A PET study of sequential finger movements of varying length in patients with Parkinson’s disease

Maria Jose Catalan,1,2 Kenji Ishii,1 Manabu Honda,1 Ali Samii1 and Mark Hallett1

1Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA and 2Servicio de Neurología, Hospital Universitario San Carlos, Madrid, Spain

Summary
To study the difficulty that patients with Parkinson’s disease have in performing long sequential movements, we used H2 15 O PET to assess the regional cerebral blood flow (rCBF) associated with the performance of simple repetitive movements, well-learned sequential finger movements of varying length and self-selected movements. Sequential finger movements in the Parkinson’s disease patients were associated with an activation pattern similar to that found in normal subjects, but Parkinson’s disease patients showed relative overactivity in the precuneus, premotor and parietal cortices. Increasing the complexity of movements resulted in increased rCBF in the premotor and parietal cortices of normal subjects; the Parkinson’s disease patients showed greater increases in these same regions and had additional significant increases in the anterior supplementary motor area (SMA)/cingulate. Performance of self-selected movements induced significant activation of the anterior SMA/cingulate in normal subjects but not in Parkinson’s disease patients. We conclude that in Parkinson’s disease patients more cortical areas are recruited to perform sequential finger movements; this may be the result of increasing corticocortical activity to compensate for striatal dysfunction.

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

Abbreviations: BA = Brodmann area; rCBF = regional cerebral blood flow; SMA = supplementary motor area

Introduction
Sequential movements are a key component of daily voluntary motor behaviour, such as speech, handwriting and typing. Patients with Parkinson’s disease experience great difficulty with volitional sequential and simultaneous movements (Benecke et al., 1986, 1987), although external cues improve performance (Georgiou et al., 1994; Martin et al., 1994). Consequently, it has been suggested that the basal ganglia may facilitate sequential movement, engaging subsequent movements in a movement sequence (Marsden, 1990). Current information on the connectivity of the basal ganglia indicates that the major output of the dorsal putamen is to the posterior supplementary motor area (SMA), while the dorsal caudate projects to the anterior SMA and dorsal prefrontal areas and the ventral striatum projects to the anterior cingulate and orbitofrontal cortices (Alexander et al., 1990). In Parkinson’s disease, there is marked depletion of dopamine in the putamen in conjunction with relatively preserved nigrocaudate dopaminergic projections (Brooks et al., 1990). Therefore, one might predict that dopamine loss would lead to varying degrees of cortical deafferentation.

Failure of movement in Parkinson’s disease must be a consequence of defective striatopallidal control of this ascending thalamocortical system (Marsden and Obeso, 1994).

Studies in humans and primates have provided information on the role of the SMA in internally generated movements (Deiber et al., 1991; Mushiake et al., 1991) and in planning and/or executing complex voluntary movements (Ogogozo and Larsen, 1979; Roland et al., 1980; Deiber et al., 1991; Grafton et al., 1992). Previous PET studies in Parkinson’s disease have shown that the ability of patients to activate the SMA and dorsolateral prefrontal cortex is impaired, and the failure of these structures might be particularly critical in explaining the difficulty these patients experience.

A recent PET study by our group describing sequential finger movements of increasing length in normal subjects showed increased regional cerebral blood flow (rCBF) in the ipsilateral premotor [Brodmann area (BA) 6] and bilateral parietal (BA 7) cortices related to the length of the sequence (Catalan et al., 1998). A previous PET study of a short
movement sequence in Parkinson’s disease patients showed the surprising finding of overactivity of the lateral premotor and parietal areas (Samuel et al., 1997). However, it is unclear what would happen in Parkinson’s disease patients with longer movement sequences. With the a priori hypothesis of involvement of the parietal and premotor cortices during the performance of sequential movements, we used H215O PET to measure rCBF in Parkinson’s disease patients while they performed sequential movements of different lengths with the fingers of the right hand. The results were compared with those from a group of normal volunteers (Catalan et al., 1998). We also studied self-paced movements in the same subjects as a comparison task, because it has already been reported that the SMA is underactivated in that task (Playford et al., 1992; Jahanshahi et al., 1995). We had the a priori hypothesis of reduced activation of the SMA and prefrontal cortex in Parkinson’s disease patients during the performance of freely selected movements.

Method

Subjects
We studied 13 patients with Parkinson’s disease (10 men, three women) aged 41–63 years (mean 52.5 years). The diagnosis of Parkinson’s disease was based on medical history, physical and neurological examinations, response to levodopa or dopaminergic drugs, and laboratory tests and MRI scans to exclude other diseases. Patients were studied only after their medication had been withdrawn for at least 12 h. Before scanning, and while off their medications, patients were assessed with the UPDRS (Unified Parkinson’s Disease Rating Scale) (Lang and Fahn, 1989), the Hoehn and Yahr disability scale (Hoehn and Yahr, 1967) and Folstein’s Mini-Mental Test (Folstein et al., 1975). The clinical data are shown in Table 1.

We also studied 13 normal volunteers (eight men, five women) aged 41–64 years (mean 51.7 years) as control subjects; they had no history of neurological disease and no abnormalities on physical and neurological examinations (Catalan et al., 1998). All patients and normal subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971). The protocol was approved by the Institutional Review Board, and all participants gave their written informed consent for the study.

Experimental design
The experimental paradigm consisted of six conditions: four conditions of sequential right finger-tapping with different length of unit sequence as an index of complexity (Table 2); one condition of self-selected movements (‘free’ condition); and one rest (control) condition. The shortest sequence involved repetitive flexion movements of the right index finger against the thumb, which is referred to as ‘simple movement’. Three sequences of variably long units involved all right fingers in their execution, and are referred to as ‘sequential conditions’ or, individually, in relation to the number of movements in each condition, as ‘sequence-4’, ‘sequence-12’ and ‘sequence-16’. For the movement conditions, subjects briskly and precisely touched the tip of the thumb with the fingers of the right hand at a frequency of 0.5 Hz, paced to the beat of the metronome. The subjects were trained to wait for the tone and after that to move as fast as possible. For the ‘free’ condition, subjects were requested to choose randomly each finger opposition movement after hearing the tone, and not move the same finger consecutively more than twice. The finger movements were monitored by an electrically equipped glove, which recorded the timing and the finger that tapped the thumb. Performance of the sequence was assessed by calculating the percentage of correct taps. No omission of taps was observed.

Before scanning, all subjects practised the sequences until they could perform them from memory 10 times in a row without error. At this level of performance, the sequences were considered ‘overlearned’, thus assuring constant performance during the experimental session at an approximately similar level of training. No training was done for the self-selected movement condition, and all subjects were instructed a few minutes before the scan.

Each subject underwent six consecutive scans at 12-min intervals, one for each of the six conditions. For the rest scan, subjects lay quietly, listening to a metronome sounding at the same rate as for the movement scans. No attempt was made to control the subject’s thought content or attention during rest. For the movement scans, the subject started finger movements when the metronome began sounding, which was simultaneous with the time of radioisotope injection, and performed repeatedly in each condition until the end of the scan. The order of the different movement conditions and rest scans was randomized across all subjects to avoid an order effect.

PET procedure
PET scans were performed with a Scanditronix PC 2048–15B (Uppsala, Sweden), which collected 15 contiguous planes with an in-plane resolution of 6.5 mm full-width half-maximum after reconstruction, and with a centre-to-centre distance of 6.5 mm, covering 97.5 mm in axial direction. Each slice was 6.5 mm thick. The field of view and pixel size of the reconstructed images were 256 and 2 mm, respectively. A transmission scan was obtained with a rotating 68Ge/68Ga source. Based on the reconstructed transmission images, the position of the head was set to cover the SMA, sacrificing views of the inferior part of the cerebellum. The subjects lay comfortably in a supine position with their eyes covered for the duration of the experiment. A small plastic catheter was placed in the left cubital vein for radioisotope injection. The subject’s head was immobilized with an individually fitted, rigid thermoplastic face mask that was attached to the scanner bed.
Table 1 Clinical details of Parkinson’s disease patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration</th>
<th>UPDRS off medication</th>
<th>H&amp;Y off medication</th>
<th>MMSE</th>
<th>Dose of L-dopa (mg/day)</th>
<th>Side most affected</th>
<th>Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>F</td>
<td>6</td>
<td>25</td>
<td>II</td>
<td>30</td>
<td>250 (p)</td>
<td>L</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>5</td>
<td>17.5</td>
<td>II</td>
<td>30</td>
<td>* (d)</td>
<td>L</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>F</td>
<td>5.5</td>
<td>25</td>
<td>II.5</td>
<td>30</td>
<td>300 (d)</td>
<td>R</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>M</td>
<td>5.5</td>
<td>22.5</td>
<td>II.5</td>
<td>30</td>
<td>100 (p)</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>8</td>
<td>22</td>
<td>II.5</td>
<td>30</td>
<td>400 (p, d)</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>7</td>
<td>16</td>
<td>II</td>
<td>30</td>
<td>400 (b, d)</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>M</td>
<td>4</td>
<td>26</td>
<td>II</td>
<td>30</td>
<td>600 (p)</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>M</td>
<td>2</td>
<td>34.5</td>
<td>II</td>
<td>30</td>
<td>* (p, d)</td>
<td>L</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>M</td>
<td>2.5</td>
<td>31</td>
<td>II.5</td>
<td>30</td>
<td>300 (L)</td>
<td>L</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>M</td>
<td>2</td>
<td>24.5</td>
<td>II</td>
<td>30</td>
<td>* (p)</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>M</td>
<td>5</td>
<td>23</td>
<td>II</td>
<td>30</td>
<td>400 (p, d)</td>
<td>L</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>46</td>
<td>F</td>
<td>1.5</td>
<td>19.5</td>
<td>1.5</td>
<td>30</td>
<td>* (b, d)</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>42</td>
<td>M</td>
<td>2</td>
<td>22</td>
<td>1.5</td>
<td>30</td>
<td>* (d)</td>
<td>L</td>
<td>No</td>
</tr>
</tbody>
</table>

Mean (SD) 52 (8.68) 4.30 (2.13) 23.73 (5.01) 2.07 (0.34) 30 343.75 (145)

H&Y = Hoehn and Yahr staging; MMSE = Mini-Mental-State Examination; F = female; M = male; (p) = plus pergolide; (d) = plus deprenyl; (b) = plus bromocriptine. *Not taking L-dopa at time of study.

Table 2 Sequences of opponent finger movements

<table>
<thead>
<tr>
<th>Task</th>
<th>Unit sequence</th>
<th>Length of unit sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Simple</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2. Sequence-4</td>
<td>1, 2, 3, 4</td>
<td>4</td>
</tr>
<tr>
<td>3. Sequence-12</td>
<td>1, 2, 3, 4, 1, 3, 2, 4, 2, 3, 1</td>
<td>12</td>
</tr>
<tr>
<td>4. Sequence-16</td>
<td>1, 2, 3, 4, 1, 3, 2, 4, 2, 3, 1, 4, 3, 2, 1</td>
<td>16</td>
</tr>
</tbody>
</table>

Unit sequence: 1 = index finger; 2 = middle finger; 3 = ring finger; 4 = little finger.

Image analysis

Data analysis was performed with statistical parametric mapping (using SPM 95 from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Natick, Mass., USA). Statistical parametric mapping combines the general linear model (to create the statistical map or SPM) and the theory of Gaussian fields to make statistical inferences about regional effects (Friston et al., 1991, 1994; Worsley et al., 1992).

Scans from each subject were realigned using the first as a reference. The six parameters of this rigid-body transformation were estimated using a least squares approach (Friston et al., 1995a). This approach is based on an approximate linear relationship between the images and their partial derivatives with respect to parameters of the transformation. Following realignment, all images were transformed into a standard space (Talairach and Tournoux, 1988). The spatial normalization involved linear and non-linear three-dimensional transformations to match each scan to a reference image that already conformed to the standard space (Friston et al., 1995a). Each image was smoothed to account for the variation in normal gyral anatomy using a Gaussian filter (full width half maximum = 16 mm for all directions). In the stereotaxic standard space, each voxel was 2 x 2 x 4 mm in size.

After specifying the appropriate design matrix, the condition effects were estimated according to the general linear model at each and every voxel (Friston et al., 1995b). Differences in global CBF between scans were removed by ANCOVA (analysis of covariance) with global flow as a confounding variable (Friston et al., 1990). Systematic difference among subjects was also removed as a confounding effect. After removing confounding effects, adjusted rCBF images were subjected to the following analysis.

Within-group analysis

Eigenimage analysis

To characterize the general pattern of the variance matrix across different conditions, principal components analysis (eigenimage analysis) for each group was applied to the
adjusted rCBF images averaged across subjects (Friston et al., 1993). Each principal component can be described in a spatial domain (eigenimage) or a profile over conditions (condition loading). From this analysis, we looked for the most predominant changes introduced by the experimental design. To identify the cortical areas spatially related to the performance of sequential movements, we applied this eigenimage analysis, including only sequential conditions. This analysis was done to explore the general pattern of activation and to support our a priori hypothesis about the greater involvement of the lateral premotor and parietal cortices in Parkinson’s disease patients.

**Subtraction analysis**

To test the hypothesis on the specific regional effects, the conditions were compared using linear contrast. The resulting set of voxel values for each contrast constitutes a statistical parametric map of the $t$ statistic; the $t$ values were then transformed to the unit normal distribution ($Z$ score) and thresholded at 3.09. The significance of each region was estimated using the probability that the peak height observed could have occurred by chance and/or that the observed number of contiguous voxels could have occurred by chance over the entire volume analyzed (Friston et al., 1994). A corrected $P$ value of 0.05 was used as a final threshold for significance.

Based on our hypotheses, four kinds of linear contrasts were examined for each group to look at the cortical areas activated with the different movement conditions. To study the cortical areas involved in executing simple and sequential movement, simple movement and the longest sequence (sequence-16) were contrasted with the rest condition. To identify the areas selectively activated by sequential movements, the shortest sequence (sequence-4) was contrasted with simple movement. To study the effect of sequence length, the most complex sequence (sequence-16) was contrasted with the simplest sequence (sequence-4). Finally, to study the effect of free choice, the simplest condition was contrasted with the average of the three sequential conditions [i.e. free – (seq4 + seq12 + seq16)/3]. Again, a corrected $P$ value of 0.05 was used as the final threshold for significance.

**Between-group analysis**

Comparison of the Parkinson’s disease patients’ resting scans with those of the normal subjects showed no significant differences (increases or decreases) in resting rCBF in any cortical area. In both normal subjects and Parkinson’s disease patients, primarily the same anatomical regions were involved in each activation condition, and the most striking difference was the magnitude of activation in some cortical areas of the patients.

To compare differences in rCBF between groups, we subtracted specific contrasts in one group from the same contrast in the other group in both ways (reverse comparisons). Such subtractions indicate relative increase or decrease in activation in one group compared with the other. The same four kinds of linear contrast done in the within-group study were done between groups to examine differences in cortical activation. Our hypothesis was that relative increases in activation of the lateral premotor and parietal cortices would be present in Parkinson’s disease patients during the performance of sequential movements. For between-group categorical contrast, activation differences at these a priori areas were compared at a threshold of 2.33 ($P < 0.01$ at each pixel). For all other areas, activation differences were considered significant at a threshold of 3.09 ($P < 0.001$ at each pixel).

**Results**

**Performance**

The percentages of error made by the normal subjects and Parkinson’s disease patients during the performance of each condition are shown in Table 3. Within groups, control subjects did not make any errors in performing simple repetitive movement and sequence-4. The Parkinson’s disease group started making errors during performance of sequence-4. In both groups, the number of errors increased with longer sequences, and for each condition the Parkinson’s disease group had more errors than normal subjects. However, the mean percentage of correct taps for each group in all movement conditions was $>98\%$ for the normal subjects and $97\%$ for the patients. The between-group differences were not statistically significant.

Mean response time by the normal subjects and Parkinson’s disease patients during performance of each condition is shown in Fig. 1A. The mean response time decreased for longer sequences in both groups. Compared with normal subjects, the Parkinson’s disease group had a shorter response time for each condition, although these differences were not statistically significant by the ANOVA (analysis of variance) test ($P = 0.32$ for simple movement, $P = 0.34$ for sequence-4, $P = 0.18$ for sequence-12, $P = 0.18$ for sequence-16 and $P = 0.06$ for free movement condition). Since both normal subjects and patients made some movements a few milliseconds before hearing the tone, these
movements had a negative response time. The percentage of movements with negative response time was <2% for normal subjects and 3% for Parkinson’s disease patients. Both groups showed a greater tendency towards the negative response time (i.e. anticipation) during the performance of longer sequences (Fig. 1B). This was more evident for the Parkinson’s disease group, but these differences were not significant ($P = 0.83$ for sequence-4, $P = 0.11$ for sequence-12, $P = 0.36$ for sequence-16 and $P = 0.70$ for free condition).

**rCBF: within-group analysis**

**Eigenimage analysis**

Figure 2A demonstrates the first principal component in the spatial domain (i.e. first eigenimage) for the Parkinson’s disease group. The distribution of the eigenvalues suggests that the first component can explain 84.3% of the total variance–covariance structure for the Parkinson’s disease group. This eigenimage includes the bilateral sensorimotor, premotor, supplementary motor and parietal cortex, contralateral basal ganglia (putamen) and cerebellum. The eigenimage was similar to that of the normal group previously described (Catalan et al., 1998), except that there was more extensive participation of the bilateral ventral premotor cortex in the Parkinson’s disease group. The condition loading scores associated with the first eigenimage were characterized by a monotonic change with increasing sequence length for the Parkinson’s disease group (Fig. 2B), whereas those of the normal group saturated after sequence-12 (Catalan et al., 1998). To identify areas selectively involved with sequential conditions for each group, we made the eigenimage analysis only with sequence-4, sequence-12 and sequence-16. The first eigenimage accounted for 85.4% of the total variance–covariance structure for the normal subjects and 88.2% for the Parkinson’s disease group. The bilateral parietal, premotor and precuneus were included in the first eigenimage for both groups (Fig. 2C and E). In addition to these areas, the normal group showed cerebellar activation and the Parkinson’s disease group showed anterior SMA/cingulate involvement.

**Subtraction analysis**

In both groups, comparison of simple movement versus rest showed increased rCBF (activation) in the contralateral primary sensorimotor, dorsal premotor and posterior supplementary motor cortices. In addition to these areas, the comparison of simple movement versus rest in the normal group showed cerebellar activation. Parkinson’s disease patients had additional activation in the contralateral parietal area and ipsilateral SMA (Fig. 3A). The pattern of increased rCBF in the subtraction of sequence-16 compared with rest was similar for Parkinson’s disease patients and normal subjects, but the Parkinson’s disease patients had larger areas of rCBF increase in the bilateral parietal and premotor cortices (Fig. 3B). In contrast to the normal subjects, the Parkinson’s disease group showed a tendency for increased rCBF in the bilateral ventral premotor cortex. Table 4 shows the maximal peak of rCBF in different cortical areas for the contrast between the longest sequence (i.e. sequence 16) compared with rest for each group.

To find any significant differences in cortical activation related to sequence performance, we performed a subtraction analysis of the shortest sequence (sequence-4) with simple repetitive movement. The pattern of increased rCBF in this subtraction was similar for Parkinson’s disease patients and normal subjects, showing significant activation in the bilateral parietal and premotor cortices. The Parkinson’s disease group had larger areas of activation in the bilateral parietal cortex. In contrast to normal subjects, they also showed ipsilateral ventral premotor activation (Fig. 3C).

The effect of sequence length, evaluated with the subtraction between the longest and the shortest sequences (sequence-16 and sequence-4) for the Parkinson’s disease group, showed activation in the precuneus, bilateral premotor and anterior SMA/cingulate cortices (Fig. 4). In contrast, this subtraction in normal subjects showed no significant cortical activation at the same level of threshold and correction.

Subtraction between free movement and the average of the three sequential conditions showed significant activation in the contralateral anterior SMA/cingulate, prefrontal and...
Fig. 2 Principal components analysis. (A) Positive component of the first principal component (eigenimage) for the Parkinson’s disease group (including five conditions, i.e. rest, simple movement, seq-4, seq-12 and seq-16). (B) Component score across conditions for the Parkinson’s disease group showing a monotonic increase with increasing complexity. (C) Positive component of the first eigenimage for the normal subjects, including the three sequential conditions. (D) Component score across sequential conditions for the normal subjects showing saturation after sequence-12. (E) Positive component of the first eigenimage for the Parkinson’s disease group, including the three sequential conditions. (F) Component score across sequential conditions for the Parkinson’s disease group showing increase with increasing complexity.
Sequential movements in Parkinson's disease

Fig. 3 Statistical parametric maps (SPMs) of increasing rCBF in the subtraction analysis (within-group study), showing the significantly activated areas for the control group (left column) and Parkinson's disease group (right column). (A) Areas with increase of rCBF during simple repetitive movement compared with rest condition. (B) Areas with increase of rCBF during sequence-16 compared with rest condition. (C) Areas with increase of rCBF during sequence-4 compared with simple repetitive movement. The voxels displayed have Z values exceeding the significance threshold of 3.09 with a Bonferroni correction for multiple comparisons ($P < 0.05$). The SPMs are displayed in the anatomical space of Talairach and Tournoux (1988) as a maximum intensity projection viewed from the right side (sagittal view), the back (coronal view) and the top (transverse view) of the brain. VAC = vertical line passing through the anterior commissure; VPC = vertical line passing through the posterior commissure. The data from the control group for A and C have been published previously (Catalan et al., 1998).
ipsilateral parietal cortices for normal subjects. In contrast, the Parkinson’s disease group showed only significant activation in the ipsilateral prefrontal cortex.

**Discussion**

Akinnesia, defined as a delay in initiating movements, can be distinguished from bradykinesia, which is slowness in executing movements (Hallett, 1990). The pathophysiology of these major symptoms of Parkinson’s disease remains incomplete. Parkinson’s disease patients slowly acquire the proper motor programme, but once it is mastered, performance is normal, although movement remains bradykinetic (Frith et al., 1986). Selection and movement sequencing are problematic in Parkinson’s disease, but patients can learn and maintain even the relative temporal patterning in a sequence of motor actions (Roy et al., 1993). In the present study, all subjects were trained before PET scanning to achieve similar performance. The slow motor performance rate in the present study (0.5 Hz) was chosen because it was possible for Parkinson’s disease patients to follow this pace more easily during PET scanning.

In our study, task performance was very good for both groups, with a high percentage of corrects taps (98% for normal subjects and 97% for Parkinson’s disease patients). Long practice before PET scanning to achieve a similar performance. The slow motor performance rate in the present study (0.5 Hz) was chosen because it was possible for Parkinson’s disease patients to follow this pace more easily during PET scanning.

In our study, task performance was very good for both groups, with a high percentage of corrects taps (98% for normal subjects and 97% for Parkinson’s disease patients). Long practice before PET scanning to achieve a similar learning stage for all subjects explains that performance. Even though errors were infrequent, their increase with longer sequences argues that task performance is more difficult with increased sequence length. The Parkinson’s disease patients made errors even while performing the shortest sequence, and made more (but not significantly more) errors than the normal subjects. The larger number of errors made by the
Fig. 4 (A) Statistical parametric maps of increasing rCBF in the subtraction analysis for the Parkinson’s disease patients showing significantly activated areas during sequence-16 compared with sequence-4. (B) Anterior SMA/cingulate superimposed on a MRI of the brain. The Z values of the voxels shown exceed the significance threshold of 3.09 with a Bonferroni correction for multiple comparisons ($P < 0.05$).

Parkinson’s disease patients suggests that they found the sequences slightly more difficult than the normal subjects. This may explain the larger areas of activation in some of the cortical association areas of Parkinson’s disease patients.

Both patients and normal subjects had a longer response time for simple and self-selected movements than for sequential movements. A more difficult task might demand more attention for correct performance, and this might induce anticipation. Alternatively, the pressure of continuing a sequence might cause a shorter reaction time. Curiously, this phenomenon was more striking in the Parkinson’s disease group. Anticipation is a paradoxical clinical phenomenon...
often seen in Parkinson’s disease patients, but apparently
has not been studied physiologically. In some reports, this
tendency of Parkinson’s disease patients to anticipate
movements has been explained by the difficulty they have in
programming subsequent movements in a sequence (Benecke
et al., 1987; Harrington and Haaland, 1991). Parkinson’s
disease patients can also use advance information to prepare
finger taps (Day et al., 1984; Stelmach et al., 1986), and
cueing could induce the predictive motor behaviour. Also,
their slowness during the movement shortens the time
between movements needed to perform all the movements.

Parkinson’s disease patients and normal subjects had very
similar cortical activation patterns during sequential finger
movement performance. The Parkinson’s disease patients
showed relative overactivity in the premotor and parietal
cortices during performance of the longer sequences, and, in
contrast to normal subjects, had increased activation of the
anterior SMA/cingulate. However, in Parkinson’s disease
patients the performance of self-selected movements did not
activate the anterior SMA/cingulate.

Different studies measuring rCBF in normal subjects
have often shown that the anterior SMA and cingulate are
significantly activated during performance of sequential finger
movements (Roland et al., 1980; Deiber et al., 1991; Paus
et al., 1993; Jenkins et al., 1994a). Our study of normal
subjects showed that the posterior SMA was involved in the
performance of sequential movements, although activation
was not significantly increased for longer sequences compared
with shorter ones (Catalan et al., 1998). In that study, although
the maximal pixel was in the posterior SMA, the anterior
SMA may also have been involved. Activation of the SMA
during performance of internally generated sequential
movements has been demonstrated by microelectrode
recordings in monkeys. Cells of the SMA were specifically
more active when the monkeys performed remembered
sequential arm movements, and a proportion of SMA cells
increased their activity only in relation to a specific order of
remembered sequential movements (Mushiake et al., 1990;
Tanji and Shima, 1994). These results support the notion that
the SMA is involved in generating sequential movements.
The fact that our Parkinson’s disease patients had more
significant anterior SMA/cingulate activation than normal
subjects when performing longer sequences supports the view
that Parkinson’s disease patients are able to activate these
cortical areas, and need to do it more vigorously to perform
sequential movements successfully. In addition, this finding
supports the crucial role of the SMA in generating sequences
in humans. Our data in fact agree with previous PET data,
where significantly reduced SMA activation was related to
short sequences (Playford et al., 1992; Jahanshahi et al.,
1995).

In contrast, in our study Parkinson’s disease patients
failed to activate properly the anterior SMA/cingulate while
performing freely selected movements. Several previous
studies using PET or SPECT (single-photon emission
computed tomography) during performance of self-generated
movements showed that the SMA is significantly
underactivated in patients with Parkinson’s disease tested
‘off’ medication relative to matched control subjects (Playford
et al., 1992; Rascol et al., 1994). Self-generated movements
have been tested in Parkinson’s disease patients with PET in
two ways: the subjects had to decide ‘what to do’ on each
trial (Jenkins et al., 1992; Playford et al., 1992), and ‘when
to do’ each movement (Jenkins et al., 1994b; Jahanshahi
et al., 1995). The self-generated movements tested in both
ways showed greater activation of the anterior SMA/cingulate
and dorsolateral prefrontal cortex in control subjects than in
Parkinson’s disease patients, but there was no significant
difference in levels of contralateral sensorimotor and lateral
premotor activation. This underactivation in the anterior
SMA and dorsolateral prefrontal cortex during self-selected
movements can be reversed by administering the
dopaminergic agent apomorphine coincident with reversal of
akinesia (Jenkins et al., 1992). The results of the present study
agree with these data. Performing self-selected movements
induced significant activation of the anterior SMA/cingulate

### Table 5 Between-group analysis of the location of relative differences in activation in Parkinson’s disease compared with
controls in the comparison of sequence-16 versus the rest condition

<table>
<thead>
<tr>
<th>Location</th>
<th>Talairach coordinates*</th>
<th>Controls</th>
<th>Parkinson’s disease patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x  y  z</td>
<td>Z score</td>
<td>% change</td>
</tr>
<tr>
<td>PMd R</td>
<td>24  6 52</td>
<td>2.50</td>
<td></td>
</tr>
<tr>
<td>PMv R</td>
<td>42  8 36</td>
<td>3.24</td>
<td></td>
</tr>
<tr>
<td>Parietal R</td>
<td>38 -68 40</td>
<td>3.29</td>
<td></td>
</tr>
<tr>
<td>Parietal L</td>
<td>-50 -32 44</td>
<td>2.73</td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>4 -60 44</td>
<td>2.82</td>
<td></td>
</tr>
<tr>
<td>SM1 L</td>
<td>-20 -20 56</td>
<td>2.89</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>-12 -56 -12</td>
<td>2.90</td>
<td></td>
</tr>
</tbody>
</table>

PM = premotor cortex; SM1 = primary sensorimotor cortex; d = dorsal; v = ventral; R = right; L = left. *Talairach coordinates and
Z score peak difference between groups. †Z score and percentage change for each group.
and prefrontal cortices in normal subjects but not in the Parkinson’s disease patients, whose difficulties in movement selection may be related to deficient function of these cortical areas.

In the present study, both normal subjects and Parkinson’s disease patients activated the bilateral parietal and premotor cortices with sequential tasks and showed increasing activation for the longer sequences. The Parkinson’s disease group had larger areas of activation for both the parietal and the premotor cortex, including the ventral part of the premotor cortex bilaterally (Figs 2A and E and 3B). Planning, initiating and executing movements are three different aspects of motor performance. Parietal areas are especially associated with spatial aspects of motor planning, while the medial and lateral premotor areas are more involved in movement initiation and selection. Imagining and executing movements activate the intermediate and caudal parts of the superior parietal lobe (BA 7, including the precuneus) (Stephan et al., 1995). Additionally, posterior parietal activation has been related to movement selection and spatial attention (Jenkins et al., 1994a; Deiber et al., 1996). Sadato et al. (1996) reported that dorsal premotor cortex activation progressively increased on the side ipsilateral to the movement as the length of the unit sequence increased. Previous data from our group showed that the parietal and premotor cortices were activated by sequential but not simple repetitive movements (Catalan et al., 1998). Weinstein et al. (1997) showed increased activity in the dorsal premotor and parietal areas for reciprocal reaching tasks since the tasks were performed under increasingly difficult conditions. Thus, the general process of task difficulty might recruit some of these additional areas.

In a recent study, Samuel et al. (1997) found overactivity in premotor and parietal areas in Parkinson’s disease patients during the performance of short sequential movements. The paradigm they used for auditory-paced movements consisted of pressing four keys sequentially in the following order: index, middle, ring and little fingers; this task is similar to the paradigm they used for auditory-paced movements (Fox et al., 1985; Seitz et al., 1990; Graf ton et al., 1992; Shibasaki et al., 1993; Sadato et al., 1996). Overactivity in the ipsilateral cerebellum in relation to rest tremor and during the performance of voluntary movements has been reported in Parkinson’s disease patients using PET and SPECT (Duffau et al., 1996; Sabatini et al., 1996). The trend for underactivation in the present study may be another indication of a switch from subcortical to cortical–cortical control when performing long sequences.

The cortical overactivity in the parietal and premotor areas seen in Parkinson’s disease patients when making sequential movements becomes more dramatic when the sequences are longer. Moreover, the anterior SMA, which is underactivated during self-selected movements and in short sequences, also becomes overactive. The brain areas related to performing sequences must work harder in Parkinson’s disease, presumably because of the basal ganglion dysfunction. The cortical overactivity appears to attempt to compensate for this dysfunction.

Acknowledgements
We wish to thank the members of the Positron Emission Tomography Department, Clinical Center, National Institutes of Health, for their expertise, and Ms B. J. Hessie and D. G. Schoenberg, MS, for skilful editing. M.J.C. was supported by Fondo de Investigaciones Sanitarias (grant 96/5058), Madrid, Spain.

References


Playford ED, Jenkins IH, Passingham RE, Nutt J, Frackowiak RSJ, Brooks DJ. Impaired mesial frontal and putamen activation in


