ACADEMIC PRESS

Available online at www.sciencedirect.com
SCIENCE DIRECT®

NeuroImage

NeuroImage 19 (2003) 163–179

www.elsevier.com/locate/ynimg

The functional anatomy of parkinsonian bradykinesia

Robert S. Turner,[a,b,*] Scott T. Grafton,[a,c] Anthony R. McIntosh,[d] Mahlon R. DeLong,[a] and John M. Hoffman[a,e]

[a] *Department of Neurology, Emory University School of Medicine, WMRB 6000, Atlanta, GA 30322, USA*
[b] *Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA 94122, USA*
[c] *Center for Cognitive Neuroscience, 6162 Moore Hall, Dartmouth College, Hanover, NH 03755, USA*
[d] *Rotman Research Institute–Baycrest Centre for Geriatric Care, University of Toronto, Ontario, Canada*
[e] *National Cancer Institute, 6130 Executive Blvd., MSC 7412, Bethesda, MD 20892, USA*

Received 23 May 2002; revised 10 December 2002; accepted 18 December 2002

Abstract

To investigate the difficulty that patients with Parkinson's disease (PD) have in performing fast movements, we used $H_2{}^{15}O$ PET to study regional cerebral blood flow (rCBF) associated with performance of a simple predictive visuomanual tracking task at three different velocities. Tracking movements in PD patients (versus tracking with the eyes alone) were associated with a general underactivation of the areas normally activated by the task (sensorimotor cortex contralateral to the moving arm, bilateral dorsal premotor cortices, and ipsilateral cerebellum). Presupplementary motor cortex (pre-SMA) ipsilateral to the moving arm had greater than normal movement-related activations. Increasing movement velocity led to increased rCBF in multiple premotor and parietal cortical areas and basal ganglia in the patients as opposed to the few cerebral locations that are normally velocity-related. The functional correlates of PD bradykinesia are: (1) impaired recruitment of cortical and subcortical systems that normally regulate kinematic parameters of movement such as velocity; and (2) increased recruitment of multiple premotor areas including both regions specialized for visuomotor control (ventral premotor and parietal cortices) and some that are not (pre-SMA). The overactivation of cortical regions observed in patients may be functional correlates of compensatory mechanisms and/or impaired suppression as a facet of the primary pathophysiology of PD.

Introduction

In Parkinson's disease (PD), loss of the dopaminergic innervation of the striatum results in akinesia and bradykinesia among other motor symptoms. The extent to which different symptoms arise from dissociable defects in the motor control apparatus remains a topic of debate. Resolution of the debate depends, first, on a careful definition of terms. Akinesia encompasses many aspects of motor control, from a paucity of spontaneous movement to lengthened response times under reaction time conditions, and impaired initiation of sequences of movement or simultaneous movements (Lakke, 1981). Although slowed and hypometric movement is often considered yet another aspect of akinesia (e.g., Paulson and Stern, 1997), numerous studies have shown that the severity of bradykinetic and akinetic symptoms varies independently (Evarts et al., 1981; Jordan et al., 1992; Meyer, 1982; van Hilten et al., 1998). The peripheral correlate of bradykinesia is a reduction in the rate of change of agonist muscle force both for onset (Corcos et al., 1996; Hallett and Khoshbin, 1980; Jordan et al., 1992) and offset (Jordan et al., 1992; Kunesch et al., 1995; Wing, 1988) of muscle contraction. PD patients can modulate the level of force in agonist muscles, but they characteristically do so at lower rates than normals (Corcos et al., 1996; Stelmach et al., 1989; Stelmach and Worringhan, 1988; Teasdale et al., 1990). Of note, PD patients with marked bradykinesia may show no abnormalities in the pattern of activation of task-related muscles (Godaux et al., 1992), or in movement accuracy when visual feedback is available (Adamovich et al., 2001). These studies indicate a clear dissociation be-

* Corresponding author. Department of Neurological Surgery, Box 0520, University of California, San Francisco, San Francisco, CA 94143-0520. Fax: +1-415-502-0613.
E-mail address: rturner@itsa.ucsf.edu (R.S. Turner).

1053-8119/03/$ – see front matter © 2003 Elsevier Science (USA). All rights reserved.
doi:10.1016/S1053-8119(03)00059-4

tween deficits in the planning, initiating, and sequencing of muscle activation patterns (akinesia) and the modulation of those activations to match the metrics of the task space (bradykinesia) (Berardelli et al., 2001).

Of the many functional imaging studies of PD, most have employed tasks that emphasize selection, initiation, and/or sequencing of discrete movements (i.e., correlates of akinesia). Playford et al. (1992) were the first to demonstrate, using $H_2{}^{15}O$ PET, that in parkinsonian patients there is a hypoactivation of the contralateral mesial premotor cortex (supplementary motor area, SMA) and dorsolateral prefrontal cortex relative to control subjects. Subsequent studies have corroborated and expanded upon this observation using PET (Jahanshahi et al., 1995; Samuel et al., 1997a; 2001), SPECT (Rascol et al., 1992), and fMRI (Haslinger et al., 2001; Sabatini et al., 2000). All of these used tasks that emphasize correlates of akinesia and working memory. Additional studies have shown that these hypoactivations are reduced following pharmacological (Haslinger et al., 2001; Jenkins et al., 1992; Rascol et al., 1992), ablative surgical (pallidotomy) (Ceballos-Baumann et al., 1994; Grafton et al., 1994, 1995; Samuel et al., 1997b), or deep brain stimulation (Davis et al., 1997; Fukuda et al., 2001; Limousin et al., 1997) therapy. Despite the consistent picture these studies provide of the functional abnormalities in PD, the near universal reliance on one type of task has clouded our ability to distinguish between abnormalities that are specific to akinesia and abnormalities that might be characteristic of bradykinesia.

In a PET study of neurologically normal subjects (Turner et al., 1998), we found that brain activity was correlated with the velocity and/or rate of movement in a small subset of the regions that were activated with movement per se. Whereas wide areas of frontal and parietal lobes were activated with movement, rate-related activations were found only in contralateral primary motor cortex (M1) and globus pallidus, and in the ipsilateral cerebellum. Given that bradykinesia is a defect in scaling the motor command resulting in reduced movement velocity, we sought to determine if the velocity-related pattern of brain activity seen in normal subjects might be altered in PD. Reasoning that impaired activation of this velocity-related subcircuit may be the functional substrate for parkinsonian bradykinesia, we used $H_2{}^{15}O$ PET to study PD patients while they performed the same tracking task. The normal subjects used for comparison included those reported previously (Turner et al., 1998). Some of these results have been reported in preliminary form (Turner et al., 1996, 2000).

Note that the term "velocity" is used here for the sake of simplicity. Many features of movement covary systematically with movement velocity and the present experiment did not attempt to dissociate these possible covariates. Thus, the term "movement velocity" should be understood as meaning movement velocity or one of its covariates.

Table 1
Clinical details of parkinsonian subjects

No.	Initials	Age	Sex	Hand	H&Y (off)	UPDRS motor	Mean mvt. ampl.
1	MS	61	F	R	*	*	10.87
2	DS	58	M	R	4.0	38.5	11.79
3	JA	61	M	R	5.0	64.0	11.01
4	FCH	37	F	R	4.0	46.0	12.84
5	LB	54	M	R	4.0	51.0	11.29
6	JW	67	M	R	3.5	56.0	17.66
7	JC	56	M	R	4.0	36.0	12.00
8	DA	54	M	R	4.5	36.5	13.11
9	WL	62	M	R	3.5	61.0	9.47
10	JG	62	M	R	3.5	34.0	12.84
11	JS	68	M	R	3.5	16.5	15.74
12	MD	45	M	L	4.0	16.0	18.18

Note. Mean Hoehn and Yahr [H&Y (Hoehn and Yahr, 1967)] and UPDRS motor scores (part III) (Fahn et al., 1987) were obtained from subjects prior to scanning (Off anti-parkinsonian medications for >12 h). Mean mvt. ampl., mean amplitude of tracking movements under the 0.7-Hz condition.

* UPDRS data not available.

Methods

Subjects

Twelve patients with moderate to severe idiopathic PD [57 ± 9 years of age (mean ± SD); 10 male, 2 female] were recruited from a clinical study of pallidotomy for medically intractable PD (Vitek et al., 1998). The clinical features for each patient are summarized in Table 1. Handedness was determined by simple enquiry. (Exclusion of the one left-handed patient did not affect the results substantially aside from the expected influence on statistical significance.) None of the patients had significant radiological, neuropsychological, or clinical abnormalities other than idiopathic PD. The parkinsonian subjects stopped taking their regular anti-parkinsonian medications at least 12 h before PET scanning. None of the patients had significant tremor or dyskinesias during scanning. Immediately prior to a PET session, a subject's clinical status was assessed by a movement disorders specialist using the UPDRS rating scale (Fahn et al., 1987). Twelve healthy right-handed adults (58 ± 12 years of age; 10 male, 2 female) were recruited as control subjects. Data from 9 of the control subjects have been reported previously (Turner et al., 1998). All subjects gave written informed consent in accordance with the Emory University Human Investigations institutional review board.

Apparatus and behavioral tasks

The behavioral apparatus and tasks have been described in detail elsewhere (Turner et al., 1998). Briefly, subjects lay supine on the scanner bed with the right upper arm resting on a padded support at the subject's side. The right

hand was strapped into a manipulandum that allowed medial and lateral longitudinal rotations of the shoulder joint. The right arm and manipulandum were hidden from view behind a curtain. A video monitor suspended over the scanner bed displayed a "target" (solid white circle, 1.5-cm diameter) and a manipulandum-controlled "cursor" (hollow red 1.5-cm square). The target moved horizontally between fixed endpoints (10 cm to the left and right of screen center) according to a sinusoidal time/position function at one of three frequencies (0.1, 0.4, and 0.7 cycles per second). Subjects were instructed to move the on-screen cursor to match the position and movement of the target as closely as possible. Rotation movements of the shoulder caused the on-screen cursor to move along the same horizontal track as the target. To follow the target's 20-cm displacement across the monitor, a matching 20-cm displacement of the joystick was required. Before the first PET scan, subjects practiced the tracking task at each target rate until tracking errors stabilized. Subjects also performed a control task in which the target moved at 0.4 Hz and the subject followed movement of the target with the eyes only. During the arm movement tasks, the subjects also moved their eyes as a natural strategy to accurately follow the target. Therefore, use of eye tracking as a control condition allowed for subtraction of cerebral activations related to visual perception and oculomotor tracking of the target. Subjects were allowed to practice the tasks prior to scanning.

Silver/silver chloride surface electrodes were placed periorbitally to allow electrooculographic (EOG) recording of horizontal movements of the eyes (gain = 1000, band pass filtering 0.1–100 Hz). Joystick position and EOG signals were digitized at 250 Hz and stored for later analysis.

Data acquisition

Eight PET scans were performed in fixed counterbalanced order: eyes only, arm tracking at 0.1, 0.4, and 0.7 Hz, and then in the reverse order (0.7, 0.4, and 0.1 Hz and eyes only). Tasks commenced 10 s before the initiation of a 90-s PET scan and continued for the duration of the scan. Regional cerebral blood flow [rCBF (Mazziotta et al., 1985)] was estimated from images of radioactivity acquired using a modified autoradiographic method (Herscovitch et al., 1983; Raichle et al., 1983). A bolus of $H_2{}^{15}O$ (45 mCi) was injected intravenously into the left arm 10 s before the initiation of a scan. Images were acquired with a Siemens ECAT 951 tomograph, which collects 31 contiguous 3.375-mm-thick slices with an intrinsic resolution of approximately 5 mm full width half maximum (FWHM). Subjects were positioned in the scanner so that the field of view covered the vertex and slices were parallel to the canthomeatal line. Thus, the inferior cerebellum was not included. Images were reconstructed with calculated attenuation and a 0.3-cm ramp filter, then smoothed with a 3D-gaussian filter to an isotropic resolution of 11.8 mm FWHM.

Data analysis

Records of joystick movement were analyzed as follows. The mean extent of movement for a scan was computed as the mean of the difference between movement extremes for each movement cycle. The mean error in movement extent equaled the difference between mean movement extent and desired extent (which was 20 cm for all movement scans). The mean absolute velocity was derived by digital low-pass filtering (5 Hz cutoff) and differentiation (Hamming, 1983) of the position signal. The mean temporal error (phase lead or lag) was computed by finding the temporal shift between arm position and target position that minimized the mean sum of positional error and velocity error throughout the record.

Records of horizontal EOG (HEOG) were detrended, low-pass-filtered (5 Hz cutoff), and then calibrated to gaze position by finding global offset and gain factors for each subject that best fit (i.e., minimized mean squared error) all of the subject's HEOG records to target position. The need to calibrate EOG signals in this way prevented analysis of any main effects of the amplitude of eye movements. The gaze position signal was digitally differentiated to determine mean absolute eye velocity (Hamming, 1983). Mean temporal error (phase lead or lag) was computed by finding the temporal shift between gaze position and target position that minimized positional error sum across a record. Positional error was computed for each HEOG record as the root mean squared error between gaze position and target position after correcting for temporal error.

Image processing was performed on SUN and Linux workstations. Within- and between-subject alignment of PET scans was performed using automated registration (Woods et al., 1998a). A mean image of the co-registered PET scans was co-registered to a PET reference atlas generated from 18 normal subjects, centered in Talairach coordinates using an affine transformation with 12 degrees of freedom (Talairach and Tournoux, 1988; Woods et al., 1998b). Co-registered PET images were smoothed to a final isotropic resolution of 15 mm FWHM.

Categorical comparisons were performed using statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Analysis of covariance (ANCOVA) was used to adjust for differences in global flow and to rescale images to a global CBF of 50 ml/min/dl. Significant changes in rCBF were detected using the general linear model in voxel-by-voxel comparisons. The results constituted voxel maps of the *t* statistic [SPM(*T*)].

Within-group analyses

Brain areas activated by movement per se were defined as areas where mean rCBF under the three movement conditions (0.1, 0.4, and 0.7 Hz) was increased above the rCBF of the eye-only control condition ($t_{69} > 3.09$, $P < 0.001$, >50 contiguous voxels). Velocity-related activations were identified in a separate ANCOVA in which the mean abso-

lute joystick velocity during a scan was entered as the covariate of interest. The eye-only control condition was not included in the ANCOVA for velocity. Velocity-related activations were considered significant if >50 contiguous voxels exceeded a threshold of $t_{47} > 3.14$ ($P < 0.001$, uncorrected). Sites with significant velocity effects were identified within the cerebral volume that demonstrated at least nominal movement-related activation (threshold $t = 3.0$, $P < 0.005$).

Between-group analyses

Second level, random effects models were used to test for between-group differences in task-related brain activation. Random effects comparisons have a notable advantage of allowing reliable inference from the current sample of subjects to the general population (Holmes and Friston, 1998; Woods, 1996). We considered reliability and generality of results to be worth the reduced statistical power in a random effects model due to fewer degrees of freedom being available for the comparison. Between-group differences were identified by subtracting the contrasts of one group from the corresponding contrasts of the other group. Two independent comparisons were performed to identify the group-related differences in brain activations related to movement per se (i.e., group differences in the linear contrasts for all movement conditions versus the eye-only control condition) and the group-related differences in brain activations related to movement velocity (i.e., differences in the covariance between rCBF and velocity). For between-group analyses, areas of the resulting SPM(T) maps were considered significant if a region of >50 contiguous voxels of activation exceeded a threshold of $t_{22} > 2.82$ ($P < 0.005$). The danger of false positives due to multiple comparisons at a low statistical threshold was controlled by comparing results from random effects analyses with those from partial least-squares (PLS), an analysis approach which implicitly controls for multiple comparisons.

Partial least-squares analyses (PLS)

It is possible that univariate hypothesis testing might not capture important sources of experimental variance that are relevant for understanding modulation of brain activity with respect to velocity. To test for brain–behavior relationships in greater detail, the method of PLS was used (McIntosh et al., 1996). PLS uses a multivariate analysis to identify multiple brain regions whose activities covary in a similar fashion with some aspect of the experimental design (e.g., similar changes in rCBF for increasing movement rates). The advantages of PLS over other analysis techniques include the avoidance of problems of multiple comparisons and parametric assumptions (by the use of permutation tests to gauge the significance of whole patterns of brain-task relations) and the identification of patterns of brain-task covariance independent of any a priori hypotheses with respect to task contrasts. This technique uses the covariance between experimental design and rCBF at individual brain voxels to calculate a set of "latent variables" (LVs). Each LV identifies both the relevant aspect of the experimental design [either an effect of task conditions alone or a task-by-group interaction (Grady et al., 1999)] and which brain voxels show that pattern. For each LV, a brain voxel has a weight, known as a salience, that indicates how well rCBF at the voxel is related to the LV. A voxel's salience can be positive or negative, depending on whether rCBF at the voxel covaries positively or negatively with the task pattern. Multiplying the rCBF value in each brain voxel for each subject by the salience for that voxel, and summing across all voxels, gives a "brain" score for each subject for each task condition on a given LV. Brain scores are analogous to factor scores in a factor analysis, and are an indication of how much each subject expresses the brain activity pattern for a given LV in each condition.

We performed three PLS analyses on the movement scans: one between-group analysis and two separate within-group analyses for normal and parkinsonian subjects. The first analysis identified the similarities and differences between groups in the relations between brain activity and movement task (i.e., across the three target speeds: 0.1, 0.4, and 0.7 cycles per second). Within-group analyses were used to estimate the contributions of each group to the patterns found in the between-group analysis. Between-group analysis was performed on the cerebral volume identified previously to be at least nominally activated by the movement task in either group ($P < 0.005$, SPM within-group analysis). Prior to group analysis, we removed global differences in rCBF between groups by proportional scaling, thereby leaving only variances attributable to task or task-by-group interactions. For each analysis, the overall significance of the LVs was assessed using a permutation test (McIntosh et al., 1996). Bootstrapping was used to estimate the standard errors of the saliencies at each voxel, thereby providing an indication of how reliably individual brain voxels contributed to an LV. Voxels with a reliability ratio (i.e., salience/standard error) >2.3 were considered to contribute reliably to an LV. Post hoc ANOVAs of brain scores were used to detect the specific effects on brain scores of task and/or group. The post hoc tests were performed using unbiased estimates of brain scores obtained by repeating the between-group PLS analysis using a design matrix that coded only target rate ignoring the group designation and group by rate interactions (Grady et al., 1999). Because these ANOVAs were performed on brain scores, their results reflect the significance of whole patterns of brain activity and not that of individual voxels. Because of this, the PLS results are immune to the statistical problems associated with multiple comparisons.

Results

Task performance

During visuomotor tracking, parkinsonian subjects produced substantially lower mean velocities ($F_{1,138} = 168$, P

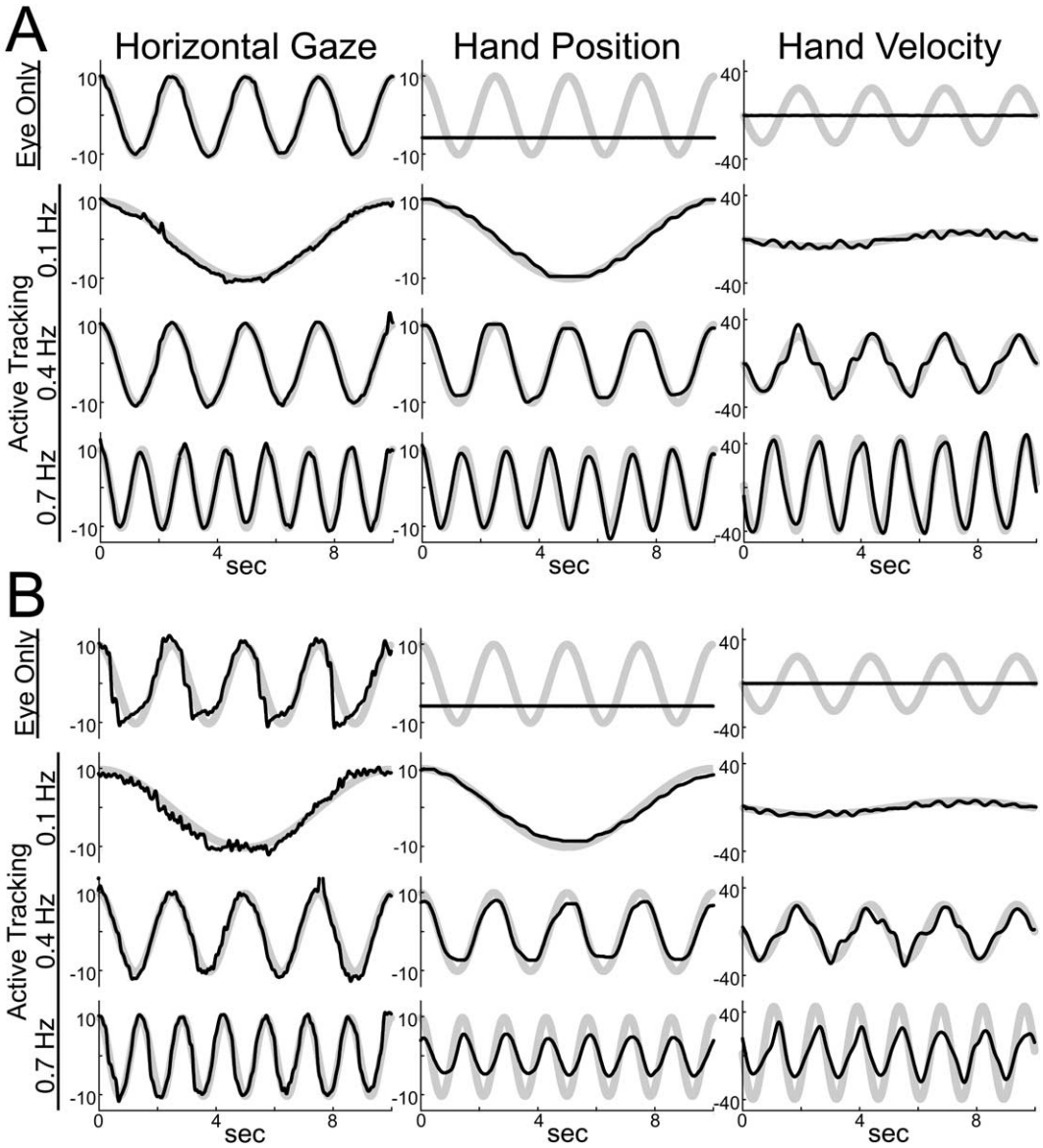


Fig. 1. Performance of representative normal (A) and PD (B) subjects during four behavioral conditions. Only 10 s of each 100-s-long record is shown. For each condition (row), horizontal gaze position [inferred from electrooculographic recordings], hand position, and hand velocity are plotted. Position or velocity of the target is shown in gray. Eye Only: During the eye-only control condition, the subject's gaze followed the target while the hand remained stationary. Active Tracking: Position and velocity of the hand closely matched those of the target at all target rates in the normal subject (A), but progressively undershot those of the target in the parkinsonian subject (B). Gaze movements did not show the same pattern of impairment.

< 0.001, group main effect) and smaller movement extents ($F_{1,138} = 69.5$, $P < 0.001$) than normal subjects. These performance deficits were exacerbated for faster target rates ($F_{2,138} = 49$ and 5.7; $P < 0.01$, group-by-task interactions for velocity and extent, respectively). The Parkinson's disease-related deficiencies in movement velocity and extent were evident both in data from individual PD subjects (Fig. 1B) and in summary data (Fig. 2). Temporal errors in tracking (i.e., leading or lagging behind the target) did not differ between normal and parkinsonian subjects ($F_{1,138} = 0.5$, $P = 0.47$, group main effect). Temporal errors did vary with target rate ($F_{2,138} = 45.6$, $P < 0.001$, task main effect), however, and in a way that differed between groups ($F_{2,138} = 20.2$, $P < 0.001$, group-by-task interaction, Fig. 2 right). Both groups lagged behind the slowly moving target (0.1 Hz), but PD subjects lagged more than normals. At faster rates, normal subjects closely synchronized with the target while PD subjects led target movements slightly. With respect to velocity and extent, the between-group differences in performance were sizable, in all cases amounting to >10% of the target values for velocity and extent. In contrast, group differences in temporal error were always small, never exceeding 3% of the duration of a target cycle.

We found no relationship between errors in movement extent or velocity (both measures of bradykinesia) and temporal error. Pearson's correlation coefficients were com-

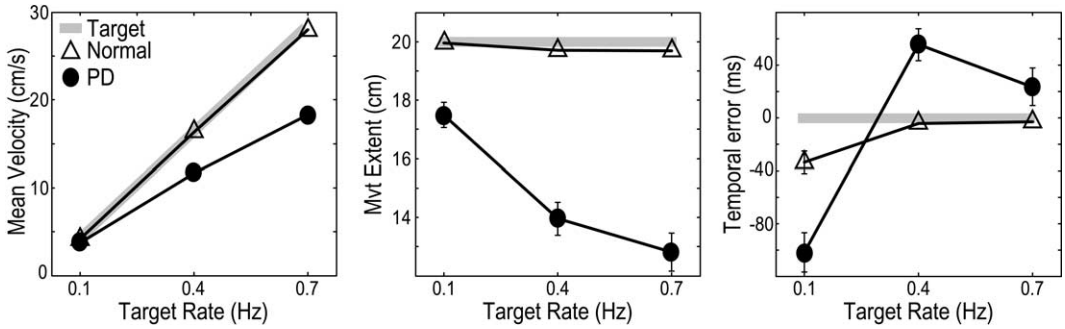


Fig. 2. Mean group performance of normal and PD subjects during active tracking. Absolute velocity (left) and movement extent (middle) of parkinsonian subjects was reduced below normal levels and this impairment was exacerbated at faster target rates. Temporal errors (right) showed a variable pattern in which parkinsonian patients led more than normals at faster target rates and lagged more at the slow rate. Error bars indicate SEMs when greater than the size of the symbol marking means.

puted between extent or velocity error vs temporal error (across subjects and task repetitions) separately for each target rate. None of the correlations approached significance ($\rho < 0.15$, $t_{22} < 0.6$). In contrast, movement velocity and extent were very closely related to each other (within group and task, $\rho > 0.98$ in normal subjects, $\rho > 0.89$ in PD subjects, $t_{22} > 9.0$, $P < 0.001$ for all comparisons). Because velocity and extent were closely correlated, either could be used as a valid bradykinesia-related measure for the current task. Movement velocity was chosen. Also because of their close correlation, it was not possible to dissociate the effects on brain activity of movement velocity vs extent.

Eye movement velocities were similar for the PD and control subjects ($P > 0.05$, $F_{1,120} = 3.6$ group main effect, $F_{2,120} = 1.6$ group-by-task interaction). HEOG records were analyzed for eight normal and eight parkinsonian subjects. (EOG signals from the remaining subjects were lost or corrupted during scanning.) For both subject groups, eye velocities under the eye-only control condition were similar to those recorded during active tracking at 0.4 Hz ($P > 0.05$, Tukey's HSD post hoc test; Fig. 1, left column). The eye movements of parkinsonian subjects were less accurate than those of control subjects. PD subjects had larger gaze position errors across all task conditions ($F_{1,120} = 95$, $P < 0.001$, group main effect) and this difference was greater at the slow target rate (0.1 Hz) and under the eye-only condition ($F_{2,120} = 5.9$, $P < 0.001$, group-by-task interaction). Unlike the hand position errors of PD subjects, gaze position errors were not due to oculomotor hypometria or bradykinesia at faster target rates (Fig. 1, left column). Rather, gaze errors in PD subjects were caused by a tendency to saccade to anticipated target positions instead of following the target using smooth pursuit (Fig. 1, left column). Consistent with this explanation, temporal errors for gaze in PD subjects also showed a consistent lead across task conditions (i.e., gaze movements preceded target movements in time; $F_{1,120} = 4.4$, $P < 0.04$, group main effect, $F_{2,120} = 0.6$, $P > 0.5$, group-by-task interaction).

Univariate analysis

Movement effects

The results of within-group analyses are summarized in Table 2 and illustrated in Figs. 3A and B. The movement vs rest comparison yielded largely similar patterns of activation in parkinsonian and control subjects. Most of the areas activated in normals corresponded closely with what was reported previously for a subgroup of the normal subjects (Turner et al., 1998). Movement-related activity was found in a large swath of cortex surrounding both left and right central sulci (Fig. 3A, 3–4), in the left and right basal ganglia (BG) and thalamus (Fig. 3A, 2), and in the cerebellum (Fig. 3A, 1). Peaks within these activated regions were found at a constellation of loci that have been implicated in the control of arm movements in many previous functional imaging studies (Table 2). Additional activations were observed in the right superior frontal gyrus (Fig. 3A, 4), left insula (Fig. 3A, 2), and in visual regions of the occipital lobe. In the PD group, many of the same regions were activated, but to a lesser degree or over a smaller extent (Fig. 3B).

A between-group random effects comparison of movement-related activations confirmed that multiple regions were less active with movement in PD subjects than in normals. Regions of hypoactivation included left frontoparietal cortical regions (Fig. 3C, 3–4, red–yellow loci), right globus pallidus, left insula, occipital lobe (Fig. 3C, 2), and ipsilateral and midline cerebellum (Fig. 3C, 1, Table 3). The only region more active with movement in PD subjects was the right pre-SMA (Fig. 3C, 4, blue–green locus; Table 3). The locations where movement-related rCBF differed significantly between groups (Fig. 3C, dotted lines and arrows) corresponded to visibly different patterns of within-group movement-related activity (compare matching regions in Figs. 3A and B).

Velocity effects

These univariate ANCOVAs used actual mean velocity of movement for individual subjects and scans as the co-

variate of interest across all active movement scans. Few cerebral locations in normal subjects had activity that covaried with movement velocity, which is consistent with a previous study that used target rate as the contrast of interest (Turner et al., 1998). Many more cerebral locations were activated with movement velocity in PD subjects. In normal subjects, velocity-related activations were found in contralateral sensorimotor cortex (Fig. 4A, 6) and dorsolateral premotor cortex (area 6, Fig. 4A, 5–6), visual regions (Fig. 4A, 2), and cerebellum (Fig. 4A, 1; Table 4). In PD subjects, velocity-related activations were observed in bilateral dorsal, ventral, and mesial premotor cortical regions (Figs. 4B, 3–6; Table 4), in the left BG (Fig. 4B, 2), and in midline cerebellum (Fig. 4B, 1).

Previously, using 9 of the current 12 normal subjects, we showed that left posterior globus pallidus (GP) was one of the three cerebral locations where rCBF correlated robustly with target rate [sensorimotor cortex and cerebellum being the other two (Turner et al., 1998)]. Here, the same left posterior GP location showed a trend toward velocity-related activation in normal subjects ($t_{47} = 2.9$, $P < 3e\text{-}3$; location = −22, −12, 4). The significant velocity-related activation of left BG found in parkinsonian subjects (Fig. 4B, 2) was anterior and dorsolateral to this subthreshold pallidal location.

Between-group differences in rCBF–velocity relationships were identified using actual velocity performance in a random-effects ANCOVA, thereby controlling for group differences in task performance and possible sampling biases. This comparison confirmed that numerous cortical sites and the left BG were more activated by velocity in PD compared with control subjects (Fig. 4C, 2–6, blue–green loci, Table 5). The cortical sites included dorsal (Fig. 4C, 5–6) and ventral premotor (Fig. 4C, 3–4) cortex bilaterally and mesial premotor cortex (pre-SMA, Fig. 4C, 5) contralateral to the moving arm. Subcortically, the left middle BG (including putamen and both segments of the pallidum) was more active with velocity in PD subjects (Fig. 4C, 2). It is noteworthy that only two regions [occipital lobe (Fig. 4C, 2; Table 5) and cerebellum (Fig. 4C, 1)] had lower than normal velocity relations in the PD subjects. Again, most of the locations where velocity-related rCBF differed significantly between groups (Fig. 4C, dotted circles) corresponded to visibly different patterns of within-group velocity-related activity (compare matching regions in Figs. 4A and B). Two additional sites, left inferior parietal lobe and left dorsal premotor (marked by cross-hairs in Fig. 4 and asterisks in Table 5), just subthreshold for significance in the univariate analysis (>50 voxels $P < 0.01$), were subsequently identified as reliable contributors to this pattern in the PLS analysis.

Table 2
Brain areas with significant movement-related increases in rCBF

Region	Location			Movement effect	
	x	*y*	*z*	*t*	*P*<
Control subjects					
R cerebellum, vermis	5	−59	−22	14.0	6.6E-22
L cerebellum, lobule 4/5	−26	−44	−22	5.7	2.5E-07
R cerebellum, lobule 4/5	14	−50	−14	16.0	5.8E-25
L inferior occipital lobe (19)	−34	−82	−4	4.0	1.3E-04
L lingual gyrus (18)	−25	−94	−1	4.6	1.9E-05
L thalamus/basal ganglia	−19	−20	7	4.0	1.4E-04
L insula (48)	−44	−1	10	4.8	7.6E-06
R basal ganglia	22	−7	11	3.8	3.3E-04
R middle frontal gyrus (46)	35	44	32	3.9	2.0E-04
L postcentral gyrus (3/48/43)	−55	−23	38	5.7	2.8E-07
L medial frontal gyrus (6), SMA	−16	−14	58	8.6	1.4E-12
R inferior parietal lobe (7)	25	−55	58	4.3	5.9E-05
L precentral gyrus (4), SMC	−35	−31	61	15.4	4.5E-24
R postcentral gyrus (3), SMC	28	−41	61	4.0	1.4E-04
R superior frontal gyrus (6), PMd	20	−16	64	8.1	1.4E-11
Parkinsonian subjects					
R cerebellum, lobule 6	−28	−50	−23	4.9	5.7E-06
L cerebellum, lobule 3	−10	−44	−16	5.4	1.0E-06
R cerebellum lobules 4/5	7	−55	−14	8.8	8.5E-13
R inferior occipital lobe (18)	29	−94	−7	3.9	2.1E-04
L basal ganglia	−25	−14	5	4.0	1.5E-04
L postcentral gyrus (2/3), SMC	−56	−25	46	6.1	6.1E-08
L middle cingulum (23), CMA	−4	−8	52	6.1	6.4E-08
L medial frontal gyrus (6), SMA	−14	−17	55	7.1	8.8E-10
R postcentral gyrus (3), SMC	25	−41	59	4.4	3.5E-05
L precentral gyrus (6/4), SMC	−32	−20	65	9.9	6.2E-15

Note. SMC, sensorimotor cortex; PMd, premotor cortex (dorsal); CMA, cingulate motor area. The approximate gyral/nuclear location of the activation was determined according to anatomical labeling (Tzourio-Mazoyer et al., 2002). Locations are in millimeters with respect to the anterior commissure at midline (Talairach and Tournoux, 1988). Approximate Brodmann areas (in parentheses) were determined in accord with the same atlas. Some activations list more than one gyrus and Brodmann's area in recognition of the inherent inaccuracies in translating from standardized stereotaxic locations to gyral and cytoarchitectonic locations (Mazziotta et al., 1995). For each locus, uncorrected *t* statistic ($df = 69$) and *P* values are shown.

Table 3
Brain regions where movement-related activity differed for control and parkinsonian groups

Region	Location			Movement effect	
	x	*y*	*z*	*t*	*P*<
Control > PD					
Cerebellum, vermis	2	−59	−22	3.6	1.5E-03
R cerebellum, lobule 6	20	−59	−16	4.6	1.5E-04
R basal ganglia (putamen/globus pallidus)	23	−11	−1	3.8	9.6E-04
L inferior occipital lobe (19)	−35	−80	−1	3.6	1.8E-03
L insula (48)	−44	−4	4	3.5	1.9E-03
R lingual gyrus (18)	7	−52	5	3.3	3.7E-03
L precentral gyrus (6), PMd	−23	−16	46	3.7	1.3E-03
L pre-/post-central gyrus (4/3), SMC	−35	−29	53	5.0	5.8E-05
PD > Control					
R medial frontal gyrus (6), pre-SMA	10	6	63	3.2	4.1E-03

Note. SMC, sensorimotor cortex; PMd, premotor cortex (dorsal); pre-SMA, presupplementary motor area. Locations are in millimeters with respect to the anterior commissure at midline (Talairach and Tournoux, 1988). Brodmann areas (in parentheses) accord with the same atlas. For each locus, uncorrected *t* statistic ($df = 22$) and *P* values are shown.

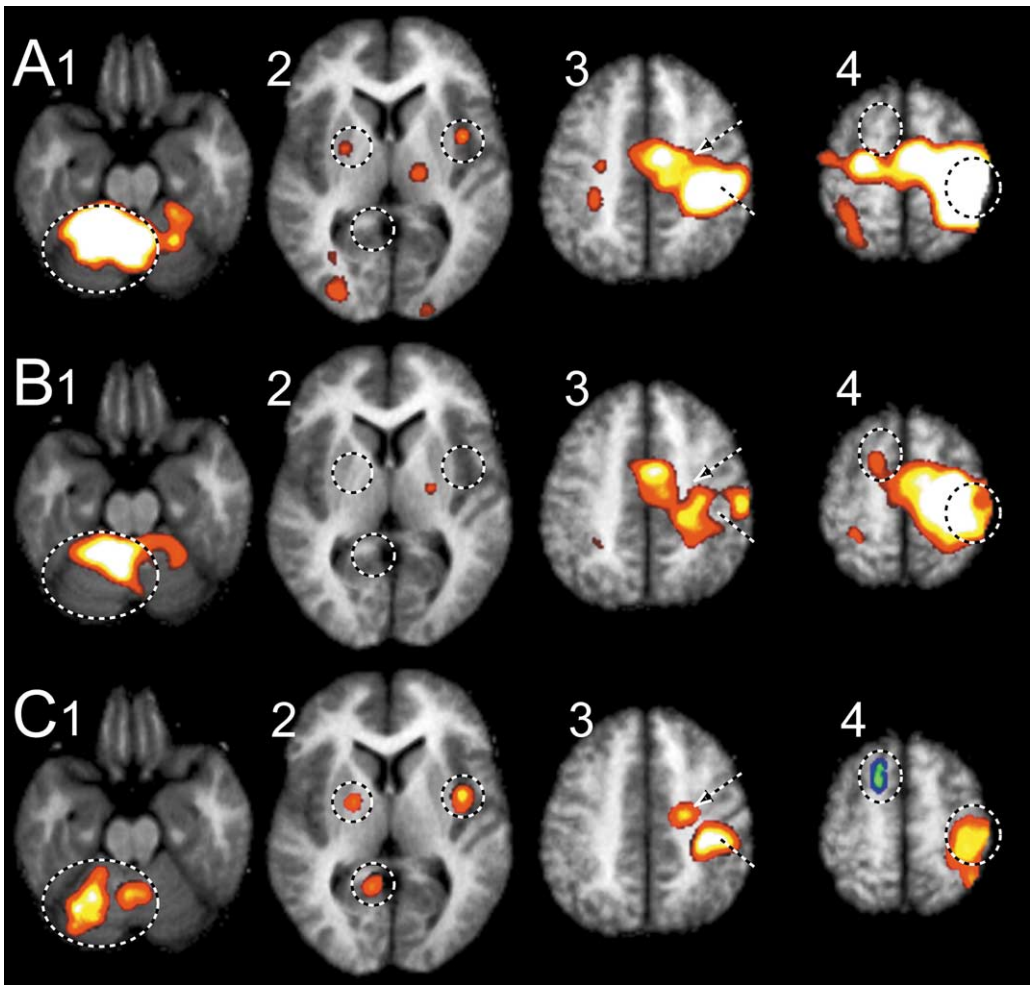
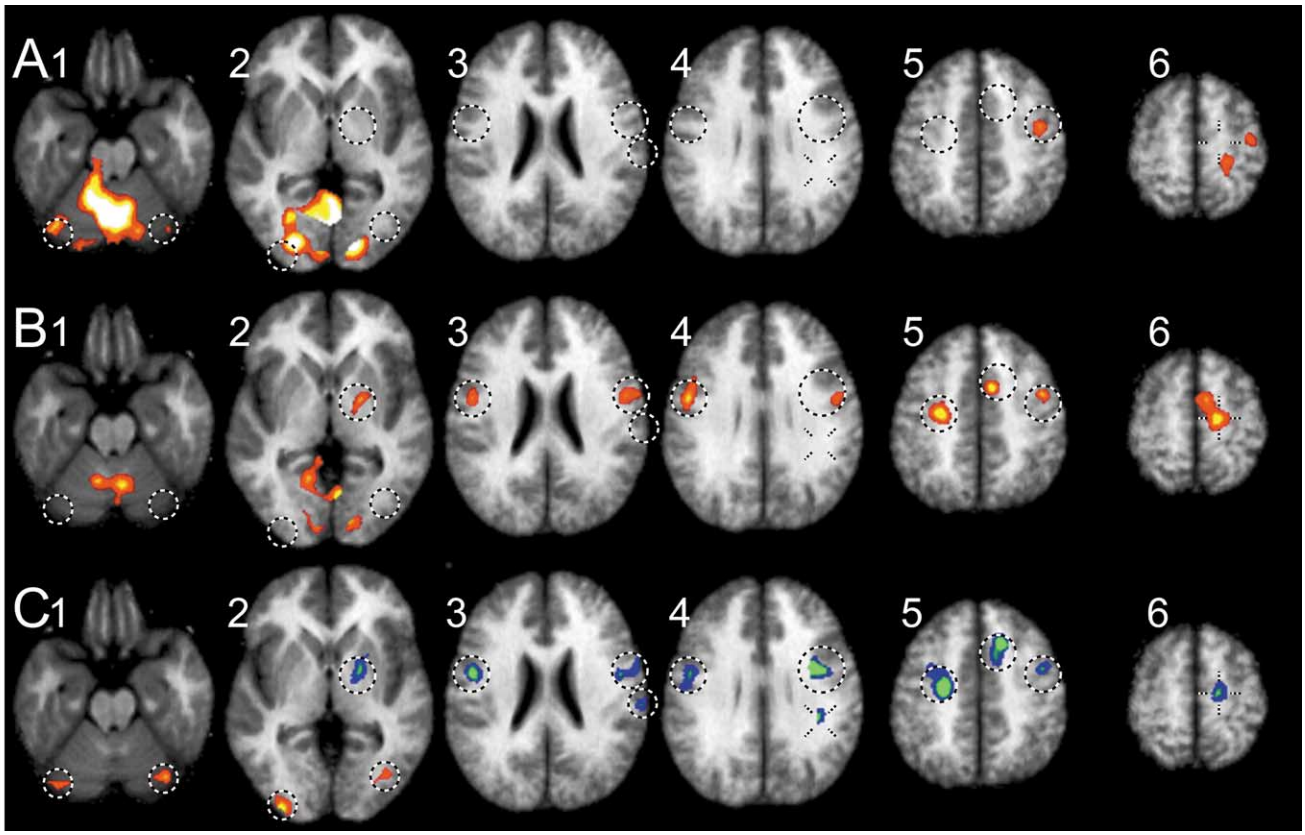


Fig. 3. Movement-related rCBF for normal (A) and parkinsonian (B) subjects and group differences in which movement-related rCBF differed for normal and parkinsonian subjects (C). Within-group comparisons were significant at $P < 0.001$ (>50 voxels) and between group comparisons were significant at $P < 0.005$ (>50 voxels, random effects model). (C) Areas in orange–red represent greater activation in normal subjects. One area in blue–green represents greater movement-related activation of right pre-SMA in parkinsonian subjects. Locations of significant between-group difference (C) are marked by dotted circles/lines so as to aid comparison of the within-group images. *T*-maps are shown superimposed on a mean magnetic resonance image from 20 normal subjects. Axial slices correspond to Talairach *z*-axis: −18, 9, 50, and 62. According to radiological convention, the right hemisphere is to the left.

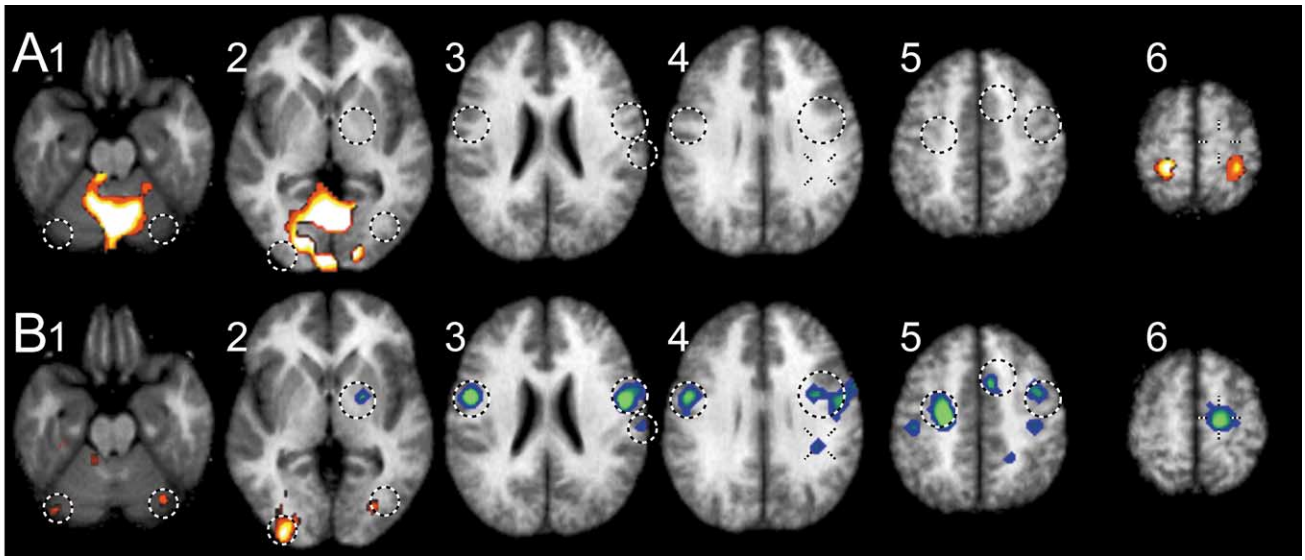
The univariate analysis of group differences in velocity-related activity identified cerebral locations where the relationship between rCBF and movement velocity differed between groups, but this analysis did not distinguish between the possible underlying explanations. Sites identified as more sensitive to velocity in PD subjects, for example, could be generated by several possible effects: (1) velocity-related activation in PD of a site not normally velocity-related; (2) the loss of velocity-related suppression at a location where activity in normals is reduced with increasing movement rate; or (3) a combination of the first two possibilities. PLS analysis was performed both to distinguish between the above explanations and to substantiate the results of the univariate analysis for velocity using a technique that is insensitive to problems of multiple comparisons and the assumptions of a priori hypotheses.

PLS analysis

The between-group PLS analysis identified two reliable LVs. The first LV ($P < 0.0001$, permutation test) identified brain regions where rCBF covaried with movement rate in a similar manner for normal and PD subjects (post hoc contrast for main effect of rate, $F_{1,138} = 38.4$, $P <$ 2e-9). Consistent with the interpretation that LV1 identified regions activated similarly in normal and PD subjects, there was no group-by-rate interaction ($F_{2,138} = 1.4$, $P = 0.72$). The brain regions contributing to LV1 included left and right primary sensorimotor cortices (Fig. 5A, 6), cerebellum (Fig. 5A, 1), and visual cortices (Fig. 5A, 2; Table 6, Control = PD). The within-group PLS analyses yielded significant positive reliability ratios (salience/standard error > 2.3) for both normal and PD subjects at all of the locations identified by LV1 (Table 6). Similar patterns of task-



4



5

Fig. 4. Velocity-related rCBF for normal (A) and parkinsonian (B) subjects and group differences in which velocity-related rCBF differed for normal and parkinsonian subjects (C). Within-group comparisons were significant at $P < 0.001$ and between-group comparisons were significant at $P < 0.005$ (random effects model). (C) Brain activity was more activated with velocity in PD subjects (blue–green) at multiple motor cortical sites (C, 3–6) and in the basal ganglia (C, 2). Brain activity was more activated with velocity in control subjects (orange–red) in cerebellum and visual cortex (C, 1–2). Axial slices correspond to Talairach *z*-axis: −18, 3, 27, 33, 51, and 62. Images are formatted otherwise as in Fig. 3.

Fig. 5. Rate-related brain areas identified by PLS analysis. (A) Brain areas identified by LV1 to have a common pattern of rate-related activity in normal and parkinsonian subjects. (B) Brain areas identified by LV2 to have greater rate-related activity in normal subjects (orange–red). Blue–green loci identify sites where rate-related activity was greater in PD subjects. Locations of significant between-group difference identified by previous univariate analysis (Fig. 4C) are marked by dotted circles/lines so as to aid comparison of the within-group images. Images threshold is a reliability ratio > 2.3 ($P < 0.05$ approx.). Axial slices correspond to Talairach *z*-axis: −18, 3, 27, 33, 51, and 62. Images are formatted otherwise as in Fig. 3.

related brain activity for normal and PD subjects were also evident in plots of rCBF (expressed as percentage change from the control condition) vs mean movement velocity (Fig. 6, top left).

The second LV ($P < 0.006$, permutation test) identified brain regions where the relation between movement rate and rCBF differed for normal and PD subjects (post hoc contrast for group-by-rate interaction, $F_{2,138} = 3.7$, $P < 0.03$). For LV2, there was no main effect of movement rate ($F_{1,138} = 1.2$, $P = 0.27$). LV2 identified two independent sets of brain areas: those where the rCBF/rate relation (i.e., the slope of the relationship) was more positive in PD subjects than in normals (PD > Control in Table 6), and those where the rCBF/rate relation was more positive in normal subjects than in PDs (Control > PD in Table 6). The two independent patterns will be described in turn.

The rCBF/rate relation was more positive for PD subjects (or more negative for normals) at a large number of cerebral locations (Fig. 5B, blue–green areas; Table 6, PD > Control). The locations of these areas of activation corresponded closely with locations identified previously by univariate between-group analysis of the effects of velocity (dotted circles in Fig. 5B). The activations identified by PLS were subdivided further according to whether the between-group difference could be attributed to an increased positive relation in PD subjects (PD ↑ in Table 6; reliability ratios >2.3 in PDs, nonsignificant in normals), loss of a negative relation that was present in normal subjects (Nor ↓, reliability ratio < −2.3 in normals, nonsignificant in PDs), or a combination of the two (PD ↑ & Nor ↓ in Table 6, reliability ratios < −2.3 in normals and >2.3 in PDs). Among the sites that followed the first pattern (i.e., PD ↑), most were in brain regions associated with motor control (bilateral dorsal premotor cortices, left ventral premotor cortex, bilateral ventral sensorimotor cortex, pre-SMA, and left BG). This pattern identified a group of brain regions that were not influenced by movement rate in normal control subjects, but were rate-related in PD. Fig. 6 (bottom) illustrates this relationship for four representative regions in plots of mean rCBF (expressed as percentage change from baseline) vs mean movement velocity. These plots show that the between-group differences in velocity-related activation were independent of group differences in task performance (a point addressed rigorously by univariate analysis).

Table 4
Brain locations with significant velocity-related increases in rCBF

Region	Location			Rate effect	
	x	*y*	*z*	*t*	*P*<
Control subjects					
R cerebellum, lobule 6	34	−71	−20	4.0	2.6E-04
Cerebellum, vermis, lobule 6	1	−68	−16	8.2	1.3E-10
R cerebellum, lobules 4/5	11	−52	−13	7.7	6.5E-10
R inferior occipital lobe (18)	22	−82	−2	5.9	4.2E-07
L lingual gyrus (18)	−6	−66	4	5.4	2.2E-06
L calcarine fissure (18)	−14	−86	10	7.5	1.5E-09
L precentral gyrus (6), PMd	−42	−6	52	3.7	6.0E-04
L pre-/post-central gyrus (4/3), SMC	−26	−28	64	3.6	7.6E-04
Parkinsonian subjects					
L cerebellum, lobule 6	−8	−63	−20	4.1	1.6E-04
R cerebellum, lobules 4/5	6	−60	−15	4.0	2.2E-04
L lingual gyrus (18)	−9	−74	−4	5.2	4.4E-06
R lingual gyrus (18)	12	−57	0	3.8	4.7E-04
L basal ganglia (putamen/globus pallidus)	−32	1	7	3.6	7.6E-04
L calcarine fissure (17)	−15	−92	11	4.2	1.1E-04
L ventral precentral gyrus (6), PMv	−53	−4	28	3.6	7.2E-04
R ventral precentral gyrus (6), PMv	46	−4	30	4.1	1.7E-04
L precentral gyrus (6), PMd	−45	−3	48	4.4	7.3E-05
L medial frontal gyrus (6), SMA	−10	−2	52	4.2	1.1E-04
R middle frontal gyrus (6), PMd	22	−15	54	4.2	1.3E-04
L precentral gyrus (6), PMd	−16	−20	63	4.1	1.5E-04

Note. SMC, sensorimotor cortex; PMd, premotor cortex (dorsal); PMv, premotor cortex (ventral); SMA, supplementary motor area (proper). Locations are in millimeters with respect to the anterior commissure at midline (Talairach and Tournoux, 1988). Brodmann areas (in parentheses) accord with the same atlas. For each locus, uncorrected *t* statistic ($df = 47$) and *P* values are shown.

Table 5
Locations at which velocity-related activations differed for control and parkinsonian subjects

Region	Location			Velocity effect	
	x	*y*	*z*	*t*	*P*<
Control > PD					
L cerebellum, lobule 6	−41	−41	−25	3.3	3.5E-03
R cerebellum, crus 1	37	−82	−13	3.4	2.5E-03
L inferior occipital lobe (19)	−41	−71	−4	3.2	3.8E-03
R middle occipital lobe (18)	30	−93	6	3.7	1.2E-03
PD > Control					
L basal ganglia (putamen/globus pallidus)	−22	−3	2	3.4	2.8E-03
L superior temporal gyrus (22)	−67	−28	19	3.8	8.9E-04
L rolandic operculum (6)	−64	2	20	3.5	1.9E-03
R ventral precentral gyrus (6/44), PMv	46	−4	28	3.3	3.0E-03
L precentral gyrus (6), PMv	−43	−2	35	4.2	4.0E-04
R precentral gyrus (6), PMd	20	−16	49	3.9	7.7E-04
L medial frontal gyrus (6), pre-SMA	−19	14	50	3.6	1.7E-03
*L supramarginal gyrus (48)	−39	−34	33	3.1	5.2E-03
*L superior frontal gyrus (6), PMd	−16	−18	62	2.9	7.9E-03

Note. SMC, sensorimotor cortex; PMd, premotor cortex (dorsal); PMv, premotor cortex (ventral); pre-SMA, presupplementary motor area. Locations are in millimeters with respect to the anterior commissure at midline (Talairach and Tournoux, 1988). Brodmann areas (in parentheses) accord with the same atlas. For each locus, uncorrected *t* statistic ($df = 22$) and *P* values are shown.

* Loci which were subthreshold in this comparison ($0.01 > P > 0.005$), but identified subsequently by PLS to contribute to the same covariance pattern.

Table 6
Local maxima from partial least-squares analysis

Region	Location			Reliability ratio		
	x	*y*	*z*	Nor	PD	Effect
LV1: Control = PD						
Cerebellum, vermis lobule 6	0	−63	−18	10.0	3.2	Nor ↑ & PD ↑
R cerebellum, lobules 4/5	6	−54	−9	13.9	3.4	
R inferior occipital lobe	3	−87	6	4.9	3.9	
L inferior occipital (18)	−21	−84	12	8.3	3.7	
R paracentral lobule (4/6), SMC	20	−29	62	4.0	4.4	
L precentral gyrus (4/6), SMC	−30	−27	66	3.2	2.4	
LV2: PD > Control						
L basal ganglia (putamen/ globus pallidus)	−24	−3	6	0.3	3.4	PD ↑
L rolandic operculum (6/ 44), PMv	−69	12	15	−0.1	2.6	
L ventral pre/post-central (6/43), PMv	−57	−3	30	−1.5	4.2	
R precentral gyrus (6/44), PMv	45	−3	33	−1.6	3.4	
L supramarginal gyrus (48)	−42	−30	39	−0.8	3.0	
L precentral gyrus (6), PMv	−42	−3	40	−1.0	5.3	
R pre-/post-central gyrus (4/3), SMC	42	−21	48	−1.3	3.0	
L pre-/post-central gyrus (4/3), SMC	−45	−21	51	−0.1	2.9	
L medial frontal gyrus (6), pre-SMA	−12	9	57	−1.3	3.4	
L superior frontal gyrus (6), PMd	−15	−21	63	1.1	4.6	
R middle frontal gyrus (6), PMd	18	−12	54	−2.3	5.4	PD ↑ & Nor ↓
R precentral gyrus (6), PMd	24	0	45	−3.5	2.5	
R middle frontal gyrus (46)	30	36	27	−3.3	−0.6	Nor ↓
L supramarginal gyrus (48)	−69	−21	30	−3.4	0.6	
LV2: Control > PD						
R cerebellum, lobule 3	9	−39	−9	4.6	−1.4	Nor ↑
R parahippocampal gyrus	27	−42	−3	0.0	−5.2	PD ↓
R middle occipital lobe (18)	24	−90	9	1.1	−5.5	
L middle occipital lobe (19)	−33	−72	9	1.5	−2.7	
R precuneus (5)	12	−54	60	−0.1	−3.2	

Note. Areas were identified by the first and second latent variables (LV1 and LV2) in a between-group PLS analysis (absolute reliability ratios > 2.3, $P < 0.05$ approximately). Coordinates and estimated Brodmann's areas are from Talairach and Tournoux (1988). Nor and PD, reliability ratios from matching within-group PLS analyses of normal and parkinsonian subjects. Effect, categorization of regional PLS results according to whether rCBF was correlated with movement rate in a positive (↑) or negative (↓) manner for normal (Nor) and/or parkinsonian (PD) subjects.

The two loci with negative relations in normal subjects (Nor ↓ in Table 6) were associative regions where rCBF normally decreases with increasing movement rate, but did not do so in the PD subjects. Brain sites marked by a combination of positive rCBF/rate relations in PD subjects and negative relations in normals were restricted to two premotor cortical regions ipsilateral to the moving arm.

Brain activity more closely related to rate in normal subjects was found at only five sites (LV2: Control > PD in Table 6). Among these, only the cerebellum (ipsilateral to the moving arm) was exclusively related to movement rate in normal subjects (Fig. 6, top right; Nor ↑ in Table 6). At the remaining sites, which were in visual and associative regions, activity was negatively related in the PD group (Fig. 6, top far right; PD ↓) and not influenced by rate in normals.

Discussion

In this study we used a visuomotor task that emphasizes the scaling of movement velocity to identify a unique pattern of abnormal brain activity in Parkinson's disease. Here, our comparison of present results with previous functional imaging studies of PD leads to the following conclusions: (1) that parkinsonian abnormalities in brain activity depend on the nature of the task being performed; (2) that brain regions normally involved in a task are underactive in PD; and (3) that brain regions not normally involved in a task may become task-related in PD (i.e., "ectopic" activations). Finally, we consider whether ectopic activations may be a facet of parkinsonism itself, or alternatively, correlates of compensatory mechanisms.

We sought in this study to avoid possible confounds by performing two independent mutually-reinforcing analyses. First, random effects ANCOVAs were used to ensure that between-group differences identified here are likely to be found in the population at large. We used movement velocity as the covariate of interest to factor out major between-group differences in performance. Second, independent of a priori hypotheses and parametric assumptions, PLS analysis identified a pattern very similar to that found using ANCOVA. PLS established significance for the entire pattern, thus dispelling concerns about multiple statistical comparisons. Despite our efforts, residual differences in performance or other confounds may influence the generality of our results. We did not control for minor group differences in temporal error and eye movements. Although anti-parkinsonian medications were withheld 12 h prior to scanning, long-acting dopamine agonists may have had a lingering influence. Finally, because our task depended heavily on visual guidance, results may not generalize to contexts in which movement is not visually guided.

Visuomotor tracking as a probe for bradykinesia-related brain activity

The performance deficits of PD subjects indicated that sinusoidal tracking was an appropriate task for isolating correlates of parkinsonian bradykinesia. PD subjects increased hand velocities with target rate, but not to the degree required to follow the full extent of target displacement. Confronted with the choice of matching target extent or

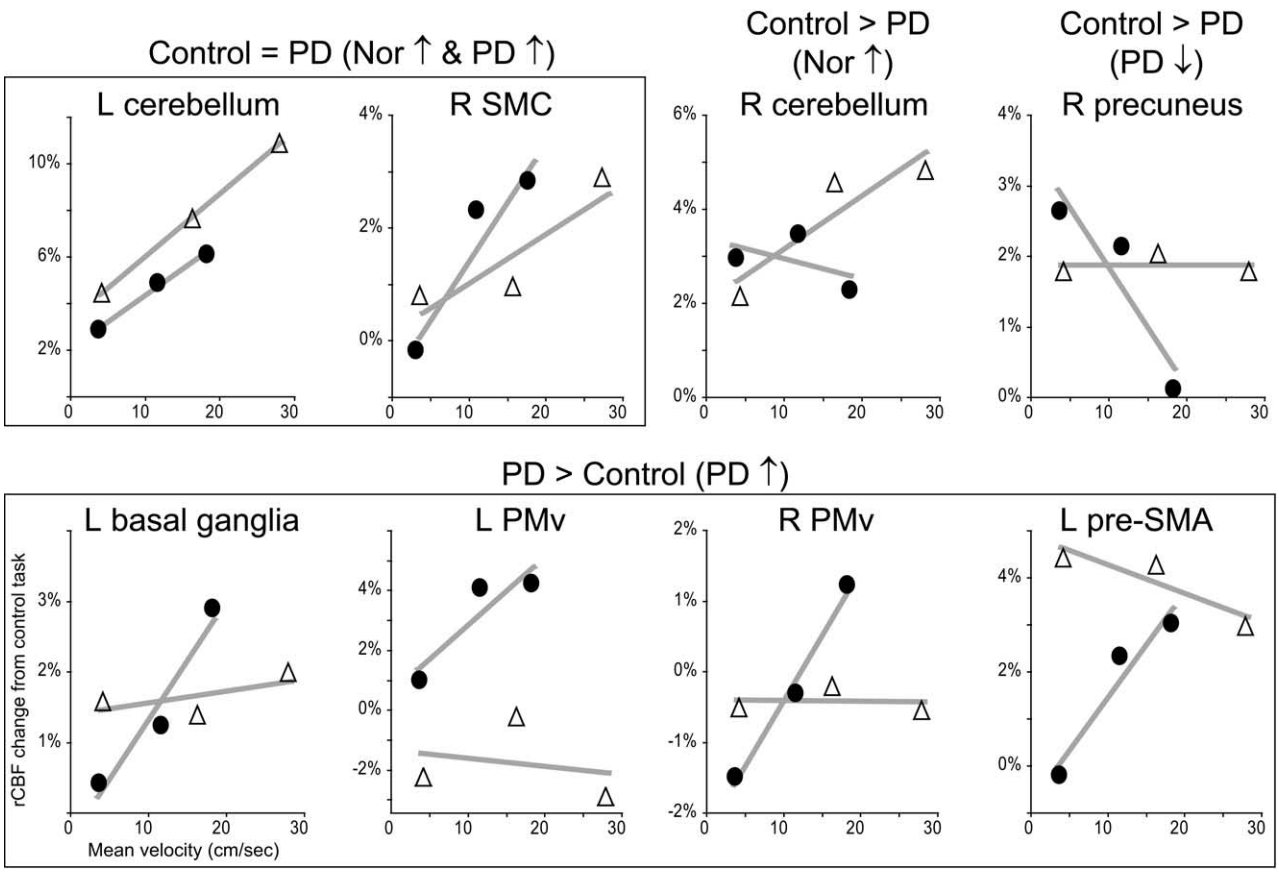


Fig. 6. Plots of mean brain scores vs target rate for LV1 and LV2. LV1 identified a group of brain areas where rCBF increased with movement rate in a similar fashion for normal and PD subjects. LV2 identified brain areas where rCBF was related to movement rate differently for normal and PD subjects.

timing, PD subjects reduced movement amplitudes so as to better synchronize their movements with those of the target. Consistent with this interpretation, PD subjects showed a pattern of temporal errors similar to that of normals: phase lag for the slow target and close synchronization at faster rates. For all three rates, between-group differences in velocity and extent were large while differences in temporal error were small. Considering that our moderate-to-severe PD subjects failed to show consistently slowed timing, whereas slowed selection and initiation of movement are considered key aspects of akinesia (Evarts et al., 1981; Lakke, 1981), we conclude that the sinusoidal tracking task put little demand on CNS mechanisms for movement selection/initiation. As further evidence that our task manipulated bradykinetic symptoms independently, errors in extent or velocity were highly correlated with each other but neither were correlated with errors in timing (consistent with, e.g., Jordan et al., 1992; Meyer, 1982; van Hilten et al., 1998). Between-group differences in eye movements were relatively subtle and likely not sufficient to account for the major differences in brain activity.

It is important to note that the present experiment did not attempt to dissociate movement velocity from other measures that covary systematically (e.g., movement accuracy, joint torques, and muscle EMG). Physical constraints required that the rate of reversals in movement direction also covary with mean velocity. The purpose of this paradigm was to manipulate the constellation of movement parameters of which impairment is termed bradykinesia.

Visuomotor tracking has been used previously in PD patients to investigate changes in control strategy (Flowers, 1978; Liu et al., 1999), kinematics (Abdel-Malek et al., 1988; Hufschmidt and Lucking, 1995; Johnson et al., 1996), reflex modulation (Johnson et al., 1996), and motor learning (Hufschmidt and Lucking, 1995; Soliveri et al., 1997). Although some studies report that PD subjects lag behind the target more than normals (Abdel-Malek et al., 1988; Flowers, 1978), the most marked differences in lag were observed when subjects tracked unpredictable targets (Abdel-Malek et al., 1988; Hufschmidt and Lucking, 1995). Temporal differences in performance between PD and normal subjects were minimal when the target followed a predictable sinusoidal displacement (Flowers, 1978).

Underactivation: a task-specific correlate of Parkinson's disease

Consistent with a well-recognized model of parkinsonian pathophysiology (Wichmann and DeLong, 1996), we found

that a large fraction of the cerebral volume activated with movement had below-normal movement-related activity in PD subjects. The underactive regions included primary sensorimotor cortex, bilateral premotor cortices, right BG, and cerebellum. Many previous studies have reported discrete sites of underactivation in mesial premotor and dorsolateral prefrontal cortices for tasks that emphasize free selection and initiation of discrete ballistic movements (Catalan et al., 1999; Haslinger et al., 2001; Playford et al., 1992; Rascol et al., 1997; Sabatini et al., 2000; Samuel et al., 1997a). The present results, however, are more in agreement with other studies showing that task-related cerebral activity may be impaired at a variety of cortical and subcortical locations depending on the task being performed (Boecker et al., 1999; Catalan et al., 1999; Hanakawa et al., 1999b; Haslinger et al., 2001; Nakamura et al., 2001). For example, Catalan et al. (1999) reported that primary sensorimotor cortex and cerebellum were underactive when PD subjects performed sequential movements, whereas mesial premotor areas were underactive when subjects had to select movements at random ("free selection"). Together, these results may be explained by a simple model of parkinsonism whereby BG dysfunction culminates in insufficient recruitment of the whole network of brain areas normally used to perform a task.

Among the cerebral locations that were velocity-related in normal subjects, only right cerebellum was also underactivated by velocity in PD. Velocity relations did not differ between groups at the remainder of the locations activated by velocity in normals (in motor and premotor cortices). Assuming that velocity-related activity identifies brain regions involved in regulating movement velocity, the present results suggest cerebellum is the chief brain region where impaired activation contributes to parkinsonian bradykinesia. A role for cerebellum in controlling velocity or rate is quite likely (Fu et al., 1997; Turner et al., 1998 and references therein) and hypoactivation of cerebellum may impair the ability to scale the level of muscle activation to meet the demands of the task. The route by which abnormal BG outflow in PD influences cerebellar function remains unknown, but certainly involves a multisynaptic pathway.

Excluding cerebellum, all of the sites hypoactive for velocity in PD were in fact deactivated (i.e., correlated negatively with velocity) in PD subjects and not influenced by velocity in normals (illustrated for right precuneus in Fig. 6). The functional significance of these velocity-related deactivations is a matter of speculation. They may be pathophysiologic correlates of impaired oculomotor function in PD. Alternatively, they may reflect a homeostatic mechanism to maintain global CBF despite increased velocity-related activation elsewhere.

Overactivation: compensation or impaired selection?

Univariate analysis revealed multiple sites where velocity-related activity was increased in PD. The importance of these overactivations was emphasized by the nearly identical network of loci identified by PLS as the most salient covariance pattern to differentiate brain activity of normal and parkinsonian subjects. This pattern included bilateral sensorimotor, ventral premotor, dorsal premotor, pre-SMA, and BG. Right pre-SMA was also overactive with respect to movement-related activity. Note that mesial premotor cortices are predicted to be underactive by the many studies that used movement selection tasks (Haslinger et al., 2001; Jahanshahi et al., 1995; Playford et al., 1992; Rascol et al., 1992; Sabatini et al., 2000; Samuel et al., 1997a). One possible explanation for these apparently divergent results is that the specific pattern of functional abnormalities in PD depends on the nature of the task being performed.

Most previous studies that found cerebral overactivations in PD have interpreted them as compensatory recruitments of alternate motor circuits—including visually driven corticocerebellar loops (Glickstein and Stein, 1991)—to overcome impaired function of mesial frontal circuits. The overactivations we found in ventral premotor and inferior parietal cortices may well be considered compensatory recruitment of visually competent regions because these regions are known to participate in visuomotor coordination (Graziano et al., 1997; Rizzolatti et al., 1990). Overactivation of dorsolateral premotor cortex may also be associated with sensory-driven compensation. Hanakawa et al. (1999a) observed increased activation at a similar location when visual stimuli prompted paradoxical improvements in parkinsonian gait.

Other overactivations cannot easily be explained as visually driven compensation. We found consistent movement- and velocity-related overactivation of mesial premotor cortex. Catalan et al. (1999) also found that mesial frontal areas were activated proportionate with sequence complexity only in PD subjects. Mesial frontal regions are thought to contribute to action selection and sequencing independent of immediate sensory feedback (e.g., Hikosaka et al., 1996; Shima and Tanji, 1998). Thus, overactivation of mesial premotor cortex cannot be described as recruitment of visually competent motor circuits although it may still reflect some form of compensation. The velocity-related overactivation of left sensorimotor cortex and BG are also difficult to account for in terms of compensatory recruitment. A possible alternative is that some overactivations reflect a facet of the primary pathophysiology of PD, such as an inability to inhibit contextually inappropriate circuits (Boecker et al., 1999). An impaired ability to control or focus regional activity could arise from dysfunction of the BG, per se (Mink, 1996), or equally likely, from dysfunction of the thalamus and/or frontal lobes secondary to abnormal BG outflow. Abnormal recruitment (or faulty suppression) has been used to explain similar "ectopic" activations found after recovery from stroke (Weiller et al., 1992) and as a correlate of cognitive decline associated with aging (Esposito et al., 1999; Logan et al., 2002). Thus,

impaired selection may be a common correlate of CNS insult.

It is unclear how to disambiguate the functional correlates of faulty suppression and compensation. Our post hoc analysis of LV2 might tempt one to conclude that only associative brain regions showed faulty suppression (i.e., "Nor ↓" regions in Table 6), whereas motor regions were overactive due to compensation ("PD ↑" regions). That interpretation is simplistic, however, because it is equally possible from a theoretical perspective for impaired suppression to appear as abnormal spread of excitation or loss of inhibition. Although much remains to be explored concerning abnormally increased brain activity, it is clear that the patterns are task-specific and thus may provide information about the functional substrates of various parkinsonian symptoms.

The present results directly address a debate of whether overactivations are present in PD only during sequential movement tasks (Praamstra et al., 1998; Samuel et al., 1997). We observed overactivations in both movement- and rate-related comparisons using a task that had little or no sequential component. Thus, it is likely that overactivations are a correlate of PD itself.

Implications for understanding the pathophysiology of bradykinesia

The physiological substrate for most motor symptoms of PD can be traced to increased firing rates, synchronous burst firing, and exaggerated responsiveness of neurons in the internal globus pallidus (GPi), the primary output nucleus of the BG motor circuit (Filion et al., 1988; Miller and DeLong, 1987; Nini et al., 1995). Several nonexclusive hypotheses attempt to link BG pathology to parkinsonian bradykinesia. Perhaps the simplest model is that increased activity of GABAergic GPi neurons inhibits thalamocortical circuits, thereby constraining the maximal rate of change in descending commands (DeLong, 1990). This model accounts well for the cortical underactivations reported widely for PD. Our observation, however, of task-related overactivity in multiple motor and premotor sites—all of which are BG-recipient (Middleton and Strick, 2000)—is inconsistent with the model's prediction that activity should be reduced across-the-board in all cortical regions directly influenced by BG outflow (Wichmann and DeLong 1996). Metabolic imaging studies also show that a diffuse deficit in resting cortical metabolism in PD does not reflect known BG-thalamocortical connectivity (Eidelberg et al., 1994; Hu et al., 2000; Piert et al., 1996). Also contrary to the simple model, transcranial magnetic stimulation and evoked potential experiments have shown that motor cortex in PD subjects is susceptible to overexcitation (Kleine et al., 2001; Praamstra and Plat, 2001; Ridding et al., 1995).

An alternative model proposes that normal BG outflow works via thalamocortical inhibition to suppress activity that might otherwise interfere with task performance (Mink, 1996; Mink and Thach, 1991; Penney and Young, 1983). Impairment of this suppressive or "focusing" function in PD may account for cortical overactivations and also for the exaggerated influence in PD of visual (Castiello et al., 2000; Murata et al., 1997; Wannier et al., 1989) or somatosensory inputs (Aminoff et al., 1997) on cortical activity and motor performance. It is also well-recognized that cortical inhibitory mechanisms are abnormal in PD (Priori et al., 1994; Ridding et al., 1995), as are cortical rhythms (Brown and Marsden, 1998; Brown et al., 2001; Goldberg et al., 2002), which depend on the activity of local inhibitory interneurons (Deans et al., 2001; Swadlow et al., 1998). Interestingly, the impairment of cortical rhythms in PD has been shown to correlate with the degree of bradykinesia (Brown et al., 2001). Although the relationship between these local cortical abnormalities and abnormal BG outflow is not understood at present, it is possible that local abnormalities also contribute to the cortical overactivations observed here and elsewhere.

The velocity-related overactivation of left BG is noteworthy because we reported previously that left posterior (i.e., "motor") GP is part of a small network of regions that contribute to the normal control of movement rate (Turner et al., 1998). Those results were seen as consistent with a role for normal BG in controlling movement speed and extent via kinematics-related modulation of thalamocortical excitability (Georgopoulos et al., 1983; Horak and Anderson, 1984; Turner and Anderson, 1997). Here, the same motor GP location had a subthreshold relation to velocity in normal subjects. The overactivated region of BG likely occupied premotor or associative BG circuits located anterodorsolateral to the motor circuit (Alexander et al., 1990; Middleton and Strick, 2000). Overactivation of this region in PD may be a simple correlate of overactivity in the cortical regions that project to this part of the BG, or it may be a product of the exaggerated neuronal responsiveness and loss of specificity in the BG secondary to nigrostriatal degeneration (Filion et al., 1988; Miller and DeLong, 1987; Nini et al., 1995). The latter explanation raises the intriguing possibility that the spread of velocity-related activation to BG circuits not normally involved in low-level motor control is the progenitor of the abnormalities observed elsewhere.

In summary, the differences we found in task-related activations can be attributed to disease-related alterations in the motor control circuitry and not merely to group differences in task performance. The structures normally activated with movement are hypoactivated in PD and additional cortical areas are recruited, possibly reflecting a facet of the primary pathophysiology of PD and/or compensatory mechanisms.

Acknowledgments

This work was supported by grants from the Dana foundation, and Public Health Service Grants NS33704 and

NS37470. The authors thank Delicia Votaw and Michael White for their technical assistance.

References

Abdel-Malek, A., Markham, C.H., Marmarelis, P.Z., Marmarelis, V.Z., 1988. Quantifying deficiencies associated with Parkinson's disease by use of time-series analysis. Electroencephalogr. Clin. Neurophysiol. 69, 24–33.

Adamovich, S.V., Berkinblit, M.B., Hening, W., Sage, J., Poizner, H., 2001. The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease. Neuroscience 104, 1027–1041.

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia thalamo-cortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog. Brain Res. 85, 119–146.

Aminoff, M.J., Siedenberg, R., Goodin, D.S., 1997. Changes of forearm EMG and cerebral evoked potentials following sudden muscle stretch during isometric contractions in patients with Parkinson's disease. Brain Res. 757, 254–259.

Berardelli, A., Rothwell, J.C., Thompson, P.D., Hallett, M., 2001. Pathophysiology of bradykinesia in Parkinson's disease. Brain 124, 2131–2146.

Boecker, H., Ceballos-Baumann, A., Bartenstein, P., Weindl, A., Siebner, H.R., Fassbender, T., Munz, F., Schwaiger, M., Conrad, B., 1999. Sensory processing in Parkinson's and Huntington's disease: investigations with 3D H(2)(15)O-PET. Brain 122, 1651–1665.

Brown, P., Marsden, C.D., 1998. What do the basal ganglia do? Lancet 351, 1801–1804.

Brown, P., Marsden, J., Defebvre, L., Cassim, F., Mazzone, P., Oliviero, A., Altibrandi, M.G., Di Lazzaro, V., Limousin-Dowsey, P., Fraix, V., Odin, P., Pollak, P., 2001. Intermuscular coherence in Parkinson's disease: relationship to bradykinesia. Neuroreport 12, 2577–2581.

Castiello, U., Bonfiglioli, C., Peppard, R.F., 2000. Dopaminergic effects on the implicit processing of distractor objects in Parkinson's disease. Exp. Brain Res. 135, 251–258.

Catalan, M.J., Ishii, K., Honda, M., Samii, A., Hallett, M., 1999. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. Brain 122, 483–495.

Ceballos-Baumann, A.O., Obeso, J.A., Vitek, J.L., DeLong, M.R., Bakay, R., Linaasoro, G., Brooks, D.J., 1994. Restoration of thalamocortical activity after posteroventrolateral pallidotomy in Parkinson's disease. Lancet 344, 814.

Corcos, D.M., Chen, C.-M., Quinn, N.P., McAuley, J., Rothwell, J.C., 1996. Strength in Parkinson's Disease: relationship to rate of force generation and clinical status. Ann. Neurol. 39, 79–88.

Davis, K.D., Taub, E., Houle, S., Lang, A.E., Dostrovsky, J.O., Tasker, R.R., Lozano, A.M., 1997. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. Nature Med. 3, 671–674.

Deans, M.R., Gibson, J.R., Sellitto, C., Connors, B.W., Paul, D.L., 2001. Synchronous activity of inhibitory networks in neocortex requires electrical synapses containing connexin36. Neuron 31, 477–485.

DeLong, M.R., 1990. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13, 281–285.

Eidelberg, D., Moeller, J.R., Dhawan, V., Spetsieris, P., Takikawa, S., Ishikawa, T., Chaly, T., Robeson, W., Margouleff, D., Przedborski, S., et al., 1994. The metabolic topography of parkinsonism. J. Cereb. Blood Flow Metab. 14, 783–801.

Esposito, G., Kirkby, B.S., Van Horn, J.D., Ellmore, T.M., Berman, K.F., 1999. Context-dependent, neural system-specific neurophysiological concomitants of ageing: mapping PET correlates during cognitive activation. Brain 122, 963–979.

Evarts, E.V., Teravainen, H., Calne, D., 1981. Reaction time in Parkinson's disease. Brain 104, 167–186.

Fahn, S., Elton, R.L., and the members of the UPDRS development committee, 1987. Unified Parkinson's disease rating scale, in: Fahn, S., Marsden, C.D., Goldstein, M., Calne, D.B. (Eds.), Recent Developments in Parkinson's Disease II, MacMillan, New York, pp. 153–163.

Filion, M., Tremblay, L., Bedard, P.J., 1988. Abnormal influences of passive limb movement on the activity of globus pallidus neurons in parkinsonian monkeys. Brain Res. 444, 165–176.

Flowers, K., 1978. Some frequency response characteristics of Parkinsonism on pursuit tracking. Brain 101, 19–34.

Fu, Q.-G., Flament, D., Coltz, J., Ebner, T., 1997. Relationship of cerebellar purkinje cell simple spike discharge to movement kinematics in the monkey. J. Neurophysiol. 78, 478–491.

Fukuda, M., Mentis, M., Ghilardi, M.F., Dhawan, V., Antonini, A., Hammerstad, J., Lozano, A.M., Lang, A., Lyons, K., Koller, W., Ghez, C., Eidelberg, D., 2001. Functional correlates of pallidal stimulation for Parkinson's disease. Ann. Neurol. 49, 155–164.

Georgopoulos, A., DeLong, M., Crutcher, M., 1983. Relations between parameters of step-tracking movements and single cell discharge in the globus pallidus and subthalamic nucleus of the behaving monkey. J. Neurosci. 3, 1586–1598.

Glickstein, M., Stein, M., 1991. Paradoxical movement in Parkinson's disease. Trends Neurosci. 14, 480–483.

Godaux, E., Koulischer, D., Jacquy, J., 1992. Parkinsonian bradykinesia is due to depression in the rate of rise of muscle activity. Ann. Neurol. 31, 93–100.

Goldberg, J.A., Boraud, T., Maraton, S., Haber, S.N., Vaadia, E., Bergman, H., 2002. Enhanced synchrony among primary motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. J. Neurosci. 22, 4639–4653.

Grady, C.L., McIntosh, A.R., Rajah, M.N., Beig, S., Craik, F.I., 1999. The effects of age on the neural correlates of episodic encoding. Cereb. Cortex 9, 805–814.

Grafton, S.T., Sutton, J., Couldwell, W., Lew, M., Waters, C., 1994. Network analysis of motor system connectivity in Parkinson's Disease: modulation of thalamocortical interactions after pallidotomy. Hum. Brain Mapping 2, 45–55.

Grafton, S.T., Waters, C., Sutton, J., Lew, M.F., Couldwell, W., 1995. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a PET study. Ann. Neurol. 37, 776–783.

Graziano, M.S., Hu, X.T., Gross, C.G., 1997. Visuospatial properties of ventral premotor cortex. J. Neurophysiol. 77, 2268–2292.

Hallett, M., Khoshbin, S., 1980. A physiological mechanism of bradykinesia. Brain 103, 301–314.

Hamming, R.W., 1983. Digital Filters. Prentice Hall, Englewood Cliffs, NJ.

Hanakawa, T., Fukuyama, H., Katsumi, Y., Honda, M., Shibasaki, H., 1999a. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann. Neurol. 45, 329–336.

Hanakawa, T., Katsumi, Y., Fukuyama, H., Honda, M., Hayashi, T., Kimura, J., Shibasaki, H., 1999b. Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. Brain 122, 1271–1282.

Haslinger, B., Erhard, P., Kampfe, N., Boecker, H., Rummeny, E., Schwaiger, M., Conrad, B., Ceballos-Baumann, A.O., 2001. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 124, 558–570.

Herscovitch, P., Markham, J., Raichle, M.E., 1983. Brain blood flow measured with intravenous $H^2{}_{15}O$. I. Theory and error analysis. J. Nucl. Med. 24, 782–789.

Hikosaka, O., Sakai, K., Miyauchi, S., Takino, R., Sasaki, Y., Putz, B., 1996. Activation of human presupplementary motor area in learning of sequential procedures: a functional MRI study. J. Neurophysiol. 76, 617–621.

Hoehn, M.M., Yahr, M.D., 1967. Parkinsonism: onset, progression and mortality. Neurology 17, 427–442.

Holmes, A., Friston, K., 1998. Generalisability, random effects and population interence. Neuroimage 7, S480.

Horak, F.B., Anderson, M.E., 1984. Influence of globus pallidus on arm movements in monkeys. I. Effects of kainic acid-induced lesions. J. Neurophysiol. 52, 290–304.

Hu, M.T., Taylor-Robinson, S.D., Chaudhuri, K.R., Bell, J.D., Labbe, C., Cunningham, V.J., Koepp, M.J., Hammers, A., Morris, R.G., Turjanski, N., Brooks, D.J., 2000. Cortical dysfunction in non-demented Parkinson's disease patients: a combined (31)P-MRS and (18)FDG-PET study. Brain 123, 340–352.

Hufschmidt, A., Lucking, C.H., 1995. Abnormalities of tracking behavior in Parkinson's disease. Mov. Disord. 10, 267–276.

Jahanshashi, M., Jenkins, I.H., Brown, R.G., Marsden, C.D., Passingham, R.E., Brooks, D.J., 1995. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 188, 913–933.

Jenkins, I.H., Fernandez, W., Playford, E.D., Lees, A.J., Frackowiak, R.S.J., Passingham, R.E., Brooks, D.J., 1992. Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. Ann. Neurol. 32, 749–757.

Johnson, M.T., Kipnis, A.N., Coltz, J.D., Gupta, A., Silverstein, P., Zwiebel, F., Ebner, T.J., 1996. Effects of levodopa and viscosity on the velocity and accuracy of visually guided tracking in Parkinson's disease. Brain 119, 801–813.

Jordan, N., Sagar, H.J., Cooper, J.A., 1992. A component analysis of the generation and release of isometric force in Parkinson's disease. J. Neurol. Neurosurg. Psychiatr. 55, 572–576.

Kleine, B.U., Praamstra, P., Stegeman, D.F., Zwarts, M.J., 2001. Impaired motor cortical inhibition in Parkinson's disease: motor unit responses to transcranial magnetic stimulation. Exp. Brain Res. 138, 477–483.

Kunesch, E., Schnitzler, A., Tyercha, C., Knecht, S., Stelmach, G., 1995. Altered force release control in Parkinson's disease. Behav. Brain Res. 67, 43–49.

Lakke, P.W.F., 1981. Classification of extrapyramidal disorders. J. Neurol. Sci. 51, 311–327.

Limousin, P., Greene, J., Pollak, P., Rothwell, J., Benabid, A.L., Frackowiak, R., 1997. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann. Neurol. 42, 283–291.

Liu, X., Tubbesing, S.A., Aziz, T.Z., Miall, R.C., Stein, J.F., 1999. Effects of visual feedback on manual tracking and action tremor in Parkinson's disease. Exp. Brain Res. 129, 477–481.

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., Buckner, R.L., 2002. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33, 827–840.

Mazziotta, J.C., Huang, S.-C., Phelps, M.E., Carson, R.E., MacDonald, N.S., Mahoney, K., 1985. A noninvasive positron computed tomography technique using oxygen-15-labeled water for the evaluation of neurobehavioral task batteries. J. Cereb. Blood Flow Metab. 5, 70–78.

Mazziotta, J.C., Toga, A.W., Evans, A., Fox, P., Lancaster, J., 1995. A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). NeuroImage 2, 89–101.

McIntosh, A.R., Bookstein, F.L., Haxby, J.V., Grady, C.L., 1996. Spatial pattern analysis of functional brain images using partial least squares. NeuroImage 3, 143–157.

Meyer, C.H., 1982. Akinesia in Parkinsonism. Relation between spontaneous movement (other than tremor) and voluntary movements made on command. J. Neurol. Neurosurg. Psychiatr. 45, 582–585.

Middleton, F.A., Strick, P.L., 2000. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn. 42, 183–200.

Miller, W.C., DeLong, M.R., 1987. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism, in: Carpenter, M.B., Jayaraman, A. (Eds.), The Basal Ganglia II, Plenum Press, New York, pp. 415–427.

Mink, J., 1996. The basal ganglia: focused selection and inhibition of competing motor programs. Prog. Neurobiol. 50, 381–425.

Mink, J., Thach, W., 1991. Basal ganglia motor control. III. Pallidal ablation: normal reaction time, muscle cocontraction, and slow movement. J. Neurophysiol. 65, 330–351.

Murata, A., Fadiga, L., Fogassi, L., Gallese, V., Raos, V., Rizzolatti, G., 1997. Object representation in the ventral premotor cortex (area F5) of the monkey. J. Neurophysiol. 78, 2226–2230.

Nakamura, T., Ghilardi, M.F., Mentis, M., Dhawan, V., Fukuda, M., Hacking, A., Moeller, J.R., Ghez, C., Eidelberg, D., 2001. Functional networks in motor sequence learning: abnormal topographies in Parkinson's disease. Hum. Brain Mapping 12, 42–60.

Nini, A., Feingold, A., Slovin, H., Bergman, H., 1995. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of Parkinsonism. J. Neurophysiol. 74, 1800–1805.

Paulson, H.L., Stern, M.B., 1997. Clinical manifestations of Parkinson's disease, in: Watts, R.L., Koller, W.C. (Eds.), Movement Disorders: Neurologic Principles and Practice, McGraw-Hill, New York, pp. 183–199.

Penney, J.B., Young, A.B., 1983. Speculations on the functional anatomy of basal ganglia disorders. Annu. Rev. Neurosci. 6, 73–94.

Piert, M., Koeppe, R.A., Giordani, B., Minoshima, S., Kuhl, D.E., 1996. Determination of regional rate constants from dynamic FDG-PET studies in Parkinson's disease. J. Nucl. Med. 37, 1115–1122.

Playford, E.D., Jenkins, I.H., Passingham, R.E., Nutt, J., Frackowiak, R.S.J., Brooks, D.J., 1992. Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. Ann. Neurol. 32, 151–161.

Praamstra, P., Plat, F.M., 2001. Failed suppression of direct visuomotor activation in Parkinson's disease. J. Cogn. Neurosci. 13, 31–43.

Praamstra, P., Stegeman, D.F., Cools, A.R., Meyer, A.S., Horstink, M.W., 1998. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements. A PET study. Brain 121, 769–772.

Priori, A., Berardelli, A., Inghilleri, M., Accornero, N., Manfredi, M., 1994. Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. Brain 117, 317–323.

Raichle, M.E., Martin, W.R.W., Herscovitch, P., 1983. Brain blood flow measured with intravenous $H_{15}^{2}O$. II. Implementation and validation. J. Nucl. Med. 24, 790–798.

Rascol, O., Sabatini, U., Chollet, F., Celsis, P., Montastruc, J.-L., Marc-Vergnes, J.-P., Rascol, A., 1992. Supplementary and primary sensory motor area activity in Parkinson's disease. Regional cerebral blood flow changes during finger movements and effects of apomorphine. Arch. Neurol. 49, 144–148.

Rascol, O., Sabatini, U., Fabre, N., Brefel, C., Loubinoux, I., Celsis, P., Senard, J.M., Montastruc, J.L., Chollet, F., 1997. The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic parkinsonian patients. Brain 120, 103–110.

Ridding, M.C., Inzelberg, R., Rothwell, J.C., 1995. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann. Neurol. 37, 181–188.

Rizzolatti, G., Gentilucci, M., Camarda, R.M., Gallese, V., Luppino, G., Matelli, M., Fogassi, L., 1990. Neurons related to reaching-grasping arm movements in the rostral part of area 6 (area 6a beta). Exp. Brain Res. 82, 337–350.

Sabatini, U., Boulanouar, K., Fabre, N., Martin, F., Carel, C., Colonnese, C., Bozzao, L., Berry, I., Montastruc, J.L., Chollet, F., Rascol, O., 2000. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. Brain 123, 394–403.

Samuel, M., Ceballos-Baumann, A.O., Blin, J., Uema, T., Boecker, H., Passingham, R.E., Brooks, D.J., 1997a. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements. A PET study. Brain 120, 963–976.

Samuel, M., Ceballos-Baumann, A.O., Boecker, H., Brooks, D.J., 2001. Motor imagery in normal subjects and Parkinson's disease patients: an H215O PET study. Neuroreport 12, 821–828.

Samuel, M., Ceballos-Baumann, A.O., Turjanski, N., Boecker, H., Gorospe, A., Linazasoro, G., Holmes, A.P., DeLong, M.R., Vitek, J.L., Thomas, D.G.T., Quinn, N.P., Obeso, J.A., Brooks, D.J., 1997b. Pallidotomy in Parkinson's disease increases supplementary motor area and prefrontal activation during performance of volitional movements: an $H_2{}^{15}O$ PET study. Brain 120, 1301–1313.

Shima, K., Tanji, J., 1998. Both supplementary and presupplementary motor areas are crucial for the temporal organization of multiple movements. J. Neurophysiol. 80, 3247–3260.

Soliveri, P., Brown, R.G., Jahanshahi, M., Caraceni, T., Marsden, C.D., 1997. Learning manual pursuit tracking skills in patients with Parkinson's disease. Brain 120, 1325–1337.

Stelmach, G.E., Teasdale, N., Phillips, J., Worringham, C.J., 1989. Force production characteristics in Parkinson's disease. Exp. Brain Res. 76, 165–172.

Stelmach, G.E., Worringhan, C.J., 1988. The preparation and production of isometric force in Parkinson's disease. Neuropsychology 26, 93–103.

Swadlow, H.A., Beloozerova, I.N., Sirota, M.G., 1998. Sharp, local synchrony among putative feed-forward inhibitory interneurons of rabbit somatosensory cortex. J. Neurophysiol. 79, 567–582.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Brain. Thieme Medical Publishers, New York.

Teasdale, N., Phillips, J., Stelmach, G.E., 1990. Temporal movement control in patients with Parkinson's disease. J. Neurol. Neurosurg. Psychiatr. 53, 862–868.

Turner, R.S., Anderson, M.E., 1997. Pallidal discharge related to the kinematics of reaching movements in two dimensions. J. Neurophysiol. 77, 1051–1074.

Turner, R.S., Grafton, S.T., Hoffman, J.M., Votaw, J.R., DeLong, M.R., 1998. Motor subcircuits mediating the control of movement velocity: a PET study. J. Neurophysiol. 80, 2162–2176.

Turner, R.S., Henry, T., Grafton, S.T., 2000. Therapeutics: surgical, in: Mazziotta, J.C., Toga, A.W., Frackowiak, R.S.J. (Eds.), Brain Mapping: The Disorders, Academic Press, San Diego, pp. 613–653.

Turner, R.S., Hoffman, J.M., Grafton, S.T., DeLong, M.R., 1996. Functional neural activation in normal and parkinsonian subjects related to movement frequency during predictive visuomotor tracking using PET. Soc. Neurosci. Abstr. 22, 2038.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.

van Hilten, J.J., van Eerd, A.A., Wagemans, E.A., Middelkoop, H.A., Roos, R.A., 1998. Bradykinesia and hypokinesia in Parkinson's disease: what's in a name? J. Neural Transm. 105, 229–237.

Vitek, J.L., Bakay, R.A., Hashimoto, T., Kaneoke, Y., Mewes, K., Zhang, J.Y., Rye, D., Starr, P., Baron, M., Turner, R., DeLong, M.R., 1998. Microelectrode-guided pallidotomy: technical approach and its application in medically intractable Parkinson's disease. J. Neurosurg. 88, 1027–1043.

Wannier, T.M.J., Maier, M.A., Hepp-Raymond, M.C., 1989. Responses of motor cortex neurons to visual stimulation in the alert monkey. Neurosci. Lett. 98, 63–68.

Weiller, C., Chollet, F., Friston, K.J., Wise, R.J.S., Frackowiak, R.S.J., 1992. Functional reorganization of the brain in recovery from striatocapsular infarction in man. Ann. Neurol. 31, 1463–1472.

Wichmann, T., DeLong, M.R., 1996. Functional and pathophysiological models of the basal ganglia. Curr. Opin. Neurobiol. 6, 751–758.

Wing, A.M., 1988. A comparison of the rate of pinch grip force increases and decreases in parkinsonian bradykinesia. Neuropsychologia 26, 479–482.

Woods, R.P., 1996. Modeling for intergroup comparisons of imaging data. NeuroImage 4, S84–S94.

Woods, R., Grafton, S., Holmes, C., Cherry, S., Mazziotta, J., 1998a. Automated image registration. I. General methods and intrasubject validation. J. Comput. Assist. Tomogr. 22, 141–154.

Woods, R.P., Grafton, S.T., Watson, J.D.G., Sicotte, N.L., Mazziotta, J.C., 1998b. Automated image registration. II. Intersubject validation of linear and nonlinear models. J. Comput. Assist. Tomogr. 22, 155–165.