with the mean control response times for both tasks, only Patient 1 showed a significant prolongation in response times for both tasks (unimanual $P = 0.003$, bimanual $P = 0.001$). A marginally significant prolongation was found for Patient 4 during unimanual sequential finger movements ($P = 0.059$).

**Task performance: errors**

Error data are presented in Table 3. Subjects made 90–99 individual finger presses during each task. The median error rate for the control group was 0% for both tasks. In contrast, the median error rate for the Parkinson’s disease group was 5.7% during performance of unimanual sequential finger movements and 7.8% during performance of bimanual sequential finger movements. Between-group differences for unimanual and bimanual sequential finger movements did not reach statistical significance (control unimanual versus Parkinson’s disease unimanual $P = 0.32$, control bimanual versus Parkinson’s disease bimanual $P = 0.32$) due to the wide variance in the Parkinson’s disease group. Parkinson’s disease Patients 1, 2 and 5 made numerous errors, whereas Patients 3, 4 and 6 were able to perform the tasks almost error-free. When the percentage error scores of each Parkinson’s disease patient when performing the unimanual and bimanual task were compared with the median percentage error scores of the control group, significantly increased error levels were observed for Patients 1, 2 and 5 ($P < 0.05$ for each patient unimanually and bimanually).

The Parkinson’s disease patients made 1.4 times as many errors during bimanual finger sequencing compared with unimanual finger sequencing, but this difference did not reach statistical significance ($P = 0.38$).

**rCBF: within-group comparisons**

**Control subjects**

When unimanual sequential right finger movements were compared with rest, in control subjects, significant activation was seen in the contralateral primary sensorimotor cortex (SMC) and bilaterally in the supplementary motor area as well as in contralateral inferolateral parietal association cortex [Brodmann area (BA) 40] and right lateral premotor cortex. Significant activation was also present in the region of the contralateral putamen, thalamus and insula. A trend towards

### Table 2 Response times recorded from the right hand during unimanual and bimanual tasks

<table>
<thead>
<tr>
<th></th>
<th>Unimanual</th>
<th>Bimanual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls ($n = 6$)</td>
<td>$0.401 \pm 0.069$</td>
<td>$0.438 \pm 0.084$</td>
</tr>
<tr>
<td>PD group ($n = 6$)</td>
<td>$0.428 \pm 0.081$</td>
<td>$0.488 \pm 0.195$</td>
</tr>
</tbody>
</table>

PD = Parkinson’s disease.

### Table 3 Percentage errors from the right hand during unimanual and bimanual tasks

<table>
<thead>
<tr>
<th></th>
<th>Unimanual</th>
<th>Bimanual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls ($n = 6$)</td>
<td>0.0 (0–5.21)</td>
<td>0.0 (0–7.81)</td>
</tr>
<tr>
<td>PD group ($n = 6$)</td>
<td>5.73 (0–29.2)</td>
<td>7.81 (0–37.5)</td>
</tr>
</tbody>
</table>

PD = Parkinson’s disease.
activation was found in the left lateral premotor cortex ($P < 0.01$).

During bimanual sequential finger movements, significant activation was present bilaterally in the SMC, supplementary motor area, lateral premotor cortex and inferior parietal cortex (BA 40) as well as in right parietal BA 7 and left insula. Significant sub-cortical activation was also present in the region of the putamen bilaterally and left thalamus.

The location of activity, in control subjects, associated with these two tasks and peak Z-scores at their foci are detailed in Table 4 and shown as SPM{$Z$} projection maps ($P < 0.001$) in Fig. 1A and B.

### Parkinson’s disease

Comparing unimanual sequential finger movements with rest, significant activation was seen in the contralateral primary sensorimotor cortex (SMC), as well as bilaterally in the supplementary motor area, lateral premotor cortex and inferolateral parietal association cortex (BA 40). Significant activation was also present contralaterally in parietal BA 7, contralateral putamen and the right insula.

During bimanual finger-sequencing movements, significant activation was present bilaterally in the SMC, supplementary motor area, lateral premotor cortex, inferior parietal association cortex (BA 40) and parietal BA 7. Trends towards activation were present bilaterally in the putamen ($P < 0.01$).

The location of activation associated with these two tasks and peak Z-scores at their foci are detailed in Table 4. The extent of the significant activation ($P < 0.001$) is shown as SPM{$Z$} projection maps in Fig. 1C and D.

### rCBF: between-group comparisons

**Differences in resting rCBF between controls and patients**

There were no significant differences (increases or decreases) in resting rCBF in the inferior parietal cortex, lateral premotor cortex, mesial frontal or prefrontal cortex in the Parkinson’s disease group compared with the controls. We detected a significant ($P < 0.001$) decrease in resting rCBF in patients in a small volume (25 voxels) of the left superior parietal cortex (coordinates $-34$, $-62$, $44$, BA 7) compared with controls.

**Relative increases in activation in the patients compared with controls**

We tested for relative increases in activation of the lateral premotor cortex and parietal cortex in the Parkinson’s disease patients compared with controls. These results are detailed in Table 5. At a threshold of $P < 0.001$, unimanual sequential finger movements resulted in relative overactivity of lateral premotor cortex and inferior parietal cortex (BA 40) bilaterally. Bimanual sequential finger movements resulted in relative overactivity bilaterally of lateral premotor cortex and in left inferior parietal cortex (BA 40). A trend towards relative overactivity was found in right inferior parietal cortex (BA 40). Figure 2A shows the location of volumes of relatively increased activation in the patient group rendered on to slices of a normalized $T_1$-weighted MRI scan.

At the locations of relative overactivity in the Parkinson’s disease group identified by the between-group comparison, we calculated the percentage change in activity compared...
Fig. 1 SPM[Z] sagittal, coronal and transverse maximum intensity projection maps showing areas of significant increase in rCBF compared with rest for (A) controls during right sequential finger movements, (B) controls during bimanual sequential finger movements, (C) Parkinson’s disease (PD) patients during right sequential finger movements and (D) Parkinson’s disease patients during bimanual sequential finger movements. SMC = sensorimotor cortex; PMC = lateral premotor cortex; SMA = supplementary motor area; PC = parietal cortex. Threshold for significance: \( P < 0.001 \).

Table 5 Between-group analyses: location of differences in activation in patients and controls during unimanual (right hand) and bimanual sequential finger movements

<table>
<thead>
<tr>
<th>Region</th>
<th>Unimanual task</th>
<th>Bimanual task</th>
<th>x,  y,  z</th>
<th>Z-score</th>
<th>x,  y,  z</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative overactivity in Parkinson’s disease compared with controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lateral premotor cortex</td>
<td>(-32, -2, 52)</td>
<td>(-34, -4, 52)</td>
<td>4.48</td>
<td></td>
<td></td>
<td>3.93</td>
</tr>
<tr>
<td>Right lateral premotor cortex</td>
<td>(38, -6, 48)</td>
<td>(34, -4, 52)</td>
<td>3.54</td>
<td></td>
<td></td>
<td>3.75</td>
</tr>
<tr>
<td>Left parietal (BA 40)</td>
<td>(-54, -24, 28)</td>
<td>(-54, -18, 32)</td>
<td>4.48</td>
<td></td>
<td></td>
<td>3.83</td>
</tr>
<tr>
<td>Right parietal (BA 40)</td>
<td>(58, -30, 28)</td>
<td>(58, -22, 28)</td>
<td>3.80</td>
<td></td>
<td></td>
<td>2.61</td>
</tr>
<tr>
<td>Relative underactivity in Parkinson’s disease compared with controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left mesial frontal cortex</td>
<td>(-2, 34, 32)</td>
<td>(-8, -2, 44)</td>
<td>2.96</td>
<td></td>
<td></td>
<td>3.28</td>
</tr>
<tr>
<td>Right mesial frontal cortex</td>
<td>(6, 10, 48)</td>
<td>(8, 30, 50)</td>
<td>2.71</td>
<td></td>
<td></td>
<td>2.33</td>
</tr>
<tr>
<td>Left prefrontal (BA 10)</td>
<td>(-18, 44, 8)</td>
<td>(-30, 50, 8)</td>
<td>3.39</td>
<td></td>
<td></td>
<td>3.15</td>
</tr>
<tr>
<td>Right prefrontal (BA 10)</td>
<td>(32, 46, 0)</td>
<td>(34, 52, 4)</td>
<td>3.39</td>
<td></td>
<td></td>
<td>2.63</td>
</tr>
<tr>
<td>Left prefrontal (BA 45/46)</td>
<td>(-42, 24, 4)</td>
<td>(-42, 24, 4)</td>
<td>4.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right prefrontal (BA 10/46)</td>
<td>(30, 44, 16)</td>
<td>(30, 44, 16)</td>
<td>2.63</td>
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Fig. 2 Areas of (A) relative overactivity and (B) relative underactivity in Parkinson’s disease (PD) compared with controls during right and bimanual sequential finger movements, superimposed onto a stereotaxically normalized MRI brain scan. $z = \text{location of area of activation above commissural plane. A threshold of } P < 0.01 \text{ has been used for display purposes.}
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cortex and striatum in the Parkinson's disease group compared with the controls during performance of sequential finger movements. At a threshold of \( P < 0.01 \), we observed a trend towards relative underactivity of the supplementary motor area/anterior cingulate gyrus in the Parkinson's disease group compared with the controls. We also detected relative underactivity of the prefrontal cortex bilaterally in the Parkinson's disease group compared with the control group but there was no significant difference in striatal activation. The locations and peak Z-scores of volumes of relative underactivity in the Parkinson’s disease patients during the two tasks are detailed in Table 5 and the locations were also displayed by rendering the activation-induced rCBF changes on to transaxial sections of a normalized structural T1-weighted MRI scan in Fig. 2B.

Fig. 3 Percentage changes in rCBF compared with rest during (A) unimanual and (B) bimanual sequential finger movements at sites of differential activity identified by the between-group comparisons. Open columns = controls; filled columns = Parkinson’s disease patients; PMC = lateral premotor cortex; IPC = inferior parietal cortex; SMA = supplementary motor area; PFC = prefrontal cortex. \( * P < 0.001 \).

with rest and interrogated the magnitude, direction and significance of the rCBF changes at each location for each task for the control and Parkinson's disease groups separately. These results are shown in Fig. 3A. At the sites of relative overactivity in Parkinson’s disease during performance of unimanual movements, left and right lateral premotor cortex in controls showed no significant changes in rCBF from resting levels, whereas left and right lateral premotor cortex showed significant 3.6% and 2.6% rCBF increases, respectively in the Parkinson’s disease group. Similarly at the sites of inferior parietal cortex where rCBF was relatively overactive in the Parkinson’s disease group during unimanual movements, the control group showed no significant changes in rCBF from resting levels but we detected a significant 6.1% increase in rCBF at the left inferior parietal cortex and a significant 5.1% increase in rCBF at the right inferior parietal cortex in the Parkinson’s disease group.

Interrogation of the ANCOVA-adjusted rCBF values at the local maxima of the lateral premotor and inferior parietal regions which showed relative overactivity in the Parkinson’s disease group during performance of the bimanual task revealed very similar results to those found during performance of the unimanual task by both groups. These results are presented in Fig. 3B.

**Relative impairment in the patient group compared with controls**

This comparison was based on the *a priori* hypothesis that there would be relative underactivity of the mesial frontal cortex and striatum in the Parkinson’s disease group compared with the controls during performance of sequential finger movements. At a threshold of \( P < 0.01 \), we observed a trend towards relative underactivity of the supplementary motor area/anterior cingulate gyrus in the Parkinson’s disease group compared with the controls. We also detected relative underactivity of the prefrontal cortex bilaterally in the Parkinson’s disease group compared with the control group but there was no significant difference in striatal activation. The locations and peak Z-scores of volumes of relative underactivity in the Parkinson’s disease patients during the two tasks are detailed in Table 5 and the locations were also displayed by rendering the activation-induced rCBF changes on to transaxial sections of a normalized structural T1-weighted MRI scan in Fig. 2B.

Analysis of the ANCOVA-adjusted rCBF values at the local maxima, identified in the mesial frontal cortex by the between-group comparison during performance of the unimanual task, confirmed that significant activation of supplementary motor area/anterior cingulate gyrus occurred in the control group but not in the Parkinson’s disease group. Relative underactivity of the ventral prefrontal cortex in the Parkinson’s disease group was also present during performance of unimanual sequential finger movements. The left ventral prefrontal cortex showed no significant change in rCBF compared with rest at this site in the control group whereas levels of rCBF fell significantly, by 2.8%, in the Parkinson's disease group. The right ventral prefrontal cortex showed a similar pattern of rCBF change to the left ventral prefrontal cortex. These results are shown in Fig. 3A.

Analysis of the ANCOVA-adjusted rCBF values at the local maxima of the mesial frontal and ventral prefrontal regions, which were relatively underactive in the Parkinson’s disease group during performance of the bimanual task, revealed similar findings to the unimanual task. These results are presented in Fig. 3B.

**Discussion**

**Sequential unimanual and bimanual movement in Parkinson's disease**

In our study, whereas the Parkinson’s disease patients were 6.7–11.4% slower to respond to the cues than the control volunteers and made more errors, there were no significant differences in the mean motor response times or the percentage error scores between the two groups. The range of response times and error scores was, however, large in the Parkinson’s disease group and inspection showed that, whereas three patients were able to perform the task efficiently, the other three patients showed significant impairment. Sequential or bimanual tasks are more difficult than unimanual ballistic movements for Parkinson’s disease patients and so we selected patients with mild to moderate parkinsonism who were capable of performing the required number of movements. This may explain our failure to
demonstrate significant differences in response times between the Parkinson’s disease and control groups. Our PET findings, however, confirmed that activation of the mesial frontal cortex is impaired in patients with Parkinson’s disease during performance of sequential finger movements, and a novel finding was that this impairment occurs in association with relative overactivity of the lateral premotor and inferior parietal cortices.

Previous studies in which rCBF was measured in normal subjects (Roland et al., 1980a; Jenkins et al., 1994) have shown the supplementary motor area to be significantly activated during performance of sequential finger movements. Evidence for selective supplementary motor area activation during performance of internally generated sequential movements has been demonstrated by microelectrode recording of supplementary motor area cells in monkeys. Mushiake et al. (1990) found that 49% of supplementary motor area cells were specifically or preferentially more active when the monkeys performed sequential arm movements which were remembered rather than guided by visual cues. Tanji and Shima (1994) have shown that a proportion of supplementary motor cortex cells increase their activity only in relation to a specific order of remembered sequential movements, and lesion studies of the supplementary motor area in monkeys (Brinkman, 1984; Chen et al., 1995) have shown that the animals are rendered impaired during performance of internally generated sequential movements but much less impaired during performance of externally cued movements. These results support the notion that the supplementary motor area is crucially involved with internal generation of movements, particularly when sequential patterns are involved.

We found that sequential unimanual and bimanual movements were associated with significant bilateral increases in mesial frontal cortex activation in both the control and Parkinson’s disease groups, but we also found trends towards relative impairment of supplementary motor area/anterior cingulate gyrus activity in Parkinson’s disease during the performance of both tasks. The fact that both tasks required high levels of mesial frontal cortex activation for successful performance may have, in part, masked the detection of relative mesial frontal impairment in Parkinson’s disease which was only evident at \( P < 0.01 \). Our results are, however, in general agreement with previous PET data from our group (Playford et al., 1992; Jahanshani et al., 1995) which have showed significantly reduced supplementary motor area activation in Parkinson’s disease compared with controls during the performance of volitional single ballistic joystick and finger movements. In further support of this concept, studies measuring movement related potentials (MRP) during movements in Parkinson’s disease have consistently shown that the early phase of the MRP measured at the vertex (thought to originate from the mesial frontal cortex bilaterally) is reduced in amplitude compared with controls (Cunningham et al., 1995; Jahanshani et al., 1995). Furthermore, the difference in the early phase of the MRP between Parkinson’s disease patients and normal subjects is most significant when subjects perform internally generated (uncued) movements, rather than externally paced movements. Relative impairment of rCBF in the mesial frontal cortex of the Parkinson’s disease patients in Jahanshani’s study (Jahanshani et al., 1995) supports the view that mesial frontal cortex underactivity contributes to the reduced early phase of the MRP and to the impairment of internally generated movements in Parkinson’s disease patients. This notion is also supported by the observation that patients with mesial frontal area lesions show similar difficulties to Parkinson’s disease patients during performance of sequential movements (Laplane et al., 1977; Dick et al., 1986).

The fact that Parkinson’s disease patients may be able to perform a given movement satisfactorily unimanually but have greater difficulty when performing asymmetrical movements bimanually suggests that they have a deficit in integrating two or more motor programmes. On comparing symmetrical with asymmetrical bimanual reaching movements in Parkinson’s disease with controls, Stelmach and Worringham (1988) found that both groups took longer to prepare bimanual movements than unimanual movements and that this increase in preparation time was greater for asymmetrical than symmetrical bimanual reaching movements. Bimanual movements in Parkinson’s disease are likely to be less impaired if the subjects perform symmetrical movements with each hand since the two motor programmes share common timing and are mirrored. In our Parkinson’s disease patients, motor performance during bimanual movements was not significantly impaired compared with unimanual movements. Although bimanual symmetrical movements are uncommon physiologically, this experimental design was used since it was within the patients’ capability during PET scanning.

**Motor reorganization in Parkinson’s disease**

Unlike single ballistic movements, sequential movements involve the patients cyclically changing the pattern of muscle activity involved and so one would expect the performance of sequential finger movements to produce greater activation of the brain circuitry responsible for monitoring the position of the body in space (parietal areas, BA 40 and 7). We found widespread activation in SMC, supplementary motor area, premotor cortex and parietal association cortex in both the control and Parkinson’s disease group but, interestingly, we found foci in the lateral premotor and parietal (BA 40) cortex which were significantly more activated in the Parkinson’s disease group compared with the control group during task performance. This implies that our Parkinson’s disease patients were activating lateral premotor cortex and parietal circuits to a greater extent than the controls and suggests that complex sequential movements caused our Parkinson’s disease patients to divert from using impaired striato-mesial frontal projections to intact lateral premotor–parietal cortex (BA 40) circuits.
The lateral premotor and inferior parietal cortex have been implicated in controlling cued movements and guiding spatial tracking respectively. Our Parkinson’s disease patients may have subconsciously been able to use sensory information to overactivate the lateral premotor–parietal circuit during performance of sequential finger movements in order to compensate for the relative deficiency of mesial frontal–striatal circuits. This finding is consistent in our previous studies comparing Parkinson’s disease patients with controls during performance of ballistic joystick movements (Playford et al., 1992) and ballistic finger extensions (Jahanshani et al., 1995). Although the previous study of ballistic joystick movements (Playford et al., 1992) detected task-associated activation of the lateral premotor cortex in Parkinson’s disease patients which appeared greater than in control subjects, a direct between-group comparison failed to demonstrate significant overactivity (Playford, 1993). These data, however, were acquired using a lower resolution 2D PET camera rather than the 3D camera used in this study and so this may have reduced the sensitivity of the study. After scatter correction the 3D PET data acquisition method is approximately six times more sensitive than the 2D approach (Bailey et al., 1991). The study of ballistic index finger extensions (Jahanshani et al., 1995) was designed to investigate regional impairment of activation in Parkinson’s disease patients compared with controls during task performance. These workers used a similar PET scanner to ours but, although mesial frontal and dorsal prefrontal underactivation was detected in the Parkinson’s disease group, an analysis to test for relative regional overactivity was not performed. We reconstructed their original data and after realignment, spatial normalization and smoothing, further analysis (using ANCOVA to normalize global blood flow) did not detect significant overactivation (P < 0.001) of lateral premotor cortex or parietal cortex in the Parkinson’s disease group during this task. These results imply that sequential rather than simple ballistic movements may require a switch to lateral premotor–parietal cortex circuits when the striatal–frontal circuits dysfunction in Parkinson’s disease.

Selective involvement of lateral premotor cortex during movements which are under sensory guidance has been suggested by Roland (1984) and Passingham (1988). Animal lesion and electrophysiological single unit recording experiments confirm an important role for the lateral premotor cortex in sensory processing. Removal of the lateral premotor cortex in macaque monkeys results in animals which are slow to perform visually cued tasks but can still perform remembered sequences of movements (Petrides, 1982; Passingham, 1985). Recordings from lateral prefrontal cortex cells in monkeys have shown that these cells increase their firing rates when monkeys see a food reward, but before reaching movements occur (Godschalk et al., 1981).

Activation of the superior and inferior parietal cortex during limb movements in extrapersonal space (moving the fingers in a maze) (Roland et al., 1980b) has been demonstrated but, interestingly, significant parietal activation was not detected during movements limited to intrapersonal space (finger apposition) (Roland et al., 1980a). Deiber et al. (1991) showed that the superior and inferior parietal cortex were relatively more activated by joystick movements in freely-selected directions compared with unidirectional repetitive movements. Jenkins et al. (1994) showed that while inferior parietal association cortex (BA 40) was significantly active during performance of learned sequential finger movements, both the inferior parietal cortex and the lateral premotor cortex were significantly more activated while learning novel sequences of finger movements. These findings all confirm a role for the inferior parietal lobe in controlling and learning complex movements in extrapersonal space.

The lateral premotor cortex receives dense and diverse projections from the parietal cortex (Petrides and Pandya, 1984). Anatomical evidence from antegrade and retrograde staining studies in the Rhesus monkey confirms that different subdivisions of the parietal cortex have selective reciprocal connections with cortical supplementary somatosensory areas, visual and limbic areas (Cavada and Goldman-Rakic, 1989b). Each parietal subdivision may have as many contralateral connections as it has ipsilateral connections. Furthermore, each subdivision is connected to a unique set of frontal areas (Cavada and Goldman-Rakic, 1989a). In the monkey, area 7m is connected to the dorsal premotor cortex and supplementary motor area while area 7b (which may be equivalent to the human inferior parietal BA 40) is connected to the ventral premotor cortex and supplementary motor area. In humans it is likely that analogous connections exist. This places the parietal cortex in an ideal position to integrate sensory, motivational and attentional inputs. An intact parietal–premotor loop could, therefore, provide a means of generating volitional movements via conscious or subconscious use of sensory cues in Parkinson’s disease, so avoiding the need for intact basal ganglia–mesial frontal circuits. It is recognized that Parkinson’s disease patients can use visual guidance to improve motor performance (Martin, 1967; Flowers, 1979; Dietz et al., 1990; Georgiou et al., 1994) and it has been suggested that Parkinson’s disease patients can use visual cues to control attention to guide movement (Brown and Marsden, 1988). Our Parkinson’s disease patients were all scanned with their eyes closed and the keypads out of sight. It is, therefore, improbable that the relative overactivity in the lateral premotor cortex and parietal association cortex occurred as a direct result of conscious visual guidance and more likely that our patients engaged the lateral premotor–parietal cortex loop subconsciously via tactile or sensory proprioceptive inputs.

During sequential finger movements, relative ventral prefrontal underactivity was apparent in the Parkinson’s disease patients. This was because the Parkinson’s disease patients developed a greater degree of deactivation in these areas than did control volunteers. Deactivation is postulated to occur when levels of rCBF, reflecting synaptic activity, fall during task performance and has been suggested to occur in cortical areas which are redundant during task performance.
A previous study of normal volunteers from our department (Jenkins et al., 1994) has shown that during performance of pre-learned and active learning of novel sequences of finger movements with eyes closed, significant deactivation occurred in orbitofrontal, peristriate and temporal cortex. Furthermore, deactivation of temporal cortex was greater while learning novel sequences of finger movements than while performing pre-learned sequences. This implies that when more extensive cerebral activity is required to perform a difficult task, deactivation in redundant areas also becomes enhanced. Our tasks were automatic and involved no decision-making; the prefrontal cortex could, therefore, be considered redundant for performance of these tasks. The greater number of errors made by the patients suggests that our patients found the task more difficult than the controls. This may be one explanation for the greater deactivation in the redundant prefrontal cortex (BA 10) in the Parkinson’s disease patients.

Motor reorganization involving recruitment of the lateral premotor cortex and inferior parietal cortex (BA 40) has been demonstrated in PET studies of patients recovering from striatocapsular infaracts (Weiller et al., 1992). Patients activated these areas more than controls when both the affected and unaffected hands were used. These findings suggest that both degenerative and ischaemic disconnections of the striatal–frontal connections can lead to abnormal recruitment of lateral premotor cortex and parietal circuits. The anatomical network and the opportunity for reorganization provided by parietal–frontal connections must therefore be extensive and bilateral. However, the mechanism of this abnormal recruitment of alternative sensorimotor cortical areas and its exact physiological role still remains uncertain.

Summary and conclusion
During automatic performance of unimanual and bimanual sequential finger movements, Parkinson’s disease patients show relative bilateral overactivity of lateral premotor and inferolateral parietal cortex (BA 40) compared with the controls along with impairment of mesial frontal activation (supplementary motor area/anterior cingulate gyrus). This finding supports the hypothesis that during complex movements, Parkinson’s disease patients can switch to using circuits normally involved in facilitating cued movement in order to overcome difficulties in generating volitional movements.

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