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► **To cite this version:**

B Ballanger, Pierre Baraduc, E. Broussolle, D. Le Bars, M. Desmurget, et al.. Motor urgency is mediated by the contralateral cerebellum in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 2008, 79 (10), pp.1110-1116. 10.1136/jnnp.2007.141689 . hal-02128274

HAL Id: hal-02128274

<https://hal.science/hal-02128274>

Submitted on 14 May 2019

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Motor urgency is mediated by the contralateral cerebellum in Parkinson's disease

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Received 5 December 2007
Revised 11 February 2008
Accepted 10 March 2008
Published Online First
20 March 2008

ABSTRACT

Background: In patients with Parkinson's disease (PD), motor performance may be dramatically improved in urgent and stressful situations.

Objective: The aim of this PET H₂¹⁵O study was to determine the changes in brain activation pattern related to this unconscious increase in motor speed observed in the context of urgency in patients with PD.

Methods: Eight right-handed patients with PD, who had been off medication for at least 12 hours, without tremor, were enrolled. A reaching task with the right hand was performed under three conditions: self-initiated (SI), externally cued (EC) and externally cued-urgent (ECu).

Results: (1) Self-initiated movements (SI-EC) revealed activations in the prefrontal cortex bilaterally, the right lateral premotor cortex, anterior cingulate cortex and cerebellum, and the left primary motor cortex and thalamus; (2) Externally driven responses (EC-SI) did not involve any statistically detectable activation; (3) Urgent situations (ECu-EC) engaged the left cerebellum. Compared with a control group previously studied, the cerebellar activation was greater in patients with PD.

Conclusions: This study demonstrates that the increase in movement speed in urgent situations in patients with PD is associated with the recruitment of the left (contralateral) cerebellum. This structure is a key node of the accessory motor circuitry typically recruited by patients with PD to compensate for basal ganglia dysfunction and by healthy subjects to increase movement velocity in urgent motor contexts.

externally cued movements was questioned based on the existence of contextual variations of movement duration in healthy subjects.¹⁴ These contextual variations were found in controls to rely on the recruitment of an accessory motor pathway involving the anterior (ie, uncrossed) corticospinal tract (ipsilateral sensorimotor cortex) and the contralateral cerebellum.¹⁵

To our knowledge, no functional imaging study has investigated directly the modifications of brain activation related to motor urgency in PD. The present PET H₂¹⁵O study aims to fill this gap.

METHODS

Subjects

Eight patients with PD with bilateral akinetic-rigid signs (7 males, 1 female; mean age 62 ± 6 years) participated in the study (table 1). All patients were right-handed and fulfilled the UK Parkinson's Disease Brain Bank criteria for idiopathic PD.¹⁶ They did not exhibit severe tremor in the Off condition. On the day of the PET scan, they were off antiparkinsonian drugs for at least 12 hours and the severity of parkinsonian symptoms was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score.¹⁷

The study was approved by the local research ethics committee. All patients participated after the aims of the study and the nature of the procedures had been fully explained. They signed an informed consent form according to the Declaration of Helsinki.

Tasks

The behavioural apparatus and tasks have been described in detail elsewhere.¹⁴ In brief, subjects lay supine on the scanner bed with the right hand in contact with a press button positioned in the middle of the abdomen in a relaxed posture 40 cm away from a large vertical contact plate (28 × 18 cm) suspended over the scanner bed. Contact with this plate controlled an electromagnetic catch located at the bottom of a tilted ramp. Patients were instructed to maintain gaze fixation on a bright green dot positioned in front of the electromagnetic catch. The apparatus is illustrated in figure 1.

Three types of conditions were considered:

1. Self-Initiated (SI). The patients were required to "wait until they felt ready and then hit the push button with the right hand with the fastest possible movement". Just after completion of the movement, an auditory beep was presented (identical to the beep presented in the externally cued conditions) and the green light switched off, instructing the subjects to

Bradykinesia is a cardinal clinical symptom of Parkinson's disease (PD). During the past 15 years, converging observations have suggested that this symptom could be overcome in some circumstances. In particular, it was reported that patients with PD exhibited bradykinesia when performing reaches to a stationary ball or a visual target, but not when reaching for a moving ball or when pressed to move fast.^{1,2} In the same vein, it was found that patients with PD did perform sequential arm movements significantly faster in the presence of external temporal cues.^{3,4} To account for these effects, it was suggested that different neural networks were involved in the control of self-initiated and externally cued movements.⁵⁻⁷ In agreement with this view, functional imaging studies, in PD, identified activation within the basal ganglia for self-initiated but not for externally cued movements.^{8,9} Other reports identified a relationship between the specific recruitment of a cerebellar-parieto-premotor circuitry and the improvement of motor performance by external cues.¹⁰⁻¹³ Recently, however, the existence of different neural networks for self-initiated and

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Table 1 Clinical characteristics of patients with Parkinson's Disease

Patients	Sex	Age (years)	H & Y (Off)	Motor UPDRS (Off) (/108)	Disease duration (years)	Medication in Ldopa equivalent (mg/day)
1	F	58	2	26	29	600
2	M	65	3	33	20	1050
3	M	66	2	18	8	750
4	M	66	2	26	9	750
5	M	56	3	28	10	1150
6	M	71	2	18	8	1050
7	M	57	3	31	11	1300
8	M	58	2	24	13	1750
<i>Mean ± SD</i>		<i>62 ± 6</i>	<i>2 ± 1</i>	<i>26 ± 5</i>	<i>14 ± 7</i>	<i>1050 ± 367</i>

F, Female; H & Y, Hoehn and Yahr; Ldopa equivalent, 100 mg L-dopa = 10 mg Bromocriptine = 5 mg Ropinirole = 1 mg Pergolide = 50 mg Piribedil; M, Male; SD, Standard Deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

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return to the starting position. Then they repeated the task at their own pace. The delay with which the light switched off was variable to ensure that the number of movements was identical in the three conditions.

- Externally Cued (EC). The patients were required to "react and move as fast as possible in response to an auditory cue". When the green light switched off, subjects were instructed to return to their starting position.
- Externally Cued-urgent (ECu). This condition was identical to the EC condition except that the auditory cue sounded as a ball was released at the top of the ramp (release mechanism was not visible). The patients were asked to stop this ball with the electromagnetic catch. Before each session, the subjects were told that they had to stop as many balls as possible. They were also told that they would be informed about their score at the end of the session. In agreement with this claim, feedback was given to the subjects at the end of each ECu session. Subjects were then told how many balls they missed (and stopped). The ramp tilt was adjusted for each patient before the experiment during a short training session so as to ensure a failure rate roughly equal to 50%. In this latter condition, vision of the rolling ball was prevented by an opaque barrier and no rolling sound could be heard. ECu did only differ from EC by the sheer knowledge of a ball rolling. After completion of

the trial, the patients had to bring their hand back to the starting point after the light had switched off. The size of this starting point (microswitch) was small (10×5 mm) and the patients had to perform this task under visual guidance. This prevented the occurrence of regular rhythmical movements in the self-generated condition. Each condition was performed during 100 sec (15 movements) and was repeated four times in a randomised order, leading to a total number of 12 scans per subject.

Behavioural analysis

Movement duration (MD, interval from start position release to contact with the vertical plate) was computed for all conditions. Reaction time (RT, interval from beep to start position release) was computed for the externally triggered conditions. This parameter has no meaning for the internally driven condition. Two planned analyses were carried out using one-sided t-tests for dependent samples. First, the effect of external cueing was assessed by contrasting movement duration for the SI and EC conditions. Second, the effect of external cueing was assessed by contrasting movement duration and reaction time for the EC and ECu conditions. The threshold for statistical significance was set at 0.05.

PET data acquisition

PET scanning was realised in the Neurology Hospital Imaging Centre (CERMEP, Lyon, France) on a CTI HR+ Siemens tomograph (CTI/Siemens, Knoxville, TN). The head was maintained in a fixed position using a moulded helmet. Head position was checked before and after each scan using a laser alignment together with reference points on the Reid's line.

A 10-min transmission scan was acquired using rotating rod sources filled with $^{68}\text{Ge}/^{68}\text{Ga}$. For each emission scan, 343 ± 77 MBq of H_2^{15}O were injected through a forearm catheter placed into the brachial vein. The integrated counts were collected for 90 seconds, starting 30 seconds after the injection. The interval between successive H_2^{15}O administrations was 9 min to allow for adequate radioactivity decay. Images were reconstructed by 3D back-filtered 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 128×128 pixel format with 63 planes creating 2 mm cubic voxels.

PET data analysis

Using CAPP software, the original emission scans in ECAT7 file format were then converted to ANALYZE file format that were then processed in MATLAB 5.3 (MathWorks, Natick, MA) using the Statistical Parametric Mapping software (SPM 99, Wellcome

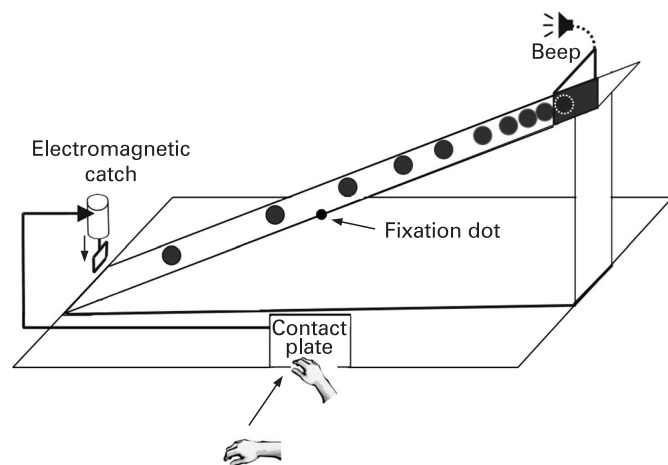


Figure 1 Experimental set-up. In the externally cued (EC) and externally cued-urgent (ECu) conditions, a beep cued the movement to the plate. In the ECu condition only, the patient had to press the plate before the ball had rolled out of the ramp. The ball could neither be seen nor heard. Ramp tilt was adjusted to ensure similar difficulty for each patient.

Department of Cognitive Neurology, MRC Cyclotron Unit, London, UK). In the first stage of analysis, the 12 images from each subject were realigned to the first scan with an automated algorithm for head movement correction and then normalised into the standard stereotactic space provided in SPM. The normalised images were smoothed with an isotropic Gaussian filter of 12 mm to account for variation in gyral anatomy and individual variability in structure–function relationships, and to improve the signal-to-noise ratio. Variations in global flow across subjects were removed by proportionally scaling each image to have an arbitrary level of 50 ml/100 ml/min. Regional cerebral blood flow (rCBF) changes were statistically analysed for all voxels exceeding 80% of the mean value of the scan.

We analysed within-group modifications of rCBF. The increase of rCBF related to the SI condition compared to the EC condition was assessed by SI–EC contrast. The increase of rCBF related to the EC condition compared with the SI condition was determined by EC–SI contrast. The increase of rCBF related to the motor urgency condition compared with the EC condition was derived from ECu–EC contrast.

We also analysed the covariation of rCBF with behavioural variables.¹⁵ In a first step, the mean MD and RT measured for each scan were used as covariates in a covariate-only model. For RT, we only selected the EC and ECu scans (RT has no meaning in the SI condition). For each scan, the mean RT was entered as a covariate. The total length of the covariate vector was 120 items (8 scans per subjects \times 15 movements for each scan). For MD, all the scans were selected (SI, EC or ECu). For each scan, the mean MD was entered as a covariate. The total length of the covariate vector was of 180 items (12 scans per subjects \times 15 movements for each scan). In a second step, the negative and positive covariations of rCBF with these covariates (RT and MD) were determined independently of the condition. The statistical threshold was the same as the one used for the between-conditions contrasts (uncorrected p -value <0.001).

Finally, we compared the brain activation profile found in a previous study in normal subjects in the ECu condition¹⁵ with the one observed in patients with PD in the present work (ECu control – ECu patient; ECu patient – ECu control). Eight healthy subjects (4 males, 4 females; mean age 54 ± 8.1 years) were involved in this study. The experimental protocol and experimental apparatus were the same as the ones used in the present experiment.

Global differences in cerebral blood flow were covaried out for all brain voxels but, because of a priori hypothesis, small volume corrections were applied for all the aforementioned analysis for voxels located into a mask that included both frontal lobes, the ACC, parietal cortex, the cerebellum and basal ganglia—all regions that are known to be involved in motor function.^{8 9 18–20} This mask was created using Matlab VoiTool (http://www.ihb.spb.ru/~pet_lab/VTO/VTOMain.html). The comparisons across conditions were made using t statistics with appropriate linear contrasts, and then converted to Z -scores. Only voxels that exceeded a threshold of an uncorrected p -value ≤ 0.001 were considered to be significant. The minimal cluster size comprised at least 10 voxels. All coordinates reported are based on the Talairach atlas²¹ and were derived from procedures developed by M. Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging>).

RESULTS

Behavioural results

External cueing

MD was significantly reduced when an external cue was present ($t = 2.30$, $p < 0.03$). This variable decreased from 271 ms in SI to 209 ms in EC.

Motor urgency

RT was significantly reduced in the urgent condition ($t = 2.82$, $p < 0.02$). This variable decreased from 262 ms in EC to 234 ms in ECu. The same trend was found for MD ($t = 2.95$, $p < 0.02$). This variable decreased from 209 ms in EC to 180 ms in ECu. These results are represented in figure 2.

We did not find any significant correlation between the motor speed observed in urgent context (ECu–EC) and the duration of the disease (RT: $p > 0.30$; MD: $p > 0.95$) or the UPDRS score (RT: $p > 0.25$; MD: $p > 0.075$). These results remained unaffected when the atypical patient 1 (early disease onset and very long disease duration; table 1) was removed from the analyses.

PET results

Activation profile during SI versus EC movements

SI-related activity was found in the right lateral premotor cortex, DLPFC (BA 9 and 46), anterior cingulate (BA 32) cerebellar hemisphere and in the left medial frontal gyrus (BA 11

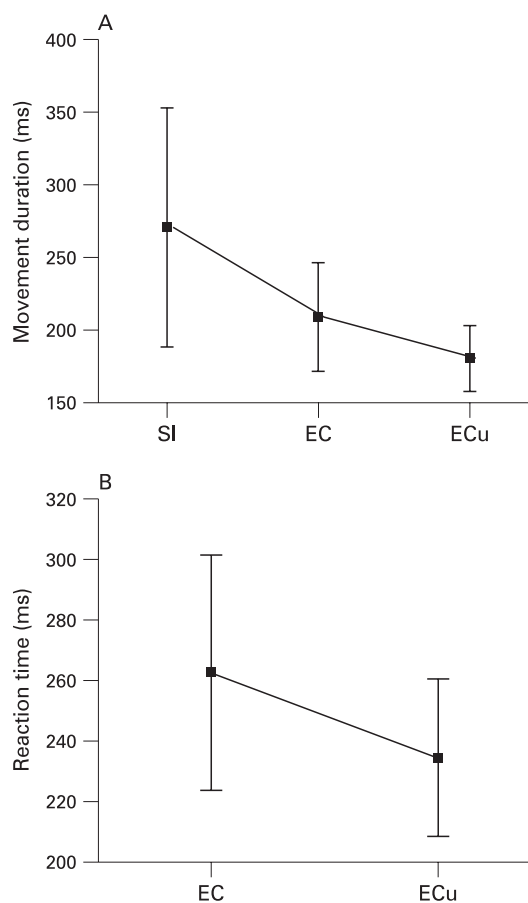


Figure 2 (A): Variations of movement duration as a function of the experimental conditions. (Symbols and error bars: mean \pm SD). (B): Variations of reaction time as a function of the experimental conditions. (Symbols and error bars: mean \pm SD). EC, externally cued; ECu, externally cued–urgent; SI, self-initiated.

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Table 2 Significant rCBF increases in parkinsonian patients

Areas	Stereotactic coordinates					Cluster size
	Left/right	x	y	z	Z score	
SI>EC						
Lateral premotor cortex (BA 6)	R	38	-3	44	3.80	106
DLPFC (BA 9, 46)	R	22	47	37	3.70	192
	R	41	41	12	3.12	200
Anterior cingulate cortex (BA 32)	R	10	32	9	3.00	161
Cerebellum	R	41	-58	-35	3.18	60
Medial frontal gyrus (BA 11)	L	-27	49	-14	3.41	13
Primary motor cortex (BA 4)	L	-52	1	28	3.12	76
Superior parietal lobe (BA 7)	L	-31	-69	45	3.09	220
EC>SI						
None						
Ecu>EC						
Cerebellum (hemisphere)	L	-22	-67	-41	3.52	1700
Anterior cingulate cortex (BA 32)		0	42	10	2.68	176
DLPFC (BA 46)	L	-36	56	16	2.67	97

DLPFC, dorsolateral prefrontal cortex; EC, externally cued; Ecu, externally cued-urgent; L, left; R, right; rCBF, regional cerebral blood flow; SI, self-initiated.

and 10), primary motor cortex (BA 4) and superior parietal lobe (BA 7). The location, coordinates and peak Z-scores of activated areas are detailed in table 2.

Activation profile during EC versus SI movements

We did not observe significant rCBF increase when comparing the EC to the SI condition.

Activation profile during Ecu versus EC condition

A significant activation foci was found in the left parasagittal cerebellar hemisphere (fig 3). At a slightly relaxed threshold ($z > 2.67$, $p = 0.001$), we also observed an activation of the left DLPFC (BA 46) and anterior cingulate cortex (BA 32). The

location, coordinates and peak Z-scores of activated areas are detailed in table 2.

Compared with the normal subjects studied in a previous experiment,¹⁵ patients with PD had greater activations in the left superior frontal gyrus (BA 11), primary motor cortex (BA 4) and DLPFC (BA 9), as well as in the cerebellum bilaterally. No area of greater activation was found in the control subjects compared to the patients. These results are reported in table 3.

Covariation of rCBF with behavioural measures

Movement duration scores showed a significant negative covariation with rCBF in the left parasagittal cerebellar hemisphere. This means that the shorter the movement time, the

Figure 3 Increased regional cerebral blood flow in the cerebellum in the externally cued-urgent condition compared with the externally cued conditions. Data are superimposed on transverse sections of a single subject brain MRI from SPM99. $p < 0.001$ uncorrected (R: Right, L: Left).

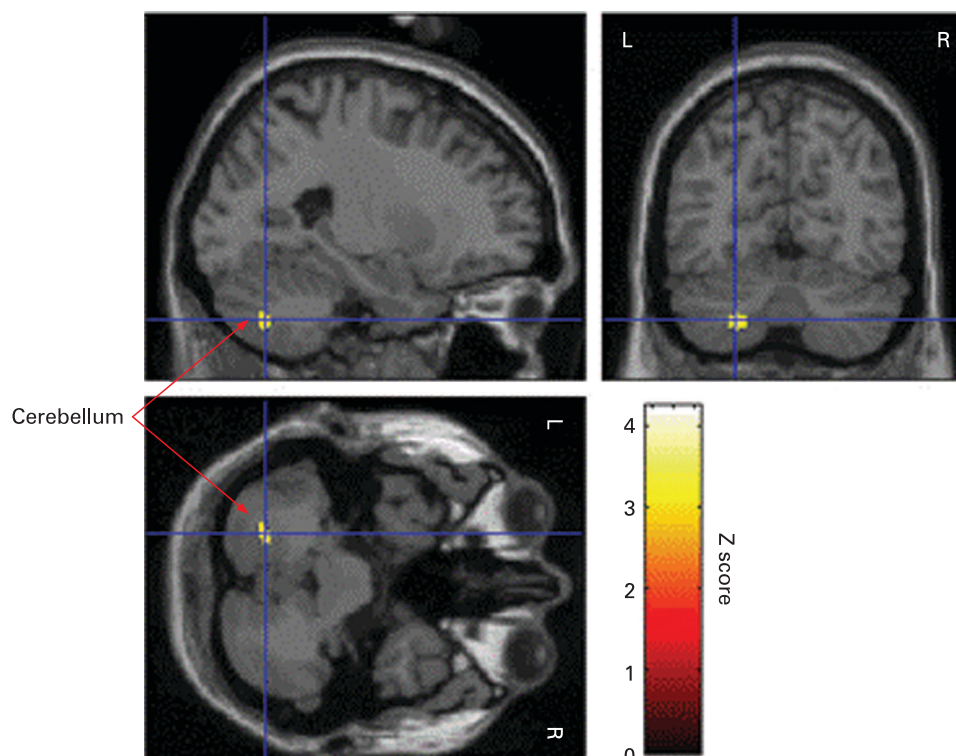


Table 3 Between-group analyses for the externally cued–urgent condition

Areas	Left/Right	Stereotactic coordinates			Z score
		x	y	z	
Controls>PD					
None					
PD>Controls					
Cerebellum (Vermis)	R	3	−46	−15	7.47
Cerebellum (Vermis)	L	−3	−50	−19	7.45
Superior frontal cortex (BA 11)	L	−4	57	−18	6.13
Primary motor cortex (BA 4)	L	−55	−15	38	5.64
DLPFC (BA 9)	L	−45	20	38	4.87

All areas were significant at $p < 0.05$ (corrected).
BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex.

greater the activation of this area. The location, coordinates and peak Z-scores of activated areas are detailed in table 4.

Reaction time showed a significant negative covariation with rCBF in the right ACC (BA 24) and the left primary motor cortex and superior frontal gyrus (BA 10). The location, coordinates and peak Z-scores of activated areas are detailed in table 4.

We did not find any significant correlation between the modulation of the cerebellar response and the severity (UPDRS motor score) or the duration of the disease.

DISCUSSION

Behavioural data

The present results indicate that: (1) Patients with PD can exceed their self-determined maximal movement speed for reaching in the context of externally cued conditions; (2) Patients with PD can exceed their externally driven maximal response speed in the context of a temporally pressing (or urgent) situation. These results are in agreement with previous behavioural studies showing that external cues and temporally constrained situations can improve bradykinesia in patients with PD.^{1–4 14 22 23}

Changes of brain activation pattern according to motor context Externally cued versus self-initiated responses

During the SI motor condition, patients with PD exhibited a much larger brain activation pattern than during the EC motor condition. This activation pattern concerned the right anterior cingulate, lateral premotor cortex and cerebellum, the left primary motor, prefrontal and superior parietal cortex and bilaterally in the prefrontal cortex. By contrast, no additional activation foci were observed in the EC compared with the SI condition. This latter finding is consistent with previous reports showing that SI and EC movements involve the same executive network.^{8 9 24}

The additional activations observed in SI condition could reflect a compensatory process through which patients with PD try to overcome a specific difficulty to act in a self-determined mode, by recruiting areas that are known to be involved in the preparation, planning and selection of voluntary movement, such as the prefrontal and lateral premotor cortex.^{8 9 18} On the other hand, the overactivation of the right cerebellum could reflect the involvement of the so-called “accessory motor pathways” that compensates for basal ganglia dysfunction in PD and has also been shown to include bilaterally the lateral premotor, primary motor and parietal cortex.^{11 13 25 26} Finally, it is of interest to note the overactivation of the left primary motor cortex, indicating that patients with PD have to recruit motor preparation in a larger manner, but also motor execution areas due to the difficulties in performing SI movements.²⁷

Interestingly, these overactivations observed in patients with PD were not associated with a normalisation of motor performance as the movement remained slower in the SI compared with the EC condition. Thus, it could be that this excess of brain activation could also reflect a lack of motor selectivity and would not be efficient. We could also hypothesise that the difficulties in performing the task induced a large recruitment of brain areas with, as a consequence, a slowdown of the movement. Similarly, in another study in PD on a working memory task, the large recruitment of brain areas was not associated with an improvement of motor performance and the rate of error was proportional to the importance of brain activation pattern.²⁸

At first glance, the absence of activation within the basal ganglia network when the SI condition was compared with the EC condition seems at odds with the claim that the basal ganglia network plays a much more essential role in internally than in externally regulated actions.^{8 9 24} Direct support to this idea has been provided by functional imaging studies showing activation within the basal ganglia network for SI but not for externally driven movements.^{8 9 24} Interestingly, however, this

Table 4 Negative covariation of regional cerebral blood flow with the basic parameters of movement

Areas	Left/Right	Stereotactic coordinates			Z score	Cluster size
		x	y	z		
Reaction time						
Anterior cingulate cortex (BA 24)	R	6	22	−3	3.78	73
Primary motor cortex (BA 4)	L	−20	−36	58	3.74	117
Superior frontal cortex (BA 10)	L	−11	53	20	3.29	29
Movement duration						
Cerebellum (hemisphere)	L	−24	−40	−38	3.60	36

All areas were significant at $p < 0.001$ (uncorrected).
BA, Brodmann area.

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dissociation was only observed when the different movements types were compared to a rest condition. No higher activation in the basal ganglia network was reported when the self-initiated and externally driven movements were compared with each other.^{8-9,24} An absence of systematic involvement of the basal ganglia for internally regulated or self-initiated movements was also reported in electrophysiological and inactivation studies in monkeys.²⁹⁻³² These data are consistent with the findings of the present study.

Influence of urgency

To explore the pattern of brain activation specific to motor urgency, we compared the ECu and EC conditions. We found that the movements executed in an urgent context were associated with a specific and restricted activation within the left (contralateral) cerebellum. This activation correlated with the movement speed observed at the behavioural level. No correlation was found between the modulation of the cerebellar response and the severity (UPDRS motor score) or the duration of the disease. This negative result is consistent with the hypothesis that the contralateral cerebellum is activated in urgent situations, irrespective of the disease. In agreement with this view, previous studies have shown that: (1) even if patients with PD are slower than healthy subjects, motor urgency speeds up the motor response by a similar amount in patients with PD and control subjects;¹⁴ (2) the contralateral cerebellar activation observed in the present experiment is also present in healthy subjects, when a similar experimental protocol is used.¹⁵ When considered together, these data strongly suggest that the contextual modulation of movement speed in urgent situations does not rely on the BG network.

Converging evidence has been provided, in primates and humans, that the parasagittal cerebellar hemisphere was involved in the control of movement velocity. In non-human primates, recording studies in the Purkinje cells of the lobules V and VI have demonstrated relations of single unit discharge to movement velocity.³³⁻³⁴ In healthy humans, imaging studies have shown velocity-related activity in the cerebellar lobule VI.³⁵⁻³⁶ In patients with cerebellar lesions or dysfunctions, movement velocity has been reported to decrease with respect to control subjects.³⁷⁻³⁹

In all the studies mentioned above, modulation of the movement velocity has been shown to involve the ipsilateral cerebellum. In the present study, the activation was identified in the contralateral hemisphere. As mentioned in previous reports, however, the contralateral cerebellum is often recruited in patients with PD¹⁰⁻¹¹ and stroke⁴⁰⁻⁴¹ to compensate for the pathological dysfunctions of the normal motor network. This structure is also activated, in healthy subjects, in urgent situations, when movement velocity needs to be "boosted".¹⁵ The cerebellar contralateral activation observed in the present study may serve the same purpose. It may be triggered by urgency and the need to increase movement velocity above a certain (standard) limit.

For the sake of completeness, it should be mentioned that recent imaging studies have linked the left cerebellum to attentional processes.⁴²⁻⁴³ However, we do not think that this constitutes a convincing explanation of our results as the cerebellar attentional area has been located repeatedly, not in the parasagittal as in our case, but in the lateral part of the cerebellar hemisphere.⁴²⁻⁴⁴ However, we readily acknowledge the need for greater attentional control in the ECu condition, as suggested by the higher activation of the anterior cingulate

cortex and left DLPFC in this condition compared with the EC condition.

Before bringing this discussion to an end, it may be worth mentioning that although urgency led to the recruitment of the left parasagittal cerebellum in both the patients and the controls, there were two important differences in the motor network recruited by these two populations in the ECu condition. First, patients with PD exhibited a larger level of activation in the cerebellar vermis and contralateral motor cortex. This pattern has been suggested to reflect a compensatory response for basal ganglia dysfunction.¹¹⁻¹³ M1, in particular, is usually not underactivated in PD, and several reports have shown that patients with PD tended to recruit this area more extensively than normal subjects to compensate for bradykinesia.^{11-13,25} Second, the patients exhibited a greater activation of the prefrontal cortex (BA 11 and DLPFC). This region is involved in the preparation, planning and selection of voluntary movement. Accordingly, the overactivation of this latter in the ECu condition observed in patients with PD is clearly abnormal. However, recently, it has been suggested that some overactivations could reflect a facet of the primary pathophysiology of PD, such as an inability to inhibit contextually inappropriate circuits.²⁷

CONCLUSION

In summary, the present PET study shows a progression of brain activation from planning regions in the SI condition to more executive areas in the EC condition, with an additional contralateral cerebellar activation, in this condition, when the action is performed in an urgent context (ECu). The contralateral cerebellum is known to be a key node of the accessory motor circuitry typically recruited by patients with PD to compensate for basal ganglia dysfunction and by healthy subjects to increase movement velocity in urgent motor contexts. Interestingly, we did not find any evidence that PD affected the ability of the patients to increase the speed of their movements in urgent situations. This suggests that contextual modulations of movement speed do not implicate the BG circuitry.

Acknowledgements: This study has been supported by a grant from the Association France Parkinson.

Competing interests: None.

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