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Mechanisms underlying gait disturbance in Parkinson's disease

A single photon emission computed tomography study

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Summary

Single photon emission computed tomography was used to evaluate regional cerebral blood flow changes during gait on a treadmill in 10 patients with Parkinson's disease and 10 age-matched controls. The subjects were injected with [^{99m}Tc]hexamethyl-propyleneamine oxime twice: while walking on the treadmill, which moved at a steady speed, and while lying on a bed with their eyes open. On the treadmill, all subjects walked at the same speed with their preferred stride length. The patients showed typical hypokinetic gait with higher cadence and smaller stride length than the controls. In the controls, a gait-induced increase in brain activity was observed in the medial and lateral premotor areas, primary sensorimotor areas, anterior cingulate contex, superior parietal cortex, visual cortex, dorsal brainstem, basal ganglia and cerebellum. The Parkinson's disease patients revealed relative underactivation in the left medial frontal area, right precuneus and left cerebellar hemisphere, whereas they showed relative overactivity in the left temporal cortex, right insula, left cingulate cortex and cerebellar vermis. This is the first experimental study showing that the dorsal brainstem, which corresponds to the brainstem locomotor region in experimental animals, is active during human bipedal gait. The reduced brain activity in the medial frontal motor areas is a basic abnormality in motor performance in Parkinson's disease. The underactivity in the left cerebellar hemisphere, in contrast to the overactivity in the vermis, could be associated with a loss of lateral gravity shift in parkinsonian gait.

Keywords: Parkinson's disease; gait disturbance; activation study; single photon emission computed tomography (SPECT); locomotor centre

Abbreviations: BA = Brodmann area; FWHM = full width at half maximum; rCBF = regional cerebral blood flow; SMA = supplementary motor area; SPECT = single photon emission computed tomography; SPM = statistical parametric map; [^{99m}Tc]HMPAO = [^{99m}Tc]hexamethyl-propyleneamine oxime

Introduction

Gait disturbance is one of the cardinal symptoms in patients with Parkinson's disease. Typically, Parkinson's disease patients walk slowly with shuffling and dragging steps, diminished arm swing and flexed forward posture. The progressive gait disturbance combined with postural instability finally deprives the patients of locomotor ability and yields medical as well as social problems.

A basic hypothesis to explain hypokinesia in Parkinson's disease is that, due to overactivity of the inhibitory projections from the basal ganglia to the thalamus, the thalamocortical projections fail to facilitate the motor-related cortical areas such as the supplementary motor areas (SMA), cingulate motor areas and primary motor areas (Alexander and Crutcher, 1990; DeLong, 1990; Rascol *et al*., 1992; Playford *et al*., 1992). By contrast, the lateral premotor cortex, parietal cortex and cerebellum were reported to be overactive during motor performance in Parkinson's disease, especially when movement was externally triggered (Rascol *et al*., 1997; Samuel *et al*., 1997a; Hanakawa *et al*., 1999). However, uncertainty remains as to whether these abnormalities also underlie hypokinetic gait in Parkinson's disease, because knowledge about the pathophysiology of hypokinesia has

been obtained mostly from studies on upper limb movements (Playford *et al*., 1992; Rascol *et al*., 1992, 1997; Samuel *et al*., 1997*a*). Moreover, little is known about the higher control mechanisms of human bipedal gait (Nutt *et al*., 1993). Although gait seems to be a highly organized, complex motor process that requires integration of the central nervous system, abundant clues suggest that basic neural substrates for locomotion exist below the diencephalon, at least in quadruped animals. For example, decerebrate animals can be induced to walk on a treadmill by electrical stimulation of the dorsal brainstem (Eidelberg *et al*., 1981; Garcia-Rill, 1986; Mori *et al*., 1989). This area is called the brainstem locomotor region, and its presence in humans remains unclear (Nutt *et al*., 1993).

In brain activation studies by functional MRI and $H_2{}^{15}O$-PET, every effort was made to limit subjects' head motion, since these techniques need functional images to be acquired at the actual time of task performance and small head motion during data acquisition would critically compromise images. Thus, these techniques cannot be applied to examining tasks accompanied by gross body movements including gait. By contrast, single photon emission computed tomography (SPECT) employing the split-dose [^{99m}Tc]hexamethyl-propyleneamine oxime ([^{99m}Tc]HMPAO) method (Pantano *et al*., 1992; Oku *et al*., 1994; Marshall *et al*., 1997) enables us to study human brain function even when subjects are moving freely during task performance (Fukuyama *et al*., 1996, 1997*a*). This is because time for the task performance and time for the image acquisition can be separated in the SPECT activation study as described below. After intravenous injection, [^{99m}Tc]HMPAO is rapidly distributed to the brain in proportion to regional cerebral blood flow (rCBF), is trapped in the tissue compartment within a few minutes, and remains stable for hours (Andersen *et al*., 1988). Therefore, we can obtain 'snapshot' brain perfusion images representing brain activity during a period of several minutes immediately after the tracer injection. By using this method, we have previously disclosed activation of the SMA, visual cortex and cerebellum during voluntary gait on a walkway in young adults (Fukuyama *et al*., 1997*a*). Our preliminary study on voluntary walk in Parkinson's disease patients showed prominent activation in the cerebellar vermis in contrast to poor activation in the SMA (Fukuyama *et al*., 1997*b*).

In the present study, we compared brain activity changes induced by gait on a treadmill in Parkinson's disease patients with changes in age-matched controls, using SPECT. Part of this study has been reported in abstract form (Hanakawa *et al*., 1998).

Methods

Subjects

Ten patients with Parkinson's disease (six men, four women) participated in this study. All of the patients fulfilled the UK Parkinson's Disease Society Brain Bank criteria for idiopathic Parkinson's disease (Hughes *et al*., 1992). Patients manifesting severe orthostatic hypotension, dementia or visual hallucination were excluded beforehand. Their age was 67 ± 4.2 years (mean ± SD), height 160 ± 8.1 cm and weight 55 ± 6.8 kg. Initial symptoms were tremor of the right hand in four patients, tremor of the left hand in three, clumsiness of the left hand in two and loss of arm swing on the left in one. The mean disease duration after clinical onset was 6.5 ± 4.4 years. All patients were withheld from their antiparkinsonian medications for at least 12 h before the study. The patients were assessed using the modified Hoehn and Yahr score and the Unified Parkinson's Disease Rating Scale (Fahn *et al*., 1987). Profiles of the patients are presented in Table 1. Ten volunteer subjects, matched with the patients in age (67 ± 4.0 years), sex (six men, four women), height (160 ± 7.3 cm) and weight (57 ± 7.6 kg), were studied as a control group. The control subjects were neurologically normal without previous history of neuropsychiatric disorders. All subjects gave written informed consent according to the study protocol approved by the Committee of Medical Ethics, Graduate School of Medicine, Kyoto University.

Experimental design

The rest and walk conditions were examined for each subject. In the rest condition, the subjects lay supine on a bed and watched a white ceiling for 5 min. They were asked to stay still and to clear their minds during the rest. In the walk condition, all the subjects walked on a treadmill moving at ~13 m/min for 5 min. This walking speed was adopted so that they could walk at the predetermined speed after a short practice, and was based on data from a preliminary investigation in three moderately hypokinetic Parkinson's disease patients. They were instructed to walk with their preferred stride length to keep the walking speed. During the walking task, the subjects walked with their bare feet on the non-slippery, artificial rubber floor of the treadmill and were allowed to hold the side-bars gently for safety. To control visual inputs between the task conditions, they were asked to keep watching a white wall in front of them during the walk so that visual information from the moving treadmill was not available. Note that the subjects had to determine freely and internally either their cadence or their stride length in this experimental condition.

Performance evaluation

Just before the SPECT study, the subjects were evaluated for their locomotor ability with the step–seconds product on a walkway (Webster, 1968). In the walk condition, gait performance of each subject was recorded on videotape for subsequent review. Cadence (steps/min) was measured for 2 min, avoiding the beginning and end of the walk. Stride length for each subject was calculated by dividing the walking speed by half of the mean cadence. These walking parameters

Table 1 *Subject profiles*

Subject	Age (years)	Sex	Height (cm)	Weight (kg)	Duration (years)	H–Y score	UPDRS motor	L-Dopa + DCI (mg)	DA agonist (mg)
Parkinson's disease patients									
1	68	M	165	61	7	3	47	800	
2	64	F	154	56	2	2.5	34	400	
3	63	M	164	57	3	1	20	300	
4	75	M	173	58	3.5	2.5	29	400	
5	61	M	168	62	8	2.5	27	400	Bro 7.5
6	64	M	160	61	1	2	33	200	
7	69	M	158	52	9	3	39	400	Bro 5
8	67	F	151	40	11	2.5	29	600	
9	71	F	147	49	5	2	41	400	
10	65	F	155	58	15	4	47	300	Per 0.1
Mean	67		160	55	6.5	2.5	35	420	
SD	4.2		8.1	6.8	4.4	0.8	8.8	170	
Control subjects									
Mean	67		160	57					
SD	4.0		7.3	7.6					

H–Y = modified Hoehn and Yahr score; UPDRS motor = motor examination section (items 18–31, full score 108) of the Unified Parkinson's Disease Rating Scale; DCI, decarboxylase inhibitors of aromatic L-amino acids (benserazide or carbidopa); DA agonist = dopamine agonist; Bro = bromocriptine; Per = pergolide.

were compared between the two groups by using non-parametric statistics. Blood pressure and pulse rate, measured before and after each task, were compared within each group by two-way analysis of variance.

Image acquisition

The subjects underwent two consecutive SPECT scans, one for each condition. The order of the task conditions was counterbalanced across subjects within each group to reduce the sequence effects. When the walk was studied first, actual procedures were as follows. Thirty seconds after walking began, 259 MBq of [^{99m}Tc]HMPAO was administered through a venous line fixed to the subject's left forearm. Thus, the maintenance of walking on the treadmill, but not its initiation, was evaluated. The subjects kept walking for 4.5 min after the tracer injection, and then they lay on a scanner bed. The subject's head was positioned under the guidance of a three-dimensional laser-reference system and was immobilized with a comfortable restraint device. The first scan was performed over a period of 20 min using a triple-head SPECT scanner (PRISM3000; Picker, Cleveland, Ohio, USA) with high-resolution fan-beam collimators, which generated a low-dose image. The axial field of view of the cameras was 24 cm and the rotation radius was set ~13 cm from the centre of rotation. For the subsequent rest condition, the subject remained supine on the scanner bed and received another 518 MBq of [^{99m}Tc]HMPAO 30 s after the beginning of the rest condition. After the head position had been adjusted, the second scan was performed for 20 min, which produced a high-dose image. Inter-scan interval was ~45 min. Since the dose of the radioactive tracer for the second administration was twice that for the first, the same scanning time for both scans was adopted to reduce incidental errors associated with comparison between the low-dose and high-dose images (Oku *et al*., 1994). [^{99m}Tc]HMPAO was used within 10 min after preparation. When the order was reversed and the rest condition was examined first, the subjects received the first low dose of [^{99m}Tc]HMPAO on the scanner bed. Thereafter they walked on the treadmill and received the second injection of [^{99m}Tc]HMPAO, at a dose twice that of the first.

The images were reconstructed on a workstation (ODYSSEY; Picker). Projection data, collected in a 128×128 matrix, were prefiltered with a Butterworth filter with order 4 and a cutoff frequency of 0.35 cycles/pixel. Transaxial images approximately parallel to the intercommissural line were reconstructed with a Ramp back-projection filter. The post-reconstruction attenuation correction was applied (attenuation coefficient 0.09 cm^{-1}). The reconstruction yielded $2 \times 2 \times 2.33$ mm voxels with a 128×128 matrix and 64 slices. In-plane spatial resolution was 7.8 mm full width at half maximum (FWHM) in the centre of view.

Image analysis

Using a SPARCstation 20 workstation (Sun Microsystems, Mountain View, Calif., USA), we analysed the SPECT images by statistical parametric mapping (SPM96 software; Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK) implemented with MATLAB (MathWorks Inc., Sherborn, Mass., USA). The low-dose image from each subject was realigned using the corresponding high-dose image as a reference to minimize the effect of reposition (Friston *et al*., 1995*a*). At the same time, a mean image of the high- and low-dose images

was generated. After the realignment, both images were transformed to fit the standard brain [International Consortium of Brain Mapping space (Evans *et al*., 1993)] using the mean image as a reference (Friston *et al*., 1995*a*). As a result, each image was resampled into $2 \times 2 \times 2$ mm with respect to the *x* (right–left), *y* (anterior–posterior) and *z* (superior–inferior) coordinates, respectively. These spatially normalized images were then smoothed with an isotropic Gaussian kernel (FWHM = 15 mm) to increase the signal-to-noise ratio and to allow for variation in the normal gyral anatomy. To test the hypothesis about regionally specific effects of task conditions, a general linear model was employed at each and every voxel (Friston *et al*., 1995*b*). The pixel values were normalized by scaling the activity in each pixel proportional to the global activity (proportional scaling) to stabilize the variance related to the substantially different global activity between the high- and low-dose images. In this process, the mean global activity of each scan was adjusted to 50. Planned comparisons between experimental conditions were performed using *t* statistics for each voxel. These analyses generated statistical parametric maps of the *t* statistic (SPM{*t*}), which were subsequently converted to unit normal distribution (SPM{Z}). The estimated final spatial resolution was $16 \times 16 \times 19$ mm (FWHM).

Within-group rCBF analysis

The brain areas showing a significant increase in activity induced by the walk compared with the rest were explored for each group. The locations of activated brain areas were identified and listed according to stereotaxic coordinates and visual inspection on the structural MRI provided by SPM96 (Talairach and Tournoux, 1988; Evans *et al*., 1993). The results were also displayed as three orthogonal projections of SPM{*Z*}. In the within-group comparisons, the statistical threshold was set at $Z > 3.09$ without correction for multiple comparisons, corresponding to $P < 0.001$ at each voxel. Gait-induced deactivation was also evaluated within each group ($P < 0.001$).

Between-group rCBF analysis

First, to establish a difference in baseline perfusion between the patients and the controls, we compared rCBF at rest between the two groups by using the SPM96 routine 'compare-groups: 1 scan per subject'. Secondly, we tested whether any brain areas in the Parkinson's disease patients might show a lower degree of gait-induced activation compared with corresponding areas in the controls: (walk minus rest in controls) minus (walk minus rest in Parkinson's disease). This analysis by itself can reflect 'gait-induced activation in the controls' or 'gait-induced deactivation in the Parkinson's disease patients', or both. To focus on the regions relevant to gait, this interaction analysis was performed for the limited voxels showing a gait-related increase in brain activity in the controls (inclusion criterion: $Z > 1.64$ uncorrected). Thirdly, we tested whether any brain areas in the Parkinson's disease patients might show a higher degree of gait-induced activation compared with corresponding areas in the controls: (walk minus rest in Parkinson's disease) minus (walk minus rest in controls). This analysis was performed in the limited voxels showing a gait-related increase in brain activity in the Parkinson's disease patients ($Z > 1.64$ uncorrected).

In these between-group comparisons, the statistical threshold was set at $Z > 3.09$ without correction for multiple comparisons, corresponding to $P < 0.001$ at each voxel. This threshold is regarded as sufficiently conservative to protect against false-positive results in PET analysis (Bailey *et al*., 1991). However, considering the relatively low sensitivity of SPECT without repeated measures, this threshold could lead to false-negative results in SPECT studies. In the present study, therefore, a brain activity increase of $Z > 2.33$ without correction, corresponding to $P < 0.01$ at each voxel, was interpreted as representing a trend towards activation. The regions showing the trend were considered to be meaningful only when our pre-existing hypotheses included those particular regions. In the analysis for (walk minus rest in controls) minus (walk minus rest in Parkinson's disease), we tested a hypothesis based on previous studies (Playford *et al*., 1992; Rascol *et al*., 1992; Fukuyama *et al*., 1997*b*), that the medial non-primary motor areas, dorsolateral prefrontal areas and putamen are underactive during gait in Parkinson's disease patients. Although we considered that the present treadmill-walk task rather belonged to the internally determined motor task, as mentioned above, it was also possible that the treadmill gave some sensory cues during gait. If this were true, the lateral premotor cortex, parietal cortex and cerebellum, which seem to underlie externally cued motor tasks, might be overactive during gait in Parkinson's disease patients (Samuel *et al*., 1997*a*; Hanakawa *et al*., 1999). Additionally, even in the internally determined task Parkinson's disease patients are reported to show compensatory overactivity in the cerebellum (Rascol *et al*., 1997). Thus, in (walk minus rest in Parkinson's disease) minus (walk minus rest in controls) we tested the hypothesis that parkinsonian gait on the treadmill is accompanied by overactivity in the lateral premotor cortex, parietal cortex and cerebellum, particularly the cerebellar vermis (Fukuyama *et al*., 1997*b*).

Results

Performance evaluation

The step–seconds product was significantly greater in the patients than in the controls (Mann–Whitney *U* test, $P < 0.001$), meaning that the present Parkinson's disease patients manifested a slow and shuffling gait on the walkway (Table 2). All subjects completed both tasks. On the treadmill, all the control subjects walked quite easily whereas most of the Parkinson's disease patients showed typical shuffling and

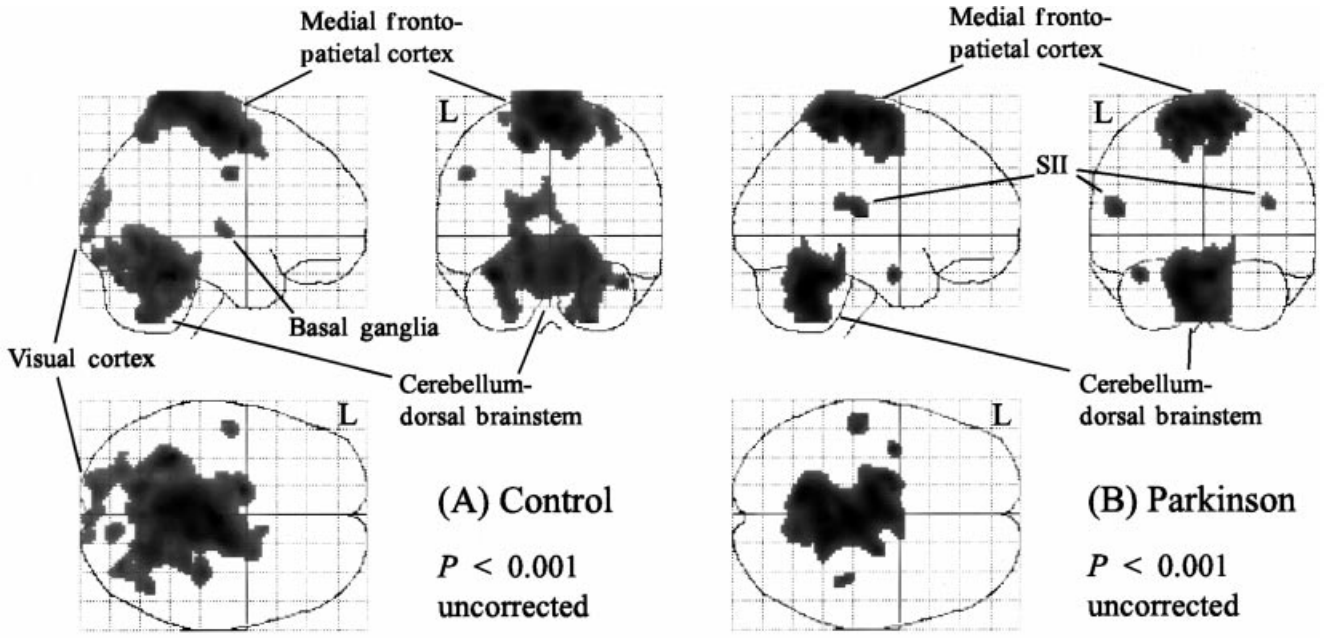

Fig. 1 Three orthogonal projections of gait-induced brain activity in control subjects (**A**) and Parkinson's disease patients (**B**). In both groups, the statistical threshold was set at $P < 0.001$ at each voxel level. The areas showing significant gait-induced activation are basically similar in the two groups. In the control group, however, the activation of the medial frontal lobe extends more rostrally, and that of infratentorial structures more widely than in the Parkinson's disease patients. See Table 3 for the anatomical locations and *Z*-score of each activation.

dragging steps with flexed forward posture. The patients showed neither freezing nor festination during performance of the task, although two patients had to be encouraged to keep up the pace. As far as we could discern, no patients manifested other symptoms that may have been associated with the task, such as excessive anxiety, pain and an increase in tremor. The cadence during treadmill-walking was significantly higher, and stride length was therefore shorter, in the Parkinson's disease patients than in the controls (Mann–Whitney *U* test, $P < 0.05$) (Table 2). Within each group, there was no significant difference in either mean blood pressure or pulse rate before and after each task. Therefore, orthostatic- or exercise-induced haemodynamic changes were less likely to affect the brain perfusion.

Table 2 *Step–seconds product for walkway and walking parameters on treadmill*

	Step–seconds product	Cadence (/min)	Stride length (m)
Parkinson' disease	143 ± 38**	103 ± 32.2*	0.28 ± 0.08*
Controls	82 ± 18	71 ± 16.8	0.40 ± 0.10

We measured the time needed for each subject to rise from a chair, walk 4.5 m, turn around and return to the chair. The time in seconds was multiplied by the number of steps taken with the right foot, thus providing a step–seconds product (Webster, 1968). The walking parameters were obtained during walking on the treadmill, moving at a steady speed (~13 m/min). The walking speed was divided by half of the cadence, giving the stride length for each subject. Cadence was significantly higher, and therefore stride length shorter, in patients with Parkinson's disease than in control subjects. $**P < 0.001$, $*P < 0.05$ (Mann–Whitney *U* test).

Within-group rCBF analysis: activation induced by treadmill-walk

In the controls, the walk-induced brain activation was mainly observed as two large clusters (Fig. 1A and Table 3). The medial frontoparietal activation included the primary sensory and motor areas [Brodmann areas (BA) 1, 2, 3 and 4], corresponding to the lower limbs and trunk representations, the SMA (BA 6), the lateral premotor cortex (BA 6), the cingulate cortex (BA 24), the superior parietal lobule (BA 5 and 7) and the precuneus (BA 7), bilaterally. The infratentorial activation included the dorsal brainstem and the anterior lobe of the cerebellar hemispheres as well as the vermis. As for the brainstem activation, there was a distinct local peak in the right dorsal midbrain whereas both peaks of the bilateral pontine activation lay near the dorsal edge, which could be somewhat affected by the adjoining cerebellar activation. However, the pontine activation was not solely explained by the partial volume effects since both peaks gave a higher *Z* score than most of the other activations in the cluster. Other activated areas consisted of the visual cortex (BA 17 and 18), the posterior part of the left basal ganglia and a region on the left precentral gyrus. The left precentral activation, consistent with hand representation of the primary motor areas, may have been due to the fact that the subjects grasped the side-bar of the treadmill during the walk. On the other hand, a significant gait-induced deactivation was observed

Table 3 *Areas significantly activated during walk compared with rest*

	Size (*k*)	Location (functional area; Brodmann area)	*Z* score	Coordinates		
				x	*y*	*z*
Control subjects						
1	6543	R medial frontal gyrus (SMA; 6)	5.62	2	–20	68
		L paracentral lobule (SI-MI; 1, 2, 3, 4)	5.21	–4	–40	69
		L medial frontal gyrus (SMA; 6)	5.08	–14	–2	56
		R paracentral lobule (SI-MI; 1, 2, 3, 4)	4.94	10	–32	78
		Precuneus (7)	4.22	0	–62	60
		R middle frontal gyrus (PMC; 6)	3.97	22	4	62
		R anterior cingulate gyrus (24)	3.60	10	10	48
		L superior parietal lobule (5, 7)	3.45	–28	–50	70
2	7311	L cerebellar hemisphere	5.26	–34	–44	–22
		L dorsal pons	4.65	–12	–42	–20
		R dorsal pons	4.52	6	–44	–22
		R cerebellar hemisphere	4.42	22	–56	–12
		Cerebellar vermis	3.84	0	–66	–24
		R dorsal midbrain	3.59	26	–44	–40
3	453	L cuneus (17, 18)	4.08	–12	–90	16
		R cuneus (17, 18)	3.45	4	–96	12
4	60	L precentral gyrus (4, 6)	4.03	–50	–8	36
5	57	L posterior basal ganglia	3.83	–20	–12	4
Parkinson's disease patients						
1	4774	R paracentral lobule (SI-MI; 1, 2, 3, 4)	5.01	2	–30	70
		L precentral gyrus (SI-MI; 1, 2, 3, 4)	4.89	–10	–19	72
		R superior parietal lobule (5, 7)	4.75	12	–44	74
		L superior frontal gyrus (PMC; 6)	4.51	–20	–6	68
		L precuneus (7)	4.38	–14	–46	64
		R superior frontal gyrus (PMC; 6)	4.35	22	–12	66
		L medial frontal gyrus (SMA; 6)	4.25	–14	–4	56
		R cingulate gyrus (24)	3.58	8	0	54
		L cingulate gyrus (23)	3.14	–14	–20	50
2	3822	R dorsal pons	4.92	4	–46	–22
		Cerebellar vermis	4.92	–12	–58	–30
			3.70	6	–60	–36
		R dorsal midbrain	3.69	2	–34	–12
3	50	L middle temporal gyrus (21)	4.44	–38	–4	–22
4	118	L inferior parietal cortex (40; SII)	4.12	–50	–26	16
5	52	R inferior parietal cortex (40; SII)	3.76	38	–32	20

The table shows stereotaxic coordinates (Evans *et al*., 1993) and locations of the activated regions, each of which had a local peak *Z* score within the clusters. *k* = number of activated voxels; SMA = supplementary motor area; PMC = lateral premotor cortex; SI-MI = primary sensory and motor areas; SII = second somatosensory area

only in the left prefrontal area [(*x*, *y*, *z*) = (–44, 34, 34); *Z* = 4.45; BA 9].

In the Parkinson's disease patients, the walk-induced activation also appeared as two separate clusters consisting of the medial frontoparietal region and the infratentorial region (Fig. 1B and Table 3). The medial frontoparietal activation in the Parkinson's disease patients included the bilateral primary sensory and motor areas (BA 1, 2, 3 and 4), SMA (BA 6), lateral premotor cortex (BA 6), cingulate cortex (BA 24 and 23), superior parietal cortex (BA 5 and 7) and precuneus (BA 7). Within the infratentorial cluster of activation, there were local activation peaks in the right dorsal pons as well as in the right midbrain. The cerebellar activation was almost confined to the vermis. Other gait-induced activations concerned a region in the left temporal lobe (BA 21) and bilateral regions on the superior bank of the sylvian fissure, corresponding to the second somatosensory areas (BA 40). No area was significantly deactivated during gait compared with rest in the Parkinson's disease patients.

Between-group rCBF analysis: difference in baseline brain perfusion

By comparing rCBF during rest between the two groups, the Parkinson's disease patients showed significantly reduced baseline perfusion in the parieto-occipital areas, including

Table 4 *Areas where baseline brain perfusion was significantly lower in Parkinson's disease patients than in controls*

	Size (*k*)	Location (Brodmann area)	*Z* score	Coordinates		
				x	*y*	*z*
1	2094	R cuneus (18)	4.22	6	–76	24
		L superior parietal lobule (7)	3.87	–14	–76	56
		L cuneus (18)	3.74	–4	–78	24
2	89	R superior frontal gyrus (8)	3.43	18	38	54
3	82	L precuneus (7)	3.21	–14	–40	54

k = *number of activated voxels.*

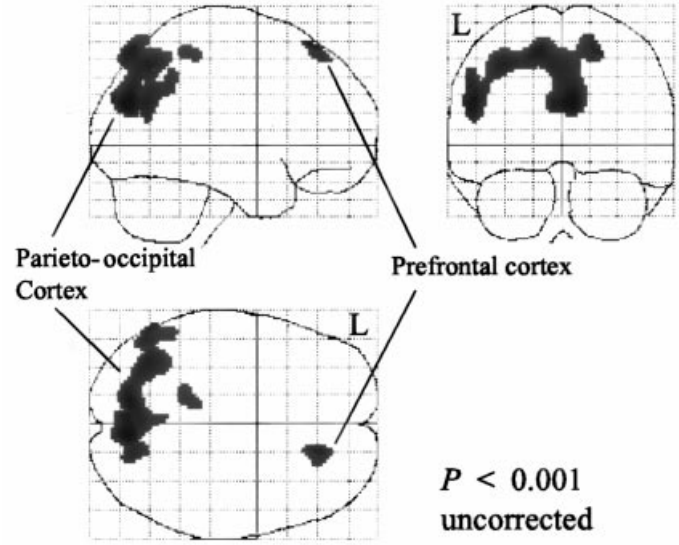

Fig. 2 Baseline hypoperfusion in the Parkinson's disease patients. Three orthogonal projections show the area where the Parkinson's disease patients had a significantly lower rCBF than the controls during rest ($P < 0.001$ at each voxel level). The areas include the parieto-occipital cortex and right prefrontal cortex (see Table 4).

the bilateral cuneus (BA 18), left superior parietal lobule (BA 7) and left precuneus (BA 7), and in the left prefrontal cortex (BA 8) (Fig. 2 and Table 4). Compared with the controls, in the Parkinson's disease patients no brain areas showed significantly higher relative rCBF.

Between-group rCBF analysis: difference in gait-induced activation

When the gait-induced activation was compared between the groups, the Parkinson's disease patients showed a significant underactivation in the right precuneus and in the left cerebellar hemisphere ($P < 0.001$). In the hypothesized areas, the left frontal region, a rostral part of the medial BA 6, showed a trend to be underactive ($P < 0.01$) in the Parkinson's disease patients (Fig. 3A and Table 5A). The left putamen also showed relative underactivity ($Z = 2.06$) in the patients, but it did not reach the criterion defining the trend towards activation.

Conversely, the Parkinson's disease patients had a greater degree of walk-induced activation relative to the controls in the left middle temporal cortex (BA 21), left cingulate cortex (BA 31) and right insula ($P < 0.001$). Among the hypothesized areas, two regions in the cerebellar vermis tended to be overactive during gait performance in the patients relative to the controls (Fig. 3B and Table 5B).

Discussion

Parkinsonian gait on treadmill

In this study, the treadmill was used to examine gait-induced rCBF changes for the following reasons: to control walking speed between the groups, to eliminate the influence of confounding factors such as a turning and a visual motion, and to allow the accurate administration of radioactive tracers during gait. One concern regarding the use of the treadmill may be whether Parkinson's disease patients show 'true' parkinsonian gait on the treadmill. In the present study, however, we consider that the basic abnormality underlying parkinsonian gait was reproduced on the treadmill. First, we observed typical parkinsonian gait on the treadmill, which was supported by the fact that the present Parkinson's disease patients had significantly higher cadence and shorter stride length than the controls. This is probably because the subjects had to determine internally either cadence or stride length, even though the walking speed was regulated. Parkinsonian gait is known to be characterized by high cadence and short stride length when walking speed is controlled (Wall and Turnbull, 1992; Morris *et al*., 1994). Secondly, sensory inputs specific to the treadmill walk might be confounding factors in the assessment of gait-induced brain activity, but they are less likely to have improved parkinsonian gait, at least to an extent as much as that of the well-known paradoxical phenomenon (i.e. that lines transversely oriented to walking direction markedly improve gait disturbance in Parkinson's disease) (Martin, 1967). Proprioceptive inputs during gait are considered to be comparable on the treadmill and the

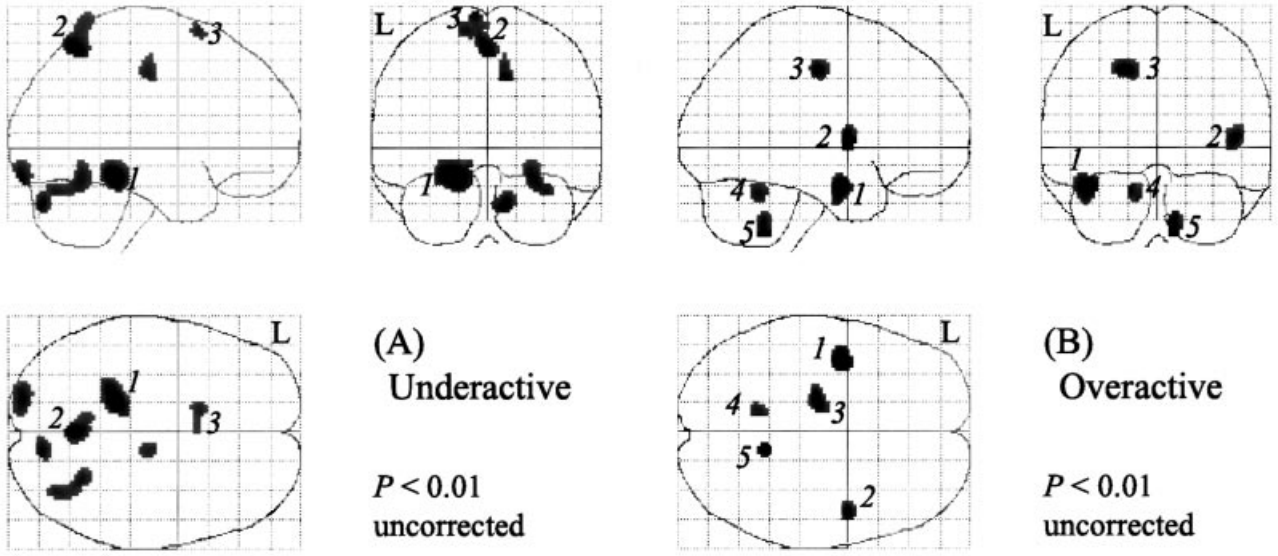

Fig. 3 Relative underactivity (**A**) and overactivity (**B**) induced by the treadmill walk in Parkinson's disease patients. In both **A** and **B**, the threshold was set at $P < 0.01$ at each voxel level for display purpose. The 'blobs' with numerals are either the areas showing a significant difference ($P < 0.001$) or those showing a moderate difference ($P < 0.01$) in the hypothesized areas. The region numbers in **A** and **B** correspond to the numbers in the leftmost column of Table 5A and B, respectively. In **A**, relative underactivity in Parkinson's disease includes the left cerebellar hemisphere (1) and precuneus (2) ($P < 0.001$), and the left medial frontal region (3) ($P < 0.01$) corresponding to the presupplementary motor areas. The four blobs without numerals are areas that showed a moderate difference ($P < 0.01$) but that are outside the pre-existing hypothesis (left visual cortex, right cerebellar hemisphere, right cingulate cortex). In **B**, relative overactivity in Parkinson's disease was found in the left middle temporal gyrus (1), right insula (2), left cingulate cortex (3) ($P < 0.001$) and cerebellar vermis (4 and 5) ($P < 0.01$).

Table 5 *Areas where gait-induced activation was significantly different between Parkinson's disease patients and controls*

	Size (*k*)	Location (functional area; Brodmann area	*Z* score	Coordinates			Change in controls*	Change in PD patients*
				x	*y*	*z*		
(A) Underactivation in Parkinson's disease patients								
1	397	L cerebellum	3.70	–16	–36	–16	6.82%	–0.21%
2	196	precuneus (7)	3.32	–2	–64	60	1.29%	–1.58%
3	54	L superior frontal gyrus (6)	2.68	–14	14	68	2.27%	–1.40%
		L medial frontal gyrus (SMA; 6)	2.42	0	10	72	3.45%	–0.50%
(B) Overactivation in Parkinson's disease patients								
1	177	L middle temporal gyrus (21)	3.55	–40	–4	–22	–0.64%	4.07%
2	85	R insula	3.21	48	0	6	0.74%	3.76%
3	125	L cingulate gyrus (24)	3.18	–18	–18	46	–0.59%	5.71%
4	69	Cerebellar vermis	2.81	12	–48	–42	4.04%	8.48%
5	55	Cerebellar vermis	2.70	–12	–52	–26	0.74%	4.11%

The table shows the areas in which there was significant difference in gait-induced activation between the groups ($P < 0.001$) or those with a trend ($P < 0.01$) in the hypothesized area. Numbers in the leftmost column of (**A**) and (**B**) correspond to the region numbers in parts A and B, respectively in Fig. 3. PD = Parkinson's disease; SMA = supplementary motor area; k = number of activated voxels. *Mean brain activity increases at the representative voxel in each region.

walkway while locomotion remains in pace, though this is not the case for gait initiation; this is an interesting issue but one that is beyond the scope of the present study. In addition, the subjects were unlikely to have made active use of visual feedback during the treadmill walk, because they were instructed to keep watching the wall and not the treadmill itself. Moreover, we have already confirmed that special visual cues normalize the above-mentioned gait abnormality during treadmill-walking in Parkinson's disease patients (Hanakawa *et al.*, 1999). Obviously, however, an interpretation of the present findings is limited, in that the present study examined not a purely

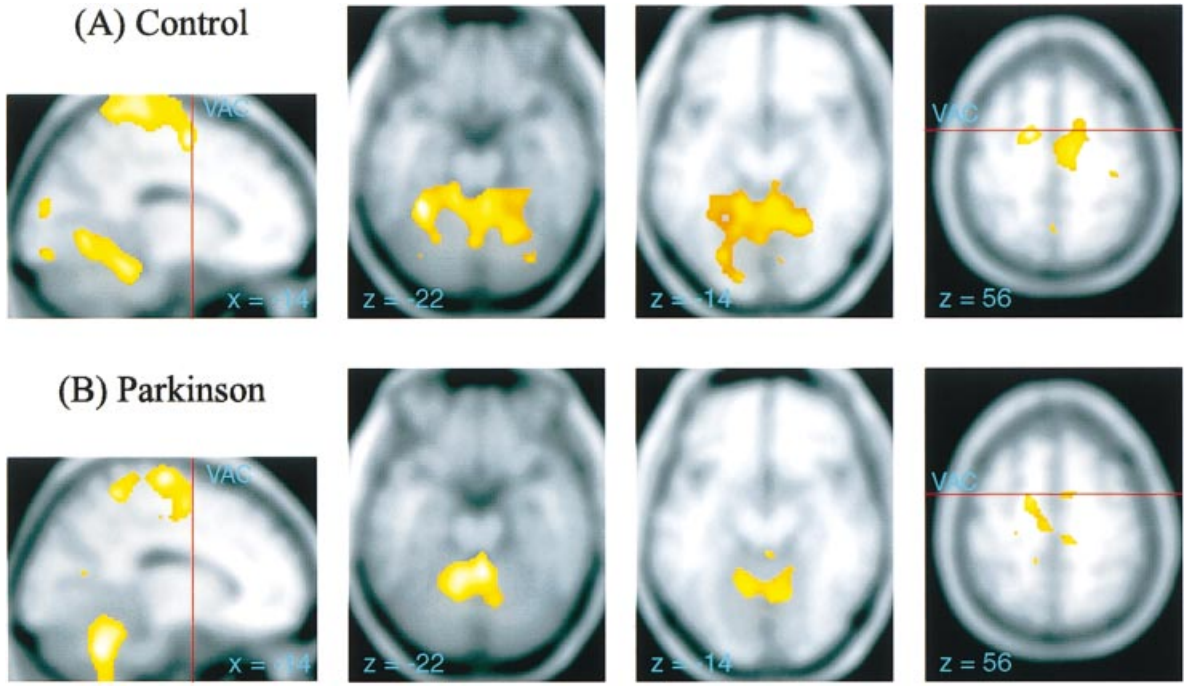

Fig. 4 Gait-induced activation in the controls (**A**) and in the Parkinson's disease patients (**B**). Significantly activated areas ($P < 0.001$) during walking were superimposed on the standard T_1-weighted structural MRI. Sagittal ($x = -14$) and horizontal ($z = -22, -14$ and 56) sections are shown. The dorsal brainstem was activated during gait in both groups. The cerebellar activation is wider in the controls than in the Parkinson's disease patients. VAC = vertical orientation line perpendicular to the anterior commissure–posterior commissure line, drawn through the ventricular margin of the anterior commissure.

spontaneous walk but forced locomotion on the treadmill, which might have altered several psycho-physiological factors, e.g. an attention level.

Baseline brain perfusion in Parkinson's disease patients

The Parkinson's disease patients showed a reduction in [^{99m}Tc]HMPAO uptake in the parieto-occipital areas during rest, as reported previously (Markus *et al*., 1994). Since the subjects kept their eyes open during the rest, this might reflect possible involvement of the retina in Parkinson's disease (Bodis-Wollner, 1990). Otherwise, the present patients might have been affected by cortical Lewy body pathology, which has been reported frequently to involve clinically diagnosed idiopathic Parkinson's disease (Hughes *et al*., 1992). This is implicated by the fact that the hypoperfusion pattern in the present patients resembles the hypometabolic pattern seen in patients with dementia with Lewy bodies (Albin *et al*., 1996).

Neural substrates underlying locomotion on treadmill

In addition to activation of the SMA, visual cortex and cerebellar activation during voluntary gait in young adults (Fukuyama *et al*., 1997*a*), the present elderly subjects also showed gait-induced activation in the lateral premotor cortex, cingulate cortex, basal ganglia and dorsal brainstem. In the Parkinson's disease patients, similar brain structures were activated by the treadmill walk. One explanation for this extensive gait-induced activation in elderly subjects could be that they have to recruit wider brain areas relative to young subjects, possibly to compensate for the ageing-related decline in musculoskeletal activity. Alternatively, the treadmill walk may have some advantages in controlling the experimental conditions, but at the same time possible treadmill-specific factors might have contributed to the additional activation detected. Among other factors, however, a refinement in methods of imaging and analysis seems to have played a substantial role here. In addition to these limitations in the interpretation, it should be noted that the present findings include not only the brain activity specific to locomotion but also activity for lower limb movements and for standing.

Dorsal brainstem

In the dorsal brainstem, the control subjects as well as the Parkinson's disease patients showed distinct activation peaks, although they were included within the large clusters (Fig. 4). Since the micturition-induced pontine activation was detected by our previous SPECT activation study (Fukuyama *et al*., 1996), it would be possible for SPECT to find brainstem activation despite the relatively low spatial resolution. Several lines of evidence indicate that part of the dorsal brainstem plays a crucial role in locomotion in quadruped animals (Eidelberg *et al*., 1981; Garcia-Rill, 1986; Mori *et al*., 1989). Taken together with the few clinical reports that have

described gait disturbance due to a lesion involving the pontomesencephalic junction (Caplan and Goodwin, 1982; Masdeu *et al*., 1994), the present study indicates that a part of the dorsal brainstem, possibly equivalent to the brainstem locomotor region in quadruped animals, may function also in human bipedal gait. In the present study, we could not find any evidence for altered function of the possible locomotor region in Parkinson's disease patients. In addition, when we reanalysed the rCBF data in another experiment of ours (Hanakawa *et al*., 1999), the dorsal brainstem activity was almost unchanged between non-enhanced parkinsonian gait and visually enhanced parkinsonian gait.

Cortical motor areas

Various gait disorders are ascribed to cerebral cortical lesions in humans, especially those involving the frontal lobe. The present study showed gait-induced activation in most of the known motor-related cortical areas (Fig. 4), supporting the view that the projections from the primary motor areas, the lateral premotor cortex, the SMA and the anterior cingulate cortex to the brainstem reticular formation may provide parallel inputs to maintain gait (Kuypers and Lawrence, 1967; Nutt *et al*., 1993).

Other areas

The activation in the basal ganglia in the controls seems quite reasonable since the basal ganglia are thought to play an important role in gait performance (Garcia-Rill, 1986). A computation of the somatosensory feedback is likely to be associated with the superior parietal activation in both groups as well as the second somatosensory area activation in the Parkinson's disease patients. The visual cortex activation was observed only in the controls despite the fact that the subjects were not allowed to use visual feedback from the treadmill itself and that they kept their eyes open even during the control task. Although no monitoring was performed, it is possible that the control subjects made substantial eye movements during the walk, which may have affected visual inputs.

Underactivation and overactivation related to parkinsonian gait

The present Parkinson's disease patients revealed the gait-induced underactivation in some brain areas, as well as the overactivation in other areas. Lateralization of these areas could be related to the laterality of walking difficulty in Parkinson's disease, which was not evaluated systematically in this study.

Cortical motor areas

A medial part of the underactive left frontal region is consistent with the pre-SMA, the function of which is more important in complex motor behaviour than in simple movements (Picard and Strick, 1996). Thus, this abnormality is likely to reflect poor integration of a complex motor regulation during walking. Previous activation studies showed that the SMA is impaired during upper limb movements in Parkinson's disease (Playford *et al*., 1992; Rascol *et al*., 1992) and, furthermore, the SMA underactivation is ameliorated by treatments (Rascol *et al*., 1992; Grafton *et al*., 1995; Samuel *et al*., 1997*b*). On the other hand, in the present study the absence of the lateral premotor cortex-parietal overactivation that seemed to accompany externally triggered movements in the Parkinson's disease patients supports the internally driven nature of the present treadmill-walk task. The left cingulate cortex, possibly belonging to a caudal part of the cingulate motor area (Picard and Strick, 1996), was shown to be overactive in the Parkinson's disease patients, the significance of which needs to be clarified by further study.

Cerebellum

In the present Parkinson's disease patients, the gait-induced activation was reduced in the anterior lobe of the cerebellar hemisphere whereas it was enhanced in the vermis. Although such a differential involvement of the cerebellar hemispheres versus the vermis in parkinsonian gait is a new finding that needs to be be verified and validated in future studies, it could be related to a loss of lateral body sway during parkinsonian gait based on a failure to shift the body's centre of gravity onto one foot. The loss of dynamic gravity shift seems to result in small shuffling steps, and it is of interest that an application of external, alternating, lateral force sometimes improves gait disturbance in Parkinson's disease (Martin, 1967). By contrast, overactivity in the cerebellar vermis may result from a compensation similar to the cerebellar hemispheric overactivity in non-cued finger movements in Parkinson's disease (Rascol *et al*., 1997). Recently, Asanome and colleagues (Asanome *et al*., 1998) showed that electrical stimulation of the output fibres of the fastigial nucleus, strongly influenced by the cerebellar vermis, results in augmentation of the postural muscle tone of cats.

Parietal cortex

As for the underactivation in the parietal cortex during gait, where the present patients showed reduced baseline perfusion, the possible involvement of cortical Lewy bodies may underlie dysfunction of the parietal cortex. It is also possible that that the apparent underactivity resulted from reduced spontaneous or reflexive ocular movements during gait in the Parkinson's disease patients relative to the controls.

Other areas

The overactivity in the right insula may represent a component of the compensatory mechanisms in Parkinson's disease, since it has been suggested that the insula functions in the

post-stroke recovery of motor function (Augustine, 1996). The right temporal cortex was significantly activated only during parkinsonian gait. Although activation of the temporal cortex has been demonstrated in several studies of motor-related tasks in normal and pathological brains (Decety *et al*., 1994; Ceballos-Baumann *et al*., 1995), there is not enough evidence to indicate that the temporal cortex plays a role in parkinsonian gait.

The present study shows that multiple cortical motor areas, the somatosensory association cortex, the cerebellum and the dorsal brainstem are active during the treadmill walk in humans. Furthermore, the results indicate that gait disturbance in Parkinson's disease may be associated with underactivity in the medial motor area and cerebellar hemispheres together with overactivity in the cerebellar vermis. However, areas that are activated in neuroimaging studies do not necessarily indicate the direct functional relevance of those areas. To complement the present findings, there is a need for further studies, for example the careful evaluation of localized brain lesions in patients manifesting parkinsonian-like gait.

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