

# Overactivation of primary motor cortex is asymmetrical in hemiparkinsonian patients

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Regional cerebral blood flow (rCBF) was measured using PET and H<sub>2</sub><sup>15</sup>O in Parkinson's disease (PD) patients with predominantly right-sided akinetic-rigid symptoms and in control subjects during the execution of an externally cued motor task either with the left or the right hand. During the execution of the task with the left, non-akinetic, hand, cerebral activation in PD patients appeared similar to that of controls. Activated areas were the primary motor cortex, premotor cortex,

parietal cortex and cerebellum. When the task was executed with the right, akinetic, hand cerebral activation in PD patients differed from that of controls subjects. The most important change was a bilateral activation of the primary motor cortex. We conclude that overactivation of primary motor cortex is asymmetrical in hemiparkinsonian patients. *NeuroReport* 11:785-789 © 2000 Lippincott Williams & Wilkins.

**Key words:** Asymmetrical signs; Motor execution; Normal subjects; Parkinson's disease; PET; Primary motor cortex; rCBF

## INTRODUCTION

Parkinson's disease (PD) is characterized clinically by the association of akinesia, rigidity and resting tremor related to a dopaminergic deficiency of the nigrostriatal pathway. In the animal model of PD, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces in monkeys a degeneration of dopaminergic neurons of the substantia nigra, resulting in dysfunction of the basal ganglia circuitry [1]. This leads to a profound inhibition of the motor thalamic nuclei and subsequently an hypoactivation of motor areas connected to the thalamus via the thalamo-cortical excitatory pathway, notably the supplementary motor area (SMA).

In normal subjects PET and single photon emission computed tomography (SPECT) regional cerebral blood flow (rCBF) studies have consistently shown that the execution of a unimanual motor task requires the recruitment of several cortical and subcortical areas. These include the contralateral primary motor cortex (M1), lateral premotor cortex and SMA, dorsolateral prefrontal cortex (DLPFC), superior parietal cortex, basal ganglia and cerebellum [2,3].

Several PET and SPECT studies have similarly investigated rCBF abnormalities in PD patients during motor execution [4]. Hypoactivation is usually displayed in several frontostriatal areas, specially in the SMA and incon-

stantly in the DLPFC, anterior cingulate cortex and contralateral putamen [5,6]. SMA hypoactivation can be reversed after administration of anti-parkinsonian medication or by neurosurgical treatment [5,7-9]. On the other hand, overactivation is reported in distinct brain regions, notably the lateral premotor and parietal cortex, and the cerebellum [10,11]. Of particular interest is the ipsilateral increase of rCBF in M1 found in two SPECT studies which is thought to be secondary to levodopa-induced dyskinesias [12,13]. However these results have been obtained by comparing two groups of PD patients, levodopa-treated *vs* patients deprived of levodopa in one study, and levodopa-treated patients with or without dyskinesias in the second study. To our knowledge, no PET study has compared, in PD patients with asymmetrical motor signs, cerebral activation during a motor task performed with the more akinetic *vs* the less akinetic hand.

The present study measured rCBF changes with PET and H<sub>2</sub><sup>15</sup>O during the execution of unimanual motor task in asymmetrical PD patients with mild to moderate akinesia affecting essentially the right hemibody and sparing the left side. rCBF pattern was assessed during execution with the more akinetic versus the less akinetic hand. Results of PD patients were compared with those of healthy control subjects. The main goal of the study was to demonstrate that, in hemiparkinsonian patients, brain activation

abnormalities are depending on the hand, akinetic or not, used to perform the motor task.

## MATERIAL AND METHODS

**Subjects:** Eight right-handed PD patients were studied (mean ( $\pm$ s.d.) age  $49.4 \pm 5.3$  years, range 37–59; five males, three females; mean disease duration  $4.9 \pm 2.6$  years). Inclusion criteria were the following: (1) idiopathic PD according to the criteria of the United Kingdom Parkinson's Disease Brain Bank [14]; (2) asymmetrical parkinsonian syndrome affecting predominantly the right hemibody; (3) prominent akinetic–rigid signs without tremor. Six patients received a dopaminergic treatment and two were drug naive with further follow-up demonstrating levodopa responsiveness. Assessment of motor signs used part III of the Unified Parkinson's Disease Rating Scale (UPDRS) [15] while patients were off drug for at least 6 h (mean score  $18.7 \pm 6$ ). The degree of asymmetry of motor signs between each hemibody was defined by the hand tapping test [16], with at least a 10% right–left difference (mean difference was actually  $17.5 \pm 15.9\%$ ), and a 2-point right–left difference on item 25 (scoring 0–4) of UPDRS part III [15]. Eight age-matched healthy control subjects were also studied (mean age  $54 \pm 12.8$  years; three males, five females).

The present study was performed after approval by the Lyon University Hospitals Ethical Committee and subjects signed informed consent form according to the declaration of Helsinki.

**Activation tasks:** Subjects were scanned while executing a predefined sequential motor task. Subjects lied down on the bed of the PET scanner with their eyes closed. Three conditions were examined according to the instructions given to the subjects: execution of the task with the right hand (ER); execution of the task with the left hand (EL) and rest condition (RC). The motor task comprised a sequential movement performed with a joystick with the right or the left hand. Each of the three motor conditions was repeated once in counterbalanced order, one in the clockwise and one in the counter clockwise order. The movement in the clockwise condition consisted in moving the joystick to the right with a return to the center, then backward with a return to the center and then to the left with a return to the center. After the completion of this sequential movement subjects had to press with the index finger a button located on the joystick which produced a low tone auditory stimulus. After a random delay of  $2000 \pm 500$  ms, a high tone stimulus indicated to the subject to start again the task. This external-cued motor task was repeated in the same manner, lasting 90 s for each condition, as fast and accurately as possible. The baseline (rest) condition was designed to replicate the finger movement (button press) and auditory stimuli present in execution trials. The subject listened to the same high tone auditory stimulus. A variable period later (range 0.5–5.5 s), the lower tone stimulus was produced which indicated to the subjects to press the button situated on the joystick. The requirement for the subjects to wait attentively for the second tone during a random delay was intended to prevent an involuntary motor imagery process. This task was then repeated for 90 s, as for the other conditions. This

minimal motor task was therefore common to all the conditions.

Prior to scanning, and after general instructions were given, a few practice trials for each condition were performed to ensure that the task was properly understood.

**Scanning procedure:** The head of the subject was maintained in a fixed position using a thermoformed mask. Control of the head position throughout the examination was made by laser alignment along with reference points on the Reid's line before and after each session. The PET tomograph was a Siemens CTI HR+. Transmission data were acquired using rotating sources filled with  $^{68}\text{Ge}/^{68}\text{Ga}$ . Images were reconstructed by 3D filtered back projection (Hanning filter; cut-off frequency, 0.5 cycles/pixel), giving a transaxial resolution of 6.5 mm full width at half maximum, and displayed in a  $128 \times 128$  pixel format with 63 planes creating  $\sim 2$  mm cubic voxels. rCBF was estimated by recording the distribution of radioactivity following an i.v. injection of 10 mCi  $\text{H}_2^{15}\text{O}$  through a forearm cannula placed into the brachial vein. The integrated counts were collected for 90 s, starting 20 s after the injection. For data analysis we only considered the 60 s corresponding to the maximum radioactivity. A 10 min interval was necessary between each test condition for adequate radioactivity decay.

**PET image and statistical analysis:** Image analysis was performed in MATLAB 4.2 (math Works, Natick, MA, USA) using the software for statistical parametric mapping (SPM 96, MRC Cyclotron Unit, London, UK) [18]. Individual PET scans were oriented along the intercommissural line using an averaged image from each subject, and then transformed (normalized) into a standard stereotactic space [17]. Global differences in cerebral blood flow were covaried out for all voxels and comparisons across conditions were made using t statistics with appropriate linear contrasts, and then converted to Z-scores.

Statistical comparisons were made within each group and assessed the main effect of actual joystick movement versus rest for each hand executing the task. These comparisons were specified by appropriately weighted categorical contrasts and performed on a voxel-by-voxel basis by means of analysis of variance. This generated statistical parametric mapping (t) maps for rCBF changes associated with each comparison. For the comparison of the activation effects, the statistical parametric mapping (t) maps were subsequently transformed into statistical parametric mapping (z) maps, and the level of significance of areas of activation was assessed by the peak height of their foci. Only regional activations significant at  $p < 0.05$ , uncorrected for multiple comparisons ( $Z > 3.10$ ) were considered.

## RESULTS

**rCBF: within-group comparisons in control subjects (Table 1):** When execution of the sequential movement with the left hand was compared with rest, significant activation were seen in the right M1 and SMA, in the left lateral premotor cortex, superior (Brodmann area (BA) 7) and inferior (BA 40) parietal cortex, in the right thalamus and

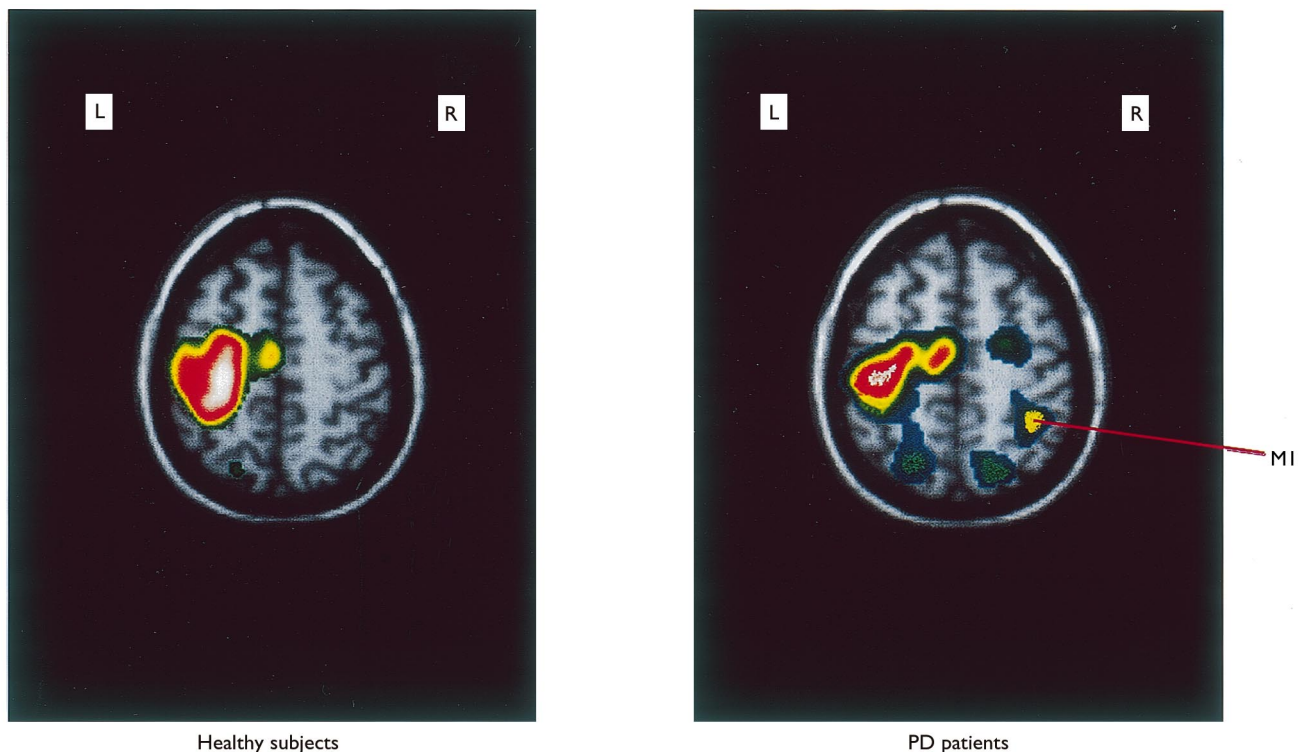
**Table 1.** Sites of activation during the actual execution of the task (Z score > 3.10).

	Activated areas	Z score	Stereotactic coordinates			
			x	y	z	
<b>Controls</b>						
Left hand	R primary motor cortex	7.66	32	-30	58	
	R SMA	6.01	6	-12	52	
	L lateral premotor cortex	4.82	-22	-10	60	
	L superior parietal lobe	4.76	-14	-60	66	
	L superior parietal lobe	4.75	-24	-64	62	
	L inferior parietal lobe	4.17	-32	-40	48	
	L inferior parietal lobe	3.99	-46	-30	32	
	L inferior parietal lobe	3.88	-36	-44	54	
	L inferior temporal gyrus	3.2	-42	-64	0	
	L cerebellar hemisphere	7.45	-18	-48	-22	
	R cerebellar hemisphere	4.91	48	-50	-36	
	Vermis	7.13	-6	-54	-6	
	R thalamus (VPL)	4.42	20	-22	10	
	Right hand	L primary motor cortex	7.68	-38	-36	64
		L SMA	5.83	-4	-14	54
		R lateral premotor cortex	3.75	24	-16	72
		L superior parietal lobe	4.95	-12	-62	66
		R superior parietal lobe	4.42	10	-70	62
L inferior parietal lobe		5.62	-42	-32	26	
R cerebellar hemisphere		7.14	22	-50	-20	
<b>PD patients</b>						
Left hand	R primary motor cortex	6.88	18	-12	62	
	L SMA	4.58	-6	-8	68	
	R SMA	4.15	10	-22	52	
	L lateral premotor cortex	5.36	-26	-10	60	
	L DLPF	3.19	-42	50	20	
	R anterior cingulate cortex	4.2	2	-2	46	
	R superior parietal lobe	6.92	18	-64	62	
	L superior parietal lobe	5.9	-18	-72	60	
	R superior parietal lobe	7.66	34	-38	66	
	L inferior parietal lobe	4.06	-22	-52	46	
	R occipital cortex	3.44	54	-68	-8	
	L cerebellar hemisphere	7.39	-18	-48	-18	
	R cerebellar hemisphere	4.8	14	-50	-44	
	Right hand	L primary motor cortex	7.55	-30	-12	62
		R primary motor cortex	4.78	24	-8	52
		L SMA	6.36	-8	-14	54
		R superior parietal lobe	6.04	16	-66	60
		L superior parietal lobe	5.92	-22	-48	68
R inferior parietal lobe		4.42	40	-46	52	
R occipital cortex		3.57	26	-64	34	
R cerebellar hemisphere		7.33	20	-54	-20	
L cerebellar hemisphere		3.86	-22	-48	-46	
Vermis		6.12	10	-52	-6	
L thalamus (VPL)	3.85	-20	-20	6		

in the cerebellum, more in the ipsilateral than the contralateral part. When execution of the sequential movement with the right hand was compared with rest, significant activation were seen in the left M1, right SMA, right and left superior parietal lobe (BA 7), left BA 40, and in the right cerebellar hemisphere (Fig. 1). The pattern of activation was very comparable to that observed in the precedent comparison.

**rCBF: within-group comparisons in PD patients (Table 1):** When execution of the sequential movement with the left non-akinetic hand was compared with rest, significant activation was seen in the right M1 and anterior cingulate cortex, bilaterally in SMA and superior (BA 7 and 5) parietal cortex, in the left lateral premotor cortex and

DLPFC, and in the cerebellar hemispheres. The pattern of activation was comparable to that observed for control subjects. When execution of the sequential movement with the right akinetic hand was compared with rest, significant activation was seen bilaterally in M1 and in the superior parietal lobe (BA 7), in the left SMA, in the right BA 40, in the left thalamus and in cerebellar hemispheres. Compared to control subjects, the main difference was the bilateral activation of M1 (Fig. 1). It is noteworthy that the maximal activation of the ipsilateral M1 was external and corresponded to the somatotopic representation of the hand. Interestingly, in contrary to the results with the left hand, activation of the DLPFC, and anterior cingulate cortex was not seen when patients executed the task with the right, akinetic, hand.



**Fig. 1.** Execution of the motor task with the right hand compared with rest condition. Statistical parametric maps (SPMs) of increased rCBF in the subtraction analysis (within-group study), showing the significantly activated areas for the control subjects group (left part) and PD patients (right part). The SPMs are displayed in the anatomical space of Talairach and Tournoux [18] as a maximum intensity projection viewed from a transverse view of the brain, superimposed on a MRI. The image plane is located 64 mm above and parallel with the AC–PC plane. In both controls and PD patients, increased rCBF is seen in the left anterior SMA and primary motor cortex. In PD patients significant activation is also disclosed in right primary motor cortex. The voxels displayed have Z values exceeding the significance threshold of 3.10 with a Bonferoni correction for multiple comparisons ( $p < 0.05$ ). L = left hemisphere; R = right hemisphere.

## DISCUSSION

**Control subjects:** The pattern of activation during motor execution appears very similar and irrespective to the hand used to complete the task. The prominent contralateral activation of M1 is a consistent finding in our study, in accordance with previous work [19].

**Parkinsonian patients:** During motor execution with the left, non-akinetic, hand, the activation pattern is very similar to that of normal subjects. In contrast, important group differences appear when the task is executed with the right, akinetic, hand. This suggests that a significant degree of akinesia is necessary to induce an abnormal pattern of cerebral activation during a motor task.

One of the most striking findings of rCBF changes during execution of the motor task with the right hand is the ipsilateral activation of M1 in PD patients. In two SPECT studies a bilateral activation of M1 during an unimanual motor task was found in PD patients [12,13]. For some patients the authors made a relationship between these hyperactivations and the presence of levodopa-induced dyskinesias. However this ipsilateral activation of M1 was also larger in non-dyskinetic patients than in controls [12]. This is also the case in our patients and could

represent a presymptomatic rCBF overactivation which is not sufficient to induce involuntary movements. A possible relation with the tremor was also raised by these authors. It should be reminded that our patients were off-drug, had no dyskinesia and no significant tremor at the time of PET scanning.

Alternatively, the greater difficulty in completing the task with the akinetic hand could also induce a more extended recruitment of cortical motor areas in order to compensate for the dysfunction of the basal ganglia motor loops as suggested in PD by recent PET studies [9,10]. Such accessory pathways linking thalamus, basal ganglia, cerebellum and cortical motor areas are well known in monkeys [20–24]. The recruitment of such accessory motor pathways has also been argued during post-stroke recovery with the activation of the ipsilateral M1 and premotor cortex resulting from the involvement of the direct corticospinal pathway [25]. The same kind of result has also been observed in healthy subjects, especially when right-handed, which showed an ipsilateral activation of M1 during the execution of a motor task with the left hand [26].

Another interesting result of our study in PD patients concerns the lack of activation of the DLPFC and anterior

cingulate cortex during execution of the task with the right akinetic hand whereas these regions are activated normally during execution of the task with the left non-akinetic hand. This is in agreement with previous PET studies and reflects the preferential deafferentation of these areas in PD, and provides another argument linking these hypoactivations to the akinesia [5]. Surprisingly, no hypoactivation of the SMA is found in our patients irrespective of the hand, akinetic or not, with which they execute the task, although this region is thought to be one of the most deafferented in PD. This finding is likely due to the mild to moderate severity of motor signs in our patients.

## CONCLUSION

The current study shows that abnormalities of cerebral activation in PD are strongly dependent on the presence of akinesia. In particular, ipsilateral activation of M1 is observed only when the akinetic hand is used. We therefore suggest that ipsilateral M1 can be recruited to compensate for impairment in the principal motor circuits in PD.

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