Brain (1999), **122,** 483–495

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 Samii[1] and Mark Hallett[1]

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

Correspondence to: Mark Hallett, MD, Clinical Director, NINDS, NIH, Building 10, Room 5N226, 10 Center Drive MSC 1428, Bethesda, MD 20892-1428, USA
E-mail: hallett@codon.nih.gov

Summary

To study the difficulty that patients with Parkinson's disease have in performing long sequential movements, we used $H_2{}^{15}O$ 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 (Orgogozo 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 $H_2{}^{15}O$ 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 $^{68}Ge/^{68}Ga$ 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*

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

Task	Unit sequence	Length of unit sequence
1. Simple	1	1
2. Sequence-4	1, 2, 3, 4	4
3. Sequence-12	1, 2, 3, 4, 1, 3, 2, 4, 4, 2, 3, 1	12
4. Sequence-16	1, 2, 3, 4, 1, 3, 2, 4, 4, 2, 3, 1, 4, 3, 2, 1	16

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

Reconstructed images were obtained by summing the activity during the 60-s period following the first detection of an increase in cerebral radioactivity after the intravenous bolus injection of 50 mCi of [^{15}O]water. No arterial blood sampling was performed, and thus the images collected were those of tissue activity. Tissue activity recorded by this method has been shown to be linearly related to rCBF (Fox *et al*., 1984; Fox and Mintun, 1989).

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*., 1995*a*). 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*., 1995*a*). 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 $2 \times 2 \times 4$ 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*., 1995*b*). 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 analysed (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 free 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 considered significant 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).

Table 3 *Performance (median percentage of errors) of sequential finger movements for controls and Parkinson's disease patients*

Task	Errors % (controls)	Errors % (Parkinson's disease)
Simple	0	0
Sequence-4	0	0.25 ± 0.8
Sequence-12	0.50 ± 1.3	1.78 ± 2.6
Sequence-16	1.78 ± 2.8	2.83 ± 3.4

Values are mean ± SD for percentage of errors (% = number of errors/total taps × 100).

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

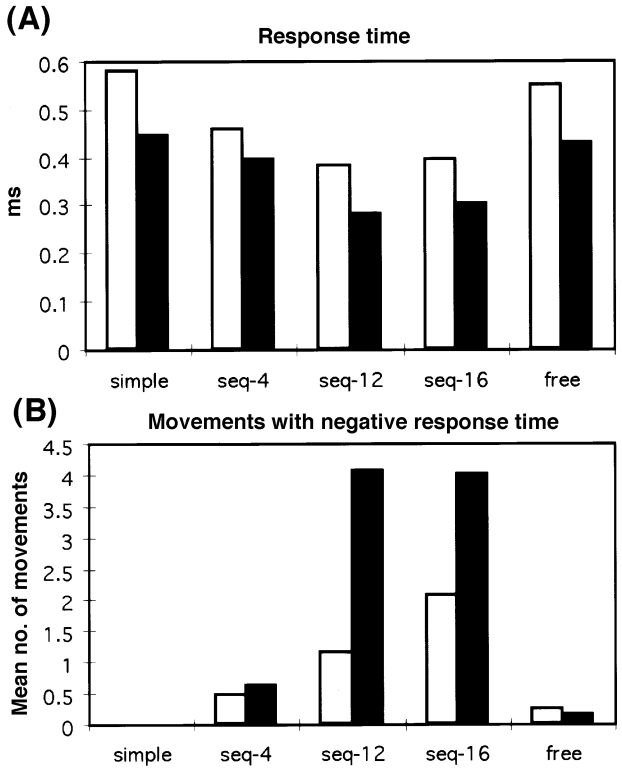

Fig. 1 Performance of sequential finger movements. (**A**) Mean response time by the control and the Parkinson's disease groups during performance of each sequential condition. (**B**) Number of finger movements with negative response time by the control and Parkinson's disease groups during performance of each sequential condition.

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

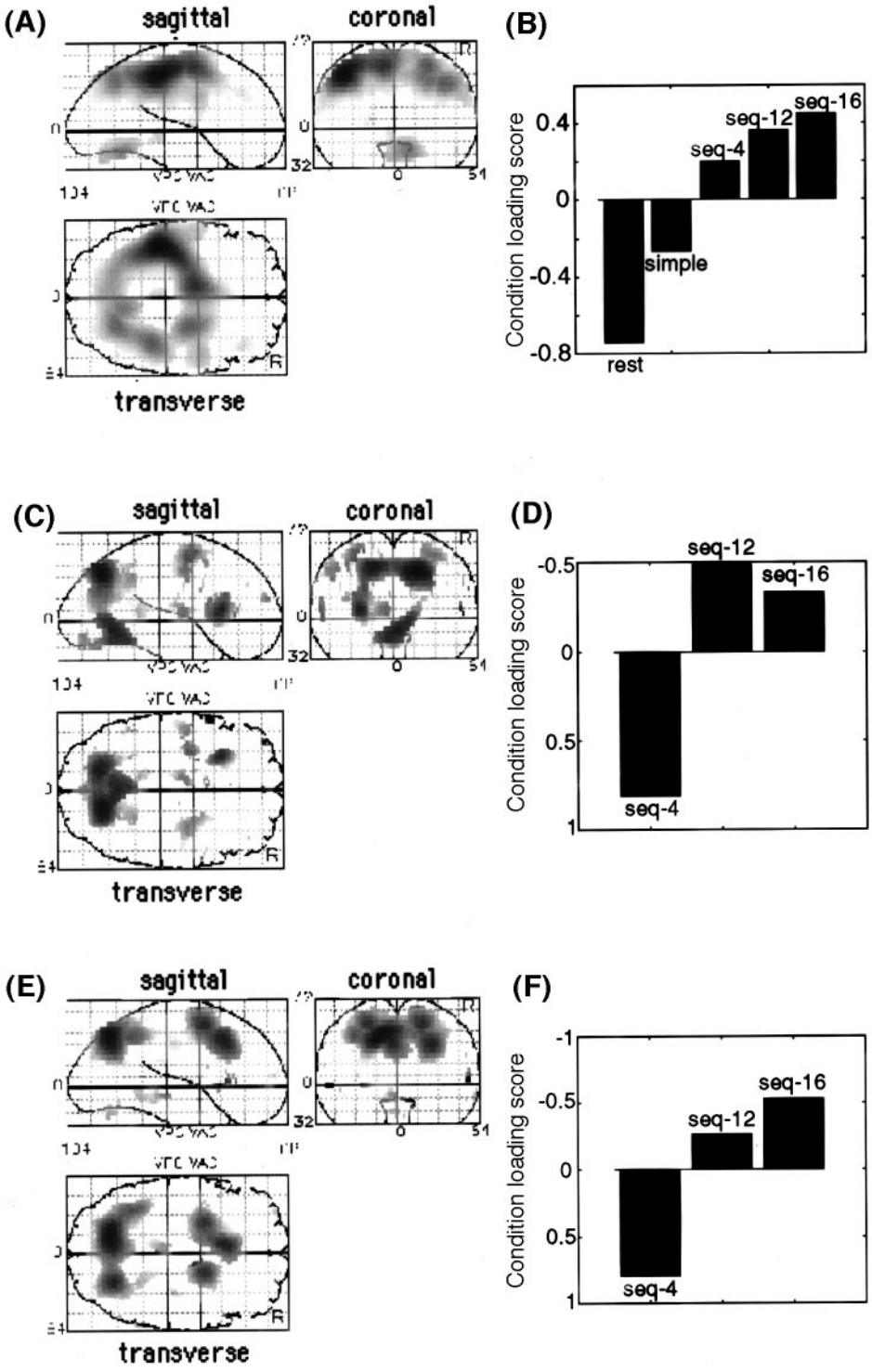

Fig. 2 Principal components analysis. (**A**) Positive component of the first principal component (eigenimage) for the Parkinson's disease group (including five conditions, i.e. rest, simple movement, seq-4, seq-12 and seq-16). (**B**) Component score across conditions for the Parkinson's disease group 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.

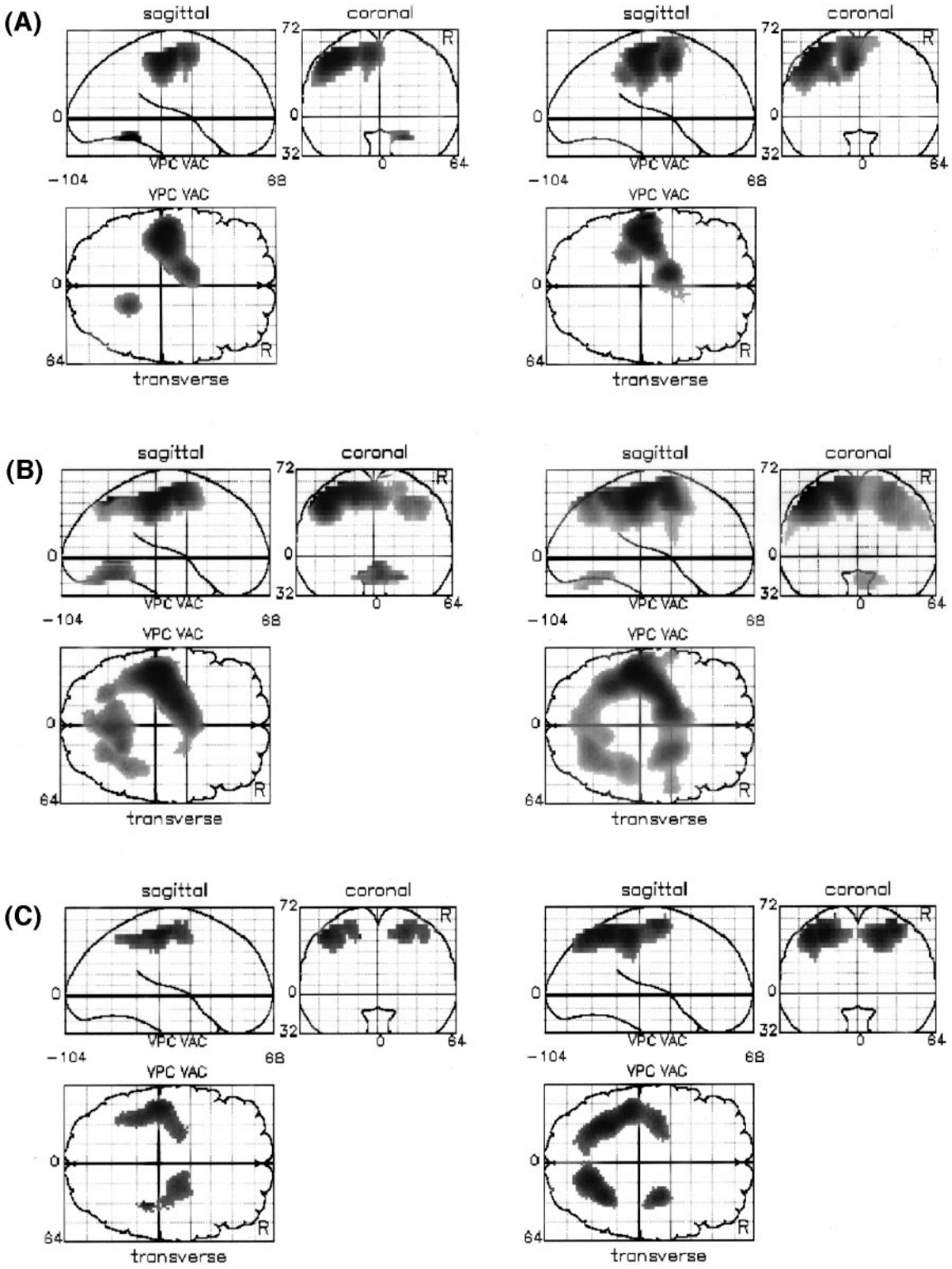

Fig. 3 Statistical parametric maps (SPMs) of increasing rCBF in the subtraction analysis (within-group study), showing the significantly activated areas for the control group (left column) and Parkinson's disease group (right column). (**A**) Areas with increase of rCBF during simple repetitive movement 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 Bonferoni 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).

Table 4 *Within-group analysis: activation of different brain regions by sequential finger movements from comparison of sequence-16 versus rest condition in controls and in the Parkinson's disease group*

Location	Talairach coordinates*: control group					Talairach coordinates*: Parkinson's disease group				
	x	*y*	*z*	*Z* score*	% change	*x*	*y*	*z*	*Z* score*	% change
SM1 L	–42	–28	48	7.69	8.97	–40	–30	48	8.46	11.29
pSMA L	–10	–8	56	5.69	6.98	–12	–2	52	7.05	8.10
aSMA L	–10	2	52	5.50	6.03	–6	6	44	6.22	5.88
PMd L	–16	–8	52	6.78	7.27	–24	–10	60	7.53	7.86
PMv L	–	–	–	–	–	–52	–8	40	3.45	4.54
Parietal L†	–30	–60	48	4.56	4.14	–30	–56	48	6.32	5.84
Parietal L‡	–40	–32	40	7.19	8.20	–36	–42	44	7.38	8.48
Precuneus L§	–18	–74	44	4.57	5.30	–18	–68	44	4.80	5.86
PMd R	18	–4	56	3.50	3.78	20	–8	56	6.47	6.40
PMv R	–	–	–	–	–	48	–2	32	4.25	4.32
Parietal R†	32	–52	44	4.59	4.23	28	–64	40	5.43	6.44
Parietal R‡	38	–36	44	3.99	3.90	38	–40	36	6.06	7.60
Precuneus R	16	–70	44	4.09	4.14	18	–68	44	5.66	6.64
Cerebellum	2	–60	–16	5.51	6.39	12	–56	–16	4.25	5.78

SM1 = primary sensorimotor cortex; SMA = supplementary motor area; PM = premotor cortex; d = dorsal; v = ventral; p = posterior; a = anterior; L = left; R = right. *Talairach coordinates and *Z* score of peak activation. §From comparison of sequence 16 versus simple movement. †BA 7, according to the atlas of Talairach and Tournoux (1988). ‡BA 40, according to the atlas of Talairach and Tournoux (1988).

ipsilateral parietal cortices for normal subjects. In contrast, the Parkinson's disease group showed only significant activation in the ipsilateral prefrontal cortex.

rCBF: between-group analysis

We looked for relative increases in activation of the premotor and parietal cortices in the Parkinson's disease patients compared with normal subjects. These results are shown in Table 5. In the subtraction between simple movement and the longest sequence (i.e. sequence-16) with the rest condition, Parkinson's disease patients showed increased activation compared with controls in the ipsilateral premotor and bilateral parietal cortices at a threshold of 3.09 ($P < 0.001$ at each pixel) and trends for relative underactivity in the contralateral primary sensorimotor cortex (SM1) and cerebellum at a threshold of 2.33 ($P < 0.01$ at each pixel). There were no significant differences in activation in the subtraction between the shortest sequence and simple movement. Contrasting the more complex sequence (sequence-16) with the simplest sequence (sequence-4), Parkinson's disease patients showed significantly increased activation compared with controls in the contralateral anterior SMA/cingulate (threshold of 3.09, $P < 0.001$ at each pixel) and in the ipsilateral premotor cortex, both dorsal and ventral, at a threshold of 2.33 ($P < 0.01$ at each pixel). They also showed a trend for relative overactivation in the ipsilateral prefrontal cortex (threshold of 2.33, $P < 0.01$ at each pixel).

In the subtractions between the free movement and the average of the three sequential conditions, the normal subjects showed increased activation in the contralateral prefrontal cortex and precuneus (threshold of 3.09, $P < 0.001$ at each pixel) and in the contralateral anterior SMA/cingulate (threshold of 2.33, $P < 0.01$ at each pixel) and trends for relative overactivation in the ipsilateral premotor and parietal cortex (threshold of 2.33, $P < 0.01$ at each pixel).

Discussion

Akinesia, 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 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

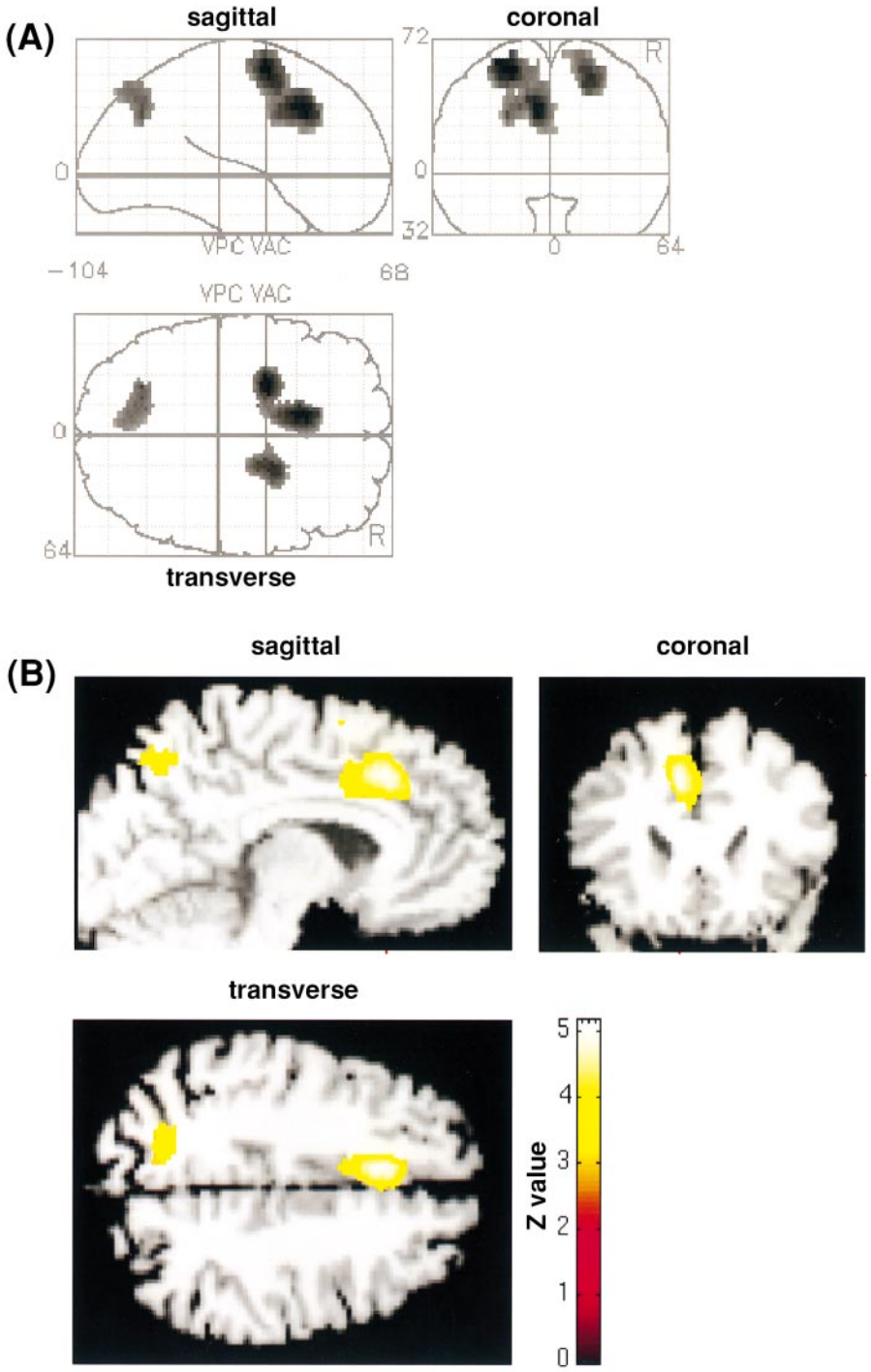

Fig. 4 (**A**) Statistical parametric maps of increasing rCBF in the subtraction analysis for the Parkinson's disease patients showing significantly activated areas during sequence-16 compared with sequence-4. (**B**) Anterior SMA/cingulate superimposed on a MRI of the brain. The *Z* values of the voxels shown exceed the significance threshold of 3.09 with a Bonferoni 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

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*

Location	Talairach coordinates*				Controls		Parkinson's disease patients	
	x	*y*	*z*	*Z* score*	*Z* score†	% change†	*Z* score†	% change†
Relative overactivity in Parkinson's disease compared with controls								
PMd R	24	6	52	2.50	1.54	1.41	4.95	4.61
PMv R	42	–8	36	3.24	–1.52	–1.28	3.11	2.57
Parietal R	38	–68	40	3.29	–0.46	–0.45	3.90	3.87
Parietal L	–50	–32	44	2.73	5.64	6.22	8.68	10.53
Precuneus	–4	–60	44	2.82	–1.37	–1.23	2.65	2.32
Relative underactivity in Parkinson's disease compared with controls								
SM1 L	–20	–20	56	2.89	7.11	8.20	3.82	3.77
Cerebellum	–12	–56	–12	2.90	3.65	3.85	–0.38	–0.36

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.

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*., 1994*a*). 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*., 1994*b*; 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

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*., 1994*a*; 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). Winstein *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 sequence-4 in the present study. Our results agree with and extend those of Samuel *et al*. (1997). As sequences get larger, the overactivity of the premotor and parietal areas becomes more dramatic and even the anterior SMA/cingulate is recruited. Previous studies in Parkinson's disease patients found no differences in premotor and parietal activation, but this could be explained because they were designed to perform simple movements, and more complex motor tasks are apparently necessary to activate these cortical areas (Playford *et al*., 1992; Jahanshahi *et al*., 1995). Parkinson's disease patients appear to increase corticocortical activity to compensate for their striatal dysfunction.

In the present study, Parkinson's disease patients showed a trend for relative underactivation in the primary sensorimotor cortex and cerebellum when performing longer sequences. There has been some controversy about the level of function of the primary motor cortex in Parkinson's disease from PET, single-photon emission computed tomography and TMS (transcranial magnetic stimulation) studies (Jenkins *et al*., 1992; Playford *et al*., 1992; Rascol *et al*., 1992, 1994; Ceballos-Baumann *et al*., 1994; Ellaway *et al*., 1995; Grafton *et al*., 1995; Jahanshahi *et al.*, 1995; Eidelberg *et al*., 1996). The cerebellum is important for the temporal order and precision in executing motor programmes (Fox *et al*., 1985; Seitz *et al*., 1990; Grafton *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

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

Benecke R, Rothwell JC, Dick JP, Day BL, Marsden CD. Performance of simultaneous movements in patients with Parkinson's disease. Brain 1986; 109: 739–57.

Benecke R, Rothwell JC, Dick JP, Day BL, Marsden CD. Disturbance of sequential movements in patients with Parkinson's disease. Brain 1987; 110: 361–79.

Brooks DJ, Ibanez V, Sawle GV, Quinn N, Lees AJ, Mathias CJ, et al. Differing patterns of striatal 18F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy [see comments]. Ann Neurol 1990; 28: 547–55. Comment in: Ann Neurol 1991; 29: 689–90.

Catalan MJ, Honda M, Weeks RA, Cohen LG, Hallett M. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. Brain 1998; 121: 253–64.

Deiber M, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RSJ. Cortical areas and the selection of movement: a study with positron emission tomography. Exp Brain Res 1991; 84: 393–402.

Deiber M, Ibañez V, Sadato N, Hallett M. Cerebral structures participating in motor preparation in humans: a positron emission tomography study. J Neurophysiol 1996; 75: 233–47.

Duffau H, Tzourio N, Caparros-Lefebvre D, Parker F, Mazoyer B. Tremor and voluntary repetitive movement in Parkinson's disease: comparison before and after L-dopa with positron emission tomography. Exp Brain Res 1996; 107: 453–62.

Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Fox PT, Mintun MA. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of $H_2{}^{15}0$ tissue activity. J Nucl Med 1989; 30: 141–9.

Fox PT, Mintun MA, Raichle ME, Herscovitch P. A noninvasive approach to quantitative functional brain mapping with $H_2{}^{15}0$ and positron emission tomography. J Cereb Blood Flow Metab 1984; 4: 329–33.

Fox PT, Raichle ME, Thach WT. Functional mapping of the human cerebellum with positron emission tomography. Proc Natl Acad Sci USA 1985; 82: 7462–6.

Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RSJ. The relationship between global and local changes in PET scans [see comments]. J Cereb Blood Flow Metab 1990; 10: 458–66. Comment in: J Cereb Blood Flow Metab 1993; 13: 1038–40.

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab 1991; 11: 690–9.

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993; 13: 5–14.

Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of local activations using their spatial extent. Hum Brain Mapp 1994; 1: 210–20.

Friston KJ, Ashburner J, Frith CD, Poline JB, Healther JD, Frackowiak RSJ. Spatial registration and normalization of images. Hum Brain Map 1995a; 3: 165–89.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995b; 2: 189–210.

Frith CD, Bloxham CA, Carpenter KN. Impairments in the learning and performance of a new manual skill in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1986; 49: 661–8.

Georgiou N, Bradshaw JL, Iansek R, Phillips JG, Mattingley JB, Bradshaw JA. Reduction in external cues and movement sequencing in Parkinson's disease. J Neurol Neurosurg Psychiatry 1994; 57: 368–70.

Grafton ST, Mazziotta JC, Presty S, Friston KJ, Frackowiak RSJ, Phelps ME. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J Neurosci 1992; 12: 2542–8.

Hallett M. Clinical neurophysiology of akinesia. [Review]. Rev Neurol (Paris) 1990; 146: 585–90.

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

Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects [see comments]. Brain 1995; 118: 913–33. Comment in: Brain 1996; 119: 1045–8.

Jenkins IH, Fernandez W, Playford ED, Lees AJ, Frackowiak RSJ, Passingham RE, et al. Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. Ann Neurol 1992; 32: 749–57.

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RSJ, Passingham RE. Motor sequence learning: a study with positron emission tomography. J Neurosci 1994a; 14: 3775–90.

Jenkins IH, Jahanshahi M, Brown R, Frackowiak RSJ, Marsden CD, Passingham RE, et al. Impaired activation of mesial frontal cortex during self-paced movements in Parkinson's disease [abstract]. Neurology 1994b; 44 Suppl 2: A353.

Lang AE, Fahn S. Assessment of Parkinson's disease. Boston: Butterworth; 1989.

Marsden CD. Neurophysiology. In: Stern GM, editor. Parkinson's disease. London: Chapman and Hall Medical; 1990. p. 57–98.

Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease [see comments]. [Review]. Brain 1994; 117: 877–97. Comment in: Brain 1995; 118: 822, Comment in: Brain 1995; 118: 1613–7.

Martin KE, Phillips JG, Iansek R, Bradshaw JL. Inaccuracy and instability of sequential movements in Parkinson's disease. Exp Brain Res 1994; 102: 131–40.

Mushiake H, Inase M, Tanji J. Selective coding of motor sequence in the supplementary motor area of the monkey cerebral cortex. Exp Brain Res 1990; 82: 208–10.

Mushiake H, Inase M, Tanji J. Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. J Neurophysiol 1991; 66: 705–18.

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

Orgogozo JM, Larsen B. Activation of the supplementary motor area during voluntary movement in man suggests it works as a supramotor area. Science 1979; 206: 847–50.

Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. J Neurophysiol 1993; 70: 453–69.

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

Parkinson's disease: a positron emission tomography study. Ann Neurol 1992; 32: 151–61.

Rascol O, Sabatini U, Chollet F, Celsis P, Montastruc JL, et al. Supplementary and primary sensory motor area activity in Parkinson's disease. Regional cerebral blood flow changes during finger movements and effects of apomorphine. Arch Neurol 1992; 49: 144–8.

Rascol O, Sabatini U, Chollet F, Fabre N, Senard JM, Montastruc JL, et al. Normal activation of the supplementary motor area in patients with Parkinson's disease undergoing long-term treatment with levodopa. J Neurol Neurosurg Psychiatry 1994; 57: 567–71.

Roland PE, Larsen B, Lassen NA, Skinhoj E. Supplementary motor area and other cortical areas in organization of voluntary movements in man. J Neurophysiol 1980b; 43: 118–36.

Roy EA, Saint-Cyr J, Taylor A, Lang A. Movement sequencing disorders in Parkinson's disease. Int J Neurosci 1993; 73: 183–94.

Sabatini U, Brefel C, Celsis P, Chollet F, Rascol O. Ipsilateral cerebellar overactivation when akinetic patients with Parkinson's disease move the hand [abstract]. Neurology 1996; 46 (2 Suppl): A453.

Sadato N, Campbell G, Ibañez V, Deiber M-P, Hallett M. Complexity affects regional cerebral blood flow change during sequential finger movements. J Neurosci 1996a; 16: 2691–700.

Sadato N, Ibañez V, Deiber M-P, Campbell G, Leonardo M, Hallett M. Frequency-dependent changes of regional cerebral blood flow during finger movements. J Cereb Blood Flow Metab 1996b; 16: 23–33.

Seitz RJ, Roland E, Bohm C, Greitz T, Stone-Elander S. Motor learning in man: a positron emission tomographic study. Neuroreport 1990; 1: 57–60.

Shibasaki H, Sadato N, Lyshkow H, Yonekura Y, Honda M, Nagamine T, et al. Both primary motor cortex and supplementary motor area play an important role in complex finger movement. Brain 1993; 116: 1387–98.

Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Baumann AO, Frith CD, et al. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. J Neurophysiol 1995; 73: 373–86.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Tanji J, Shima K. Role for supplementary motor area cells in planning several movements ahead. Nature 1994; 371: 413–6.

Winstein CJ, Grafton ST, Pohl PS. Motor task difficulty and brain activity: investigation of goal-directed reciprocal aiming using positron emission tomography. J Neurophysiol 1997; 77: 1581–94.

Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for rCBF activation studies in human brain [see comments]. J Cereb Blood Flow Metab 1992; 12: 900–18. Comment in: J Cereb Blood Flow Metab 1993; 13: 1040–2.

Received July 6, 1998. Revised September 21, 1998.
Accepted October 21, 1998