



## Left hemisphere specialization for the control of voluntary movement rate

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Received 21 August 2003; revised 18 December 2003; accepted 23 December 2003

Although persuasive behavioral evidence demonstrates the superior dexterity of the right hand in most people under a variety of conditions, little is known about the neural mechanisms responsible for this phenomenon. As this lateralized superiority is most evident during the performance of repetitive, speeded movement, we used parametric rate variations to compare visually paced movement of the right and left hands. Twelve strongly right-handed subjects participated in a functional magnetic resonance imaging (fMRI) experiment involving variable rate thumb movements. For movements of the right hand, contralateral rate-related activity changes were identified in the precentral gyrus, thalamus, and posterior putamen. For left-hand movements, activity was seen only in the contralateral precentral gyrus, consistent with the existence of a rate-sensitive motor control subsystem involving the left, but not the right, medial premotor corticostriatal loop in right-handed individuals. We hypothesize that the right hemisphere system is less skilled at controlling variable-rate movements and becomes maximally engaged at a lower movement rate without further modulation. These findings demonstrate that right- and left-hand movements engage different neural systems to control movement, even during a relatively simple thumb flexion task. Specialization of the left hemisphere corticostriatal system for dexterity is reflected in asymmetric mechanisms for movement rate control.

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**Keywords:** Basal ganglia; Corticostriatal; Motor loop; Handedness; Laterality; Premotor

### Introduction

An early and frequent observation made in studies of manual dexterity is the superior proficiency of the right hand when engaged in rapid repetitive movement (Reitan and Davison, 1974). This lateralized skill is exhibited by over 90% of the population, a proportion that has remained remarkably stable over

5000 years of recorded history (Coren and Porac, 1977). Although hand preference varies for different activities, in subjects with a generally strong right-hand preference, a right-hand performance advantage is invariably seen for tasks involving speeded finger movement. Examples of this lateralized distal motor skill asymmetry include sequential finger movements (Edwards and Elliott, 1987), goal-directed drawing movements (Woodworth, 1899), and rapid single-finger tapping (Todor et al., 1982). These behavioral results, when combined with the evidence that the cortical systems controlling limb movements are largely crossed (Kuypers, 1981), strongly suggest the existence of lateralized motor control subsystems specialized for the control of rapid, repetitive, contralateral hand movements.

Clinical investigations of the effects of focal brain injury on hand motor performance have demonstrated differences between the left and right hemisphere motor control systems as estimated by the residual motor capabilities of the ipsilateral limb following focal vascular injury. If the left hemisphere is relatively specialized for movement control in right-handed individuals, such that right hemisphere motor areas are dependent on left hemisphere regions for motor planning and execution, then left-sided injury should result in greater effects on ipsilateral motor performance than right-sided injury. In general, ipsilateral limb movements of patients with left-hemisphere damage are more impaired than patients with right-hemisphere damage (Goldenberg et al., 1996; Kimura and Archibald, 1974; Maher et al., 1997). More specifically, ipsilateral dexterity, measured 1 month post-stroke in patients with left-hemisphere damage, is more impaired when compared to individuals with right-hemisphere damage (Sunderland et al., 1999). A follow-up study at 6 months indicated that although dexterity of the ipsilateral hand had recovered significantly, patients with left-hemisphere damage still had more residual impairment (Sunderland, 2000). Finally, a study examining the effects of right- and left-hemisphere vascular damage on maximal finger flexion rate and grip strength demonstrated that right-sided lesions reduced grip strength while left-hemisphere lesions reduced the rate at which a finger flexion task was performed, consistent with the idea that the left hemisphere has a relative specialization for the control of rapid movements while the right hemisphere is relatively more important in the control of slower, sustained movements (Robinson et al., 1990). In these studies of the effects of focal brain injury, damage to the left

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hemisphere resulted in impaired performance on speeded movement tasks, supporting the notion of left hemisphere specialization for the control of rapid, repetitive movements.

Functional brain imaging has allowed more direct observation of the neural basis for left-hemisphere motor control specialization. Several functional neuroimaging studies have compared movements made with the right and left hands, finding activity within the primary motor cortex related to movement of the ipsilateral hand. These comparisons have been made using both positron emission tomography (Kawashima et al., 1993) and functional magnetic resonance imaging (fMRI) techniques (Alkadhi et al., 2002; Cramer et al., 1999; Dassonville et al., 1997; Kim et al., 1993). Of these studies, two found that there was greater activity within the left precentral gyrus during movement of the left hand (Kawashima et al., 1993; Kim et al., 1993), a finding supporting specialization of the left sensorimotor cortex for voluntary movement control.

It is possible that the neural mechanisms responsible for left hemisphere superiority in the control of rapid and repetitive hand movements in right-handed individuals might be related to the processes controlling rate modulation. Movement rate is known to have a strong parametric relationship with activity in many parts of the sensorimotor control system. The evidence supporting this relationship comes from experiments demonstrating a positive relationship between movement rate and neuronal activity in contralateral sensorimotor cortex (Blinkenberg et al., 1996; Jancke et al., 1998b; Khushu et al., 2001; Rao et al., 1996; Sadato et al., 1996a, 1997; Schlaug et al., 1996; VanMeter et al., 1995), the SMA (Deiber et al., 1999; Khushu et al., 2001; Sadato et al., 1996b; VanMeter et al., 1995), and ipsilateral cerebellar cortex (Sadato et al., 1996a; VanMeter et al., 1995). Rate-related effects have also been seen in subcortical structures (Sadato et al., 1996a; Turner et al., 1998; VanMeter et al., 1995).

The role of subcortical structures, including the basal ganglia, in motor control has been extensively investigated using animal models, which have demonstrated that the caudate, putamen, globus pallidus, and the subthalamus have a complex pattern of connectivity and functional interdependence with their cortical targets. The basal ganglia participate in at least five “loops” with the cerebral cortex, including a motor loop, an oculomotor loop, and three nonmotor loops involving the frontal cortex (Alexander et al., 1990; Middleton and Strick, 2000b). The motor loop is comprised of the striatum, globus pallidus, thalamic nuclei VA and VL, the primary motor cortex, and the supplementary motor area (McFarland and Haber, 2000). These cortical areas project to the striatum, which returns these projections via the globus pallidus and the thalamic nuclei and it is believed that information within each loop remains relatively segregated as it passes through the basal ganglia, thalamus, and cortex (Middleton and Strick, 2000b). The demonstration of regional specialization of these subcortical structures in relation to movement rate would be consistent with the existence of a lateralized motor subsystem underlying the performance advantages commonly observed during movements of the right hand.

In this study, we explore the neural mechanisms responsible for the superior motor proficiency seen with right hand use through examination of movements executed over a range of rates by right-handed subjects. Visually paced left or right thumb flexion movements were executed at three different rates using blood oxygen level dependent (BOLD)-contrast magnetic resonance imaging (MRI) signal change as a measure of neuronal activity. Although

this task does not reveal dexterity differences between the hands, it was deliberately chosen to ensure equal performance during movements of the right and left thumbs, thereby eliminating a potential confound to the interpretation of the functional neuroimaging results. The patterns of task-related activity seen during performance of these rate-modulated tasks provide new evidence that hemispheric specialization for control of movement rate is mediated by a lateralized premotor corticostriatal control loop.

## Methods

### Subjects

Twelve right-handed subjects (five male, seven female; average age 27.6 years, range 18–39) participated in this study. All gave written informed consent and were paid for their participation. In an initial telephone interview, subjects were asked a series of standard questions to establish their medical background. Individuals with neurological or medical conditions known to affect brain function or first-degree relatives with neurological, psychiatric, or developmental disorders were excluded. Current use of psychoactive or vasoactive medications and the consumption of excessive amounts of alcohol, caffeine, or tobacco were grounds for exclusion, based on their effects on neural activity and cerebral blood flow (Mulderink et al., 2002). Individuals with cardiac pacemakers, neural pacemakers, surgical clips in the brain or blood vessels, surgically implanted metal plates, screws or pins, cochlear implants or metal objects in the body, especially the eyes, were excluded from the study. After the initial screening, hand preference was measured using the Edinburgh Handedness Scale (EHS) (Oldfield, 1971). Scores could range from –100 for a subject that was completely left-handed to +100 for a right-handed subject. All subjects in this study were strongly right-handed with an average EHS score of  $93 \pm 14$ . Approximately 90% of individuals will demonstrate this degree of right-hand preference (Coren and Porac, 1977); the inferences we draw from this study are confined to this segment of the population.

### Tasks

Subjects executed thumb flexions in time to a repeating visual stimulus, used to avoid the interference that would occur between an auditory stimulus and the gradient noise present in the MRI system. Before entering the scanner, subjects were trained on the task using the same response pad used inside the scanner. They practiced the task until stable response rates were achieved. Stimuli consisted of a fixation cross and, during the task condition, a bright  $2^\circ$  annulus that flashed around the fixation cross with a duration of 100 ms. Subjects were instructed to execute a button press response in time with the stimulus and their response time and accuracy were recorded using a fiber optic response pad (fORP; Current Designs, Inc., Philadelphia, PA). During the course of the experiment, subjects lay supine in the MRI scanner with their arms fully extended at their sides and their forearms supinated. In the palm of each hand, they held a fiber optic response pad with the buttons on the front face accessible only to the thumb. The buttons were directly beneath the thumb and could be pressed via a simple thumb movement, not requiring movement of the wrist, elbow, or shoulder. Subjects held the response box for the entire experiment. Subjects' heads were restrained to prevent rotation around the long

axis of the body and a support was placed under the neck to prevent nodding of the head. Subjects were instructed to avoid extraneous movement, especially of the head and shoulders. The experiment was designed to be a pacing task, in which the stimulus served to keep the subject's response rate entrained, rather than a stimulus-response task. Subjects were instructed at the beginning of each imaging run to respond with their right or left thumb. During the fixation periods, subjects were instructed to continue holding the response box and not make extraneous movements.

Previous parametric studies of the motor system have used movement rates between 0.25 and 5 Hz. The rates used in this experiment were selected to be within the range used in previous studies. In the MRI system, each subject participated in six data acquisition runs during a single imaging session, executing movements of either the right or left thumb at three different rates: 0.3, 1, and 3 Hz, with a pseudorandom order of presentation. Ten blocks of task and control alternated in each acquisition run.

#### Data acquisition

##### Functional data

A Siemens Magnetom Vision 1.5 T MRI with a circularly polarized head coil was used to acquire 128 whole head volumes per run (EPI, TE = 40 ms, TR = 4200 ms,  $64 \times 64$  matrix, 230 mm FOV, 3.6-mm cubic voxels). At each time point, 46 3.0-mm-thick axial slices with  $3.6 \times 3.6$  mm in plane resolution were collected in superior-to-inferior order with a 0.6-mm gap. The first eight time points were discarded, allowing time to reach equilibrium in longitudinal relaxation. Each imaging run was of an ABAB design, where A represents control and B represents task. A run was 9-min long and consisted of 60 whole brain volumes during each condition. The total imaging session of six runs lasted an hour.

##### Anatomical data

In a separate session, three high-resolution structural images of the brain (MPRAGE; TE = 7 ms, TR = 15 ms,  $256 \times 256$  matrix, 230 mm FOV, 1.0-mm cubic voxels) were collected, spatially registered, and averaged. In this procedure, one image was the template and the other two images were registered to this image using AIR 3.08 (Woods et al., 1998). Once all three images were coregistered, they were averaged to produce a composite image that had improved gray/white matter contrast, enabling more accurate identification of anatomical structures.

#### Data analysis

##### Kinematic analysis

The average intermovement interval and its standard deviation were calculated for each run. For both metrics, a  $2 \times 3$  repeated measures analysis of variance (ANOVA) was performed to identify main effects of hand (right vs. left), movement rate (0.3 vs. 1 vs. 3 Hz), or their interaction.

##### Image analysis

EPI data were analyzed using MEDx 3.28 (Sensor Systems, Sterling, VA). Data for each run of each subject were processed using (1) head motion correction, (2) spatial and temporal filtering, (3) contrast image generation, and (4) spatial normalization to a generalized coordinate space.

As there was some concern that subjects might exhibit differential head motion during execution of the tasks at varying rates,

EPI time series were analyzed to quantify subjects' head motion both before and after motion correction by registration. Head motion was detected using a center of intensity model with the intensity threshold set to 10% of the maximum image intensity. The center of intensity was computed for each time point using all voxels above threshold and then plotted as a function of time. Two measures of head motion were derived: path length<sub>3D</sub> and mean square error<sub>3D</sub>. These measures have been used previously to characterize head motion during functional neuroimaging (Eden et al., 1999; Seto et al., 2001). Path length<sub>3D</sub> represents the total distance traveled by the center of intensity in three-dimensional space. This provides a measure of total head motion over the course of a run, but does not differentiate between slow drift of head position and more rapid fluctuations around a baseline. Mean square error characterizes the high-frequency variation around the general trend. The use of both metrics allows estimation of two different aspects of total head motion, relatively slow postural adjustments, and more rapid fluctuations about a stable position.

Head motion was corrected by calculating a mean image of all the time points in one run and then aligning the individual time points within the run to that mean image using rigid-body realignment (Woods et al., 1998). After motion correction, motion detection was again performed and path length<sub>3D</sub> and mean square error<sub>3D</sub> recalculated. A  $2 \times 3 \times 2$  repeated measures ANOVA was performed to determine whether there were significant effects of hand (right vs. left), commanded movement rate (0.3 vs. 1 vs. 3 Hz), or motion correction (before vs. after).

To remove global intensity variance among conditions and subjects, global image intensity was first determined and then adjusted with ratio normalization. Images were then spatially smoothed using a three-dimensional Gaussian kernel (FWHM 7.2 mm; twice the voxel size). High-pass temporal filtering with a period twice that of the behavioral cycle length (task + control; 100.8 s) was applied to reduce temporal signal variation due to cardiac and respiratory effects.

For the first-level statistical analysis, subject-specific areas of task-related signal change were identified by comparing movement with rest, resulting in mean-difference contrast images and *t*-statistic images for each run of each subject. The single-run *t*-statistic maps were then converted to probability images, which were then converted to *Z* score maps.

To facilitate estimation of group effects, the mean EPI image from each run was registered to the Talairach EPI template provided with SPM99 (Functional Imaging Laboratory, London, UK) using AIR 3.08 in a 12 degrees of freedom transformation mode. The resulting transformation matrix was saved and applied to both the previously computed *Z* score maps and the task minus control contrast images derived from each run. The contrast images were used for the second-level analysis. The SPM99 EPI template, aligned with the ICBM152 space, is known to be larger than the standard Talairach template, especially in the *y* and *z* planes. Therefore, to localize and label peaks of functional activity using a Talairach atlas (Talairach and Tournoux, 1988), coordinates were transformed from the SPM99 EPI space to Talairach space using spatial transformation equations (Brett et al., 2001). This transformation was done to facilitate region labeling using the published Talairach atlas; all coordinates reported in this manuscript are in the SPM99 EPI coordinate system, hereafter called SPM99–Talairach space.

Two analyses were conducted at the second-level. First, a categorical analysis was performed in which voxels that exhibited

task-related activity in the experimental group as a whole were identified with single-group *t* tests performed on the spatially normalized contrast images derived from each run of each subject. In this mixed-effects analysis, multiple comparisons in the *t*-statistic maps were controlled by adjusting the critical *Z* score threshold to 3.1 ( $P < 0.001$ , uncorrected) to protect from false positives.

Second, linear regression analysis was used to characterize the relationship between movement rate and the change in signal intensity using nonlinear weights ( $-4$ ,  $+1$ , and  $+3$ ). These weights model a less than linear (asymptotic) increase in signal intensity, with a sharp increase in BOLD contrast signal intensity between 0.3 and 1 Hz and a more gradual increase between 1 and 3 Hz.

Previous studies of rate-related activity modulation in the motor system have taken two approaches. The first was to simply describe any increases or decreases observed between different movement rates (Khushu et al., 2001; Sadato et al., 1996a, 1997; Schlaug et al., 1996). The second approach uses regression models to identify relationships between the percent signal change (Rao et al., 1996), rCBF (VanMeter et al., 1995) or normalized counts (Blinkenberg et al., 1996) and the observed movement rate. Some studies (Blinkenberg et al., 1996) investigated only linear relationships between signal and movement rate. Another study (VanMeter et al., 1995) used two different models to characterize the relationship between movement rate and task-related activity. The first was a linear model, which predicted that rCBF would increase linearly with movement rate. The second was a step function, which predicted that a region would become active during performance of the task, but that, with increasing movement rate, its activity would not exhibit any further increase. These two models were used to characterize the behavior of the primary motor cortex, medial premotor cortex, lateral premotor cortex, thalamus, and cerebellum.

The model chosen for the current study differed from models previously used in that it was nonlinear, predicting a sharp increase in BOLD contrast signal between 0.3 and 1 Hz and a more gradual increase in signal intensity between 1 and 3 Hz. Data from previous studies (Jancke et al., 1998b; Khushu et al., 2001; VanMeter et al., 1995) have shown that there is a sharp increase in task-related activity within the primary motor cortex between slow ( $<1$  Hz) movements and movements at 1 Hz. These data further show that task-related activity continues to increase, albeit at a slower rate, beyond 1 Hz. Data from the 12 participants in the current study are in accord with these findings and a nonlinear curve was generated to model the behavior of the magnetic resonance signal in the left and right primary motor cortex during movements of the contralateral thumb (see Fig. 1). For the purposes of the regression analysis, weights had to be chosen such that they summed to 0 and no individual value was 0. Within these constraints, a regression vector with weights of  $-4$ ,  $+1$ , and  $+3$  was generated. Although alternative models could have been employed that more closely matched activity within other portions of the motor system, we opted to model the behavior of the primary motor cortex, as this region is part of both the corticocerebellar and corticostriatal motor control loops. In addition, many studies have identified and characterized relationships between the activity within primary motor cortex and movement parameters such as force (Dettmers et al., 1995) or rate (Blinkenberg et al., 1996; Jancke et al., 1998b; Rao et al., 1996; Sadato et al., 1996b, 1997; VanMeter et al., 1995).

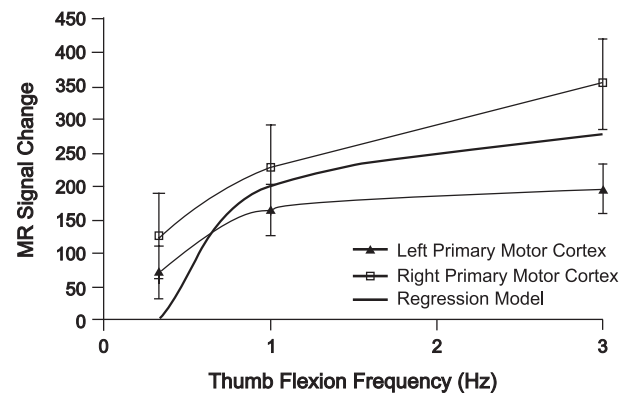


Fig. 1. MR signal change vs. movement frequency. MR signal change within the contralateral primary motor cortex during flexion of the right thumb is depicted with solid triangle markers and that with the left thumb is indicated by open square markers. Values are the average of MR signal at the peak identified in Tables 1 and 2. Error bars represent standard deviation. The proposed regression model is plotted as a thick solid line.

For this regression analysis, the task minus control contrast images for all three rates performed using each hand for all 12 subjects were grouped together and the regression vector was applied to estimate model parameters at each voxel across subjects to identify regions whose intensity changed as a function of movement rate. This procedure generated two statistical maps, an *r* value map and a corresponding *Z* score map representing the Gaussian probability ( $Z > 2.33$ ,  $P < 0.01$  uncorrected). A mask of task-related activity was then generated by thresholding the *Z* maps for the categorical contrasts at  $Z > 3.1$  ( $P < 0.001$  uncorrected) and making a binary mask of the voxels that exceeded this value. The masks from all three rates were combined using a logical OR function and the resulting mask identified regions in which there was significant task-related signal change at any of the movement rates. This mask was then applied to the correlation map to constrain the map to regions that had shown categorical task-related activity.

In a separate analysis, the spatially normalized single-subject *Z* score maps were used in an analysis of spatial extent to determine the number of voxels activated within the primary motor cortex during thumb flexion with either hand. To correct for varying effect sizes among subjects, for each subject, the *Z* score critical threshold was set at 70% of the maximum *Z* score in the posterior bank of the precentral gyrus during performance of the 1-Hz task and the same threshold was used for both hands and all rates. A rectangular region of interest was defined such that it encompassed the rostral and caudal primary motor cortex representations on the group map. This ROI was placed over the hand representations in the posterior precentral gyrus within the left and right hemispheres. The ROI had dimensions of  $46 \times 26 \times 20$  mm with one vertex located at  $\pm 66$ ,  $+4$ ,  $+58$  and the opposite vertex at  $\pm 20$ ,  $-20$ ,  $+38$  in the SPM99–Talairach coordinate system. Whether the *x* coordinate was positive or negative depended on whether the left or right motor cortex was being investigated. Within this ROI, the number of voxels above the threshold defined above was recorded, combining voxels from the rostral or caudal primary motor cortex representations. Data were collected for the 1 and 3 Hz movement conditions, because several subjects had no active voxels within the ROI at the chosen threshold in the 0.3 Hz condition, a finding in accord with previous studies (Sadato et al., 1996b, 1997). A  $2 \times$



2 ANOVA was performed to identify significant differences related to movement rate or hand.

The following anatomical boundaries were used to identify motor system regions. The primary somatosensory cortex (BA 3,1,2) is located on the anterior bank of the postcentral gyrus. The primary motor cortex (BA 4) is anterior to the primary somatosensory cortex, on the posterior bank of the precentral gyrus. Within the primary motor cortex, the hand area is localized to an omega-shaped knob, as described by Yousry et al. (1997). Although there is no distinct boundary between the primary motor and lateral premotor cortices (Lang et al., 1994), the lateral premotor cortex (BA 6) is localized on the anterior bank of the precentral gyrus and the posterior portions of the superior and middle frontal gyri (Lang et al., 1994). On the medial surface of the hemisphere, the supplementary motor area (BA 6) extends from the dorsal bank of the cingulate sulcus to the superior pole. In the posterior–anterior direction, the supplementary motor area (SMA) extends from the posterior commissure (PC) to the anterior commissure (AC) and the pre-SMA was anterior to the AC and terminated at a Talairach coordinate of approximately  $y = +20$  (Geyer et al., 2000; Picard and Strick, 1996). Subcortical regions such as the caudate nucleus, putamen, thalamus, and cerebellum were defined with reference to standard atlases of human brain anatomy (Schmahmann et al., 2000; Talairach and Tournoux, 1988).

## Results

Our exploration of the neural mechanisms responsible for the superior motor proficiency commonly seen when right-handed individuals perform a simple sensorimotor task addressed two principal questions: (1) How do activities within the cortical and subcortical components of the motor system vary as a function of parametric variation in movement rate? and (2) Is there lateralized hemispheric specialization for the control of voluntary movement rate, as measured by differential parametric rate effects during movements of the right and left hands? Based on previous studies, we hypothesized that rate-related activity would be observed in the primary motor cortex, the cerebellum and possibly in the SMA, basal ganglia, and thalamus.

### Kinematic results

Behavioral data were examined both to assess subject compliance with the requested thumb flexion rate and to determine the variability in the observed movement rate. Subjects consistently pressed the right button when instructed to respond with the right hand and the left button when instructed to respond with the left hand. There were no errors on this aspect of the task. To determine whether subjects were moving at the instructed rate, a correlation analysis was performed between the executed and requested thumb flexion rates. The high values of the correlation coefficient ( $r^2 = 0.97$  for the right hand;  $0.98$  for the left hand) indicated that subjects were performing as instructed. A two-way repeated measures ANOVA was calculated using the movement rate data using hand (right vs. left) and requested rate (0.3 vs. 1 vs. 3 Hz) as factors. Only the main effect of requested rate was significant [ $F(2, 9) = 946.45, P < 0.0001$ ], with movement rate increasing as requested rate increased. The movement data were also analyzed to determine whether there were any significant

differences between the right and left hands in movement variability. The variance of the intermovement interval was calculated for each subject for each run and a two-way repeated measures ANOVA calculated. The results indicated that there were no significant differences in movement rate variability between the right and the left hands [ $F(1, 10) = 0.549, P > 0.05, n.s.$ ] and no significant interactions between hand and requested rate [ $F(2, 9) = 1.139, P > 0.05, n.s.$ ]. For the variance of the intermovement interval, only the main effect of requested rate was marginally significant [ $F(2, 9) = 3.943, P = 0.036$ ] with movement variability increasing with rate.

### Estimation and correction of head motion

A three-way repeated measures ANOVA indicated that motion correction significantly reduced head motion, as measured both by path length<sub>3D</sub> [ $F(1, 10) = 22.27, P = 0.0006$ ] and mean square error<sub>3D</sub> [ $F(1, 10) = 9.42, P = 0.0107$ ]. No other significant effects of hand, movement rate, or their interactions were identified, demonstrating that head motion did not differ with hand or movement rate and that the realignment procedure reduced the effects of interscan head motion across all conditions.

### Group-level categorical contrasts

#### Right-hand movement vs. rest

The 1 Hz right thumb flexion vs. rest contrast identified cortical and subcortical areas associated with visually paced movement. In structures contralateral to the movement, we observed task-related signal change in (1) the postcentral gyrus, (2) the two foci within the posterior bank of the precentral gyrus (rostral and caudal thumb representations), (3) the SMA, (4) the thalamus, and (5) the posterior putamen. Bilateral activation was seen in the pre-SMA, occipital cortex, and anterior putamen. In the cerebellum, there was task-related activity in the ipsilateral anterior intermediate lobe (lobule V), the anterior cerebellum (crus I) and bilateral foci of activity in lobule VI. This pattern is consistent with activity involving both the corticostriatal and corticocerebellar motor systems. Movement at slower and faster rates resulted in activation of the same regions as did movement at 1 Hz. Group statistical Z score images are shown in Fig. 2A and SPM99–Talairach coordinates and Z scores for the three tasks are shown in Table 1.

#### Left-hand movement vs. rest

Movement of the left thumb at 1 Hz was also associated with activity in both the corticostriatal and corticocerebellar motor control loops. As was the case for movement of the right thumb, movement of the left thumb activated the contralateral postcentral gyrus, two foci within the posterior precentral gyrus (rostral and caudal thumb representations), bilateral pre-SMA, bilateral occipital cortex, contralateral thalamus, contralateral posterior putamen, and bilateral activation of the anterior putamen. In the cerebellum, there was task-related activity in the ipsilateral anterior intermediate lobe (lobule V), the anterior cerebellum (crus I) and lobule VI. In addition to these areas, foci of activation were seen in the ipsilateral precentral gyrus and thalamus, areas not identified during right thumb movements (Fig. 2B). These categorical task vs. control contrasts reveal differences in the neural systems used to control movement of the right and left hands. While movement of either thumb results

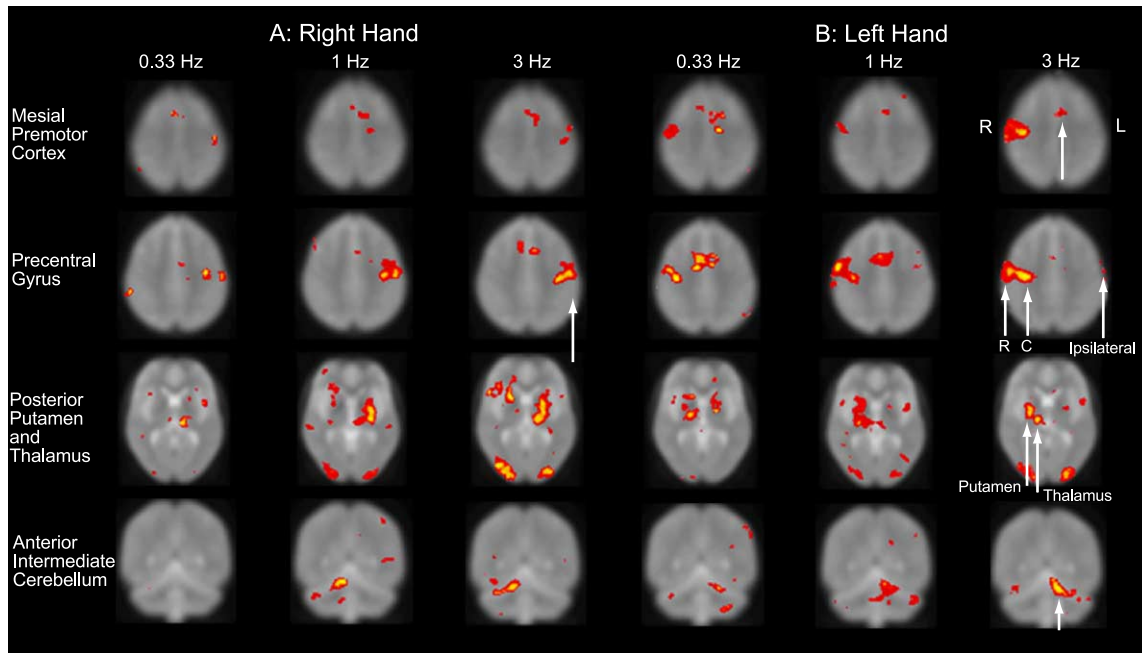


Fig. 2. SPM of task-related activity during unimanual movement. Statistical parametric maps showing task-related activity during unimanual flexion of the right (A) and left (B) thumb. Data is shown for the medial premotor cortex, the rostral (R) and caudal (C) representations in the precentral gyrus, posterior putamen, and anterior intermediate cerebellum. All images represent group data and are thresholded at  $Z > 3.1$ .

in activation of both corticostriatal and corticocerebellar motor control loops, areas in the ipsilateral precentral gyrus and thalamus were only activated during movement of the left thumb.

Standardized spatial coordinates and  $Z$  scores for movement vs. rest contrasts of the left-hand movements at all three rates are shown in Table 2.

Table 1  
SPM99–Talairach coordinates and  $Z$  scores for right-hand thumb flexion

Region	BA	0.3R				1R				3R			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>
Anatomical label													
Right caudal precentral gyrus	4												
Left caudal precentral gyrus	4	−34	−12	48	4.17	−36	−16	48	4.30	−36	−18	46	4.79
Right rostral precentral gyrus	4												
Left rostral precentral gyrus	4	−52	−22	52	4.31	−48	−16	48	4.84	−46	−12	46	4.85
Right postcentral gyrus	3,1,2												
Left postcentral gyrus	3,1,2	−54	−16	48	3.87	−50	−16	48	4.81				
Right pre-SMA	6	8	12	62	3.74	6	14	58	3.50	6	14	58	3.98
Left pre-SMA	6	−4	8	60	3.62	−10	4	60	4.18	−6	8	62	3.88
Left SMA	6	−6	−4	50	3.77					−6	−6	52	3.83
Right occipital lobe	18	30	−94	−2	3.70	28	−94	0	4.53	32	−92	4	5.01
Left occipital lobe	18	−20	−98	−8	3.11	−22	−98	−2	4.72	−22	−92	4	4.68
Right anterior putamen		14	4	20	3.24	20	4	12	3.53	22	8	20	3.65
Left anterior putamen		−16	4	2	2.91 <sup>a</sup>	−20	4	8	4.59	−22	6	0	4.81
Right posterior putamen													
Left posterior putamen		−22	−12	2	3.46	−28	−14	−4	5.50	−24	−8	0	4.75
Right thalamus													
Left thalamus		−16	−14	6	3.86	−16	−18	2	4.58	−14	−16	2	4.73
Right cerebellum lobule V		10	−52	−12	2.49 <sup>a</sup>	8	−54	−20	6.33	14	−52	−24	5.23
Left cerebellum lobule V													
Right cerebellum lobule VI		36	−58	−26	4.12	28	−66	−26	3.49	28	−64	−24	4.70
Left cerebellum lobule VI		−30	−66	−32	3.68	−28	−64	−24	4.40	−32	−62	−32	4.72
Right cerebellum crus I		18	−90	−22	3.22	14	−86	−18	3.31	20	−90	−26	4.72
Left cerebellum crus I													

<sup>a</sup> Activation below the critical threshold.

Table 2  
SPM99–Talairach coordinates and Z scores for left-hand thumb flexion

Region	BA	0.3L				1L				3L			
		x	y	z	Z	x	y	z	Z	x	y	z	Z
Anatomical label													
Right caudal precentral gyrus	4	38	−14	50	4.93	38	−14	50	4.75	36	−16	48	5.91
Left caudal precentral gyrus	4												
Right rostral precentral gyrus	4	44	−6	48	4.39	44	−8	54	4.40	54	−8	46	4.74
Left rostral precentral gyrus	4	−52	10	46	2.99 <sup>a</sup>	−54	0	52	3.36	−54	2	50	3.63
Right postcentral gyrus	3,1,2	60	−24	48	3.12	60	−22	50	3.90	56	−20	56	4.67
Left postcentral gyrus	3,1,2												
Right pre-SMA	6	6	6	52	4.33	8	10	48	4.76	2	6	46	3.42
Left pre-SMA	6					−4	10	60	4.03	−4	10	62	3.81
Left SMA	6	−12	−10	44	2.44 <sup>a</sup>					−12	−6	50	3.93
Right occipital lobe	18	34	−90	0	3.09	26	−94	2	4.16	32	−92	8	5.10
Left occipital lobe	18	−28	−100	4	3.50	−22	−94	4	4.55	−30	−88	−2	5.64
Right anterior putamen		28	2	0	3.54	22	−2	4	5.11	28	2	0	5.16
Left anterior putamen		−14	10	−4	3.90	−18	8	−2	3.39	−18	18	2	2.53 <sup>a</sup>
Right posterior putamen		26	−20	−6	3.66	26	−16	−2	5.14	28	−24	0	3.02 <sup>a</sup>
Left posterior putamen													
Right thalamus		4	−18	2	3.96	8	−14	4	4.17	14	−14	4	5.16
Left thalamus						−8	−18	4	4.14	−8	−18	0	3.19
Right cerebellum lobule V													
Left cerebellum lobule V		−6	−58	−16	4.75	−10	−54	−18	4.71	−14	−54	−20	5.68
Right cerebellum lobule VI		32	−58	−28	3.34	28	−66	−26	3.37	28	−62	−26	4.43
Left cerebellum lobule VI		−32	−58	−28	3.61					−34	−58	−26	4.64
Right cerebellum crus I													
Left cerebellum crus I		−42	−56	−34	3.20	−44	−58	−32	3.91	−46	−58	−34	4.25

<sup>a</sup> Activation below the critical threshold.

### Spatial extent of activation

The results described above demonstrate that the differences in the patterns of task-related activity detected using categorical task minus control contrasts principally involve the ipsilateral thumb representation in primary motor cortex. In addition to differences in response magnitude, there are also differences in response extent as estimated by the volume of cortical activity associated with movement of either hand. Previous functional neuroimaging studies comparing right- and left-hand movement have found a greater volume of activation in contralateral precentral gyrus during movement of the left hand (Kawashima et al., 1993; Kim et al., 1993). Our results agree with these previous findings. A  $2 \times 2$  ANOVA with rate and hand as factors indicated that 3-Hz movements activated a significantly greater volume of brain tissue than did 1-Hz movements [ $F(1, 34) = 11.570$ ,  $P < 0.05$ ]. In addition, left-hand movement elicited a significantly greater volume of activation in contralateral primary motor cortex than did right-hand movement [ $F(1, 34) = 4.850$ ,  $P < 0.05$ ], as shown in Fig. 3. Analysis of the peak and mean percent signal change within the clusters indicated that there were no significant differences between the right and left hands for mean signal change [ $F(1, 40) = 1.48$ ,  $P = 0.23$ , n.s.] or peak signal change [ $F(1, 40) = 1.89$ ,  $P = 0.18$ , n.s.]. There was a significant effect of rate in the peak signal change [ $F(1, 40) = 5.30$ ,  $P = 0.03$ ], with movement at 3 Hz resulting in a greater peak signal change compared to movement at 1 Hz. There was no effect of rate for the mean signal change data [ $F(1, 40) = 3.42$ ,  $P = 0.07$ , n.s.] and no significant interactions.

### Correlation of MR signal with nonlinear model

In the results described above, we used categorical contrasts to identify regions in which the BOLD contrast signal was significantly greater during the task compared to the control condition. An alternative approach is to parametrically vary the rate at which the subject moves and identify regions in which the signal change is related to movement rate. We conducted this analysis using a nonlinear model of neuronal activity as the regression vector. For the right hand, activity within the ipsilateral anterior intermediate cerebellum and two foci within the contralateral precentral gyrus showed a strong correlation with flexion frequency, as did the pre-SMA and contralateral thalamus and posterior putamen (Fig. 4; Table 3).

During movement of the left thumb, activity in the ipsilateral anterior intermediate cerebellum and the contralateral precentral gyrus showed a strong correlation with flexion rate. However, no significant correlation was identified between movement rate and MR signal change in the pre-SMA, contralateral thalamus, or posterior putamen (Fig. 4; Table 3). Plots of average percent signal change vs. movement rate for both the right and left hands are shown in Fig. 5. Percent signal change data was generated within MEDx on a group-wise basis as part of the between-group  $t$  test function during the second-level analysis of preprocessed single-subject data. These findings reveal an interaction between hand and rate sensitivity in the pre-SMA, thalamus, and posterior putamen. Activity within these components of a medial premotor cortico-striatal-thalamo-cortical loop was strongly correlated with the rate of voluntary movement of the right hand.

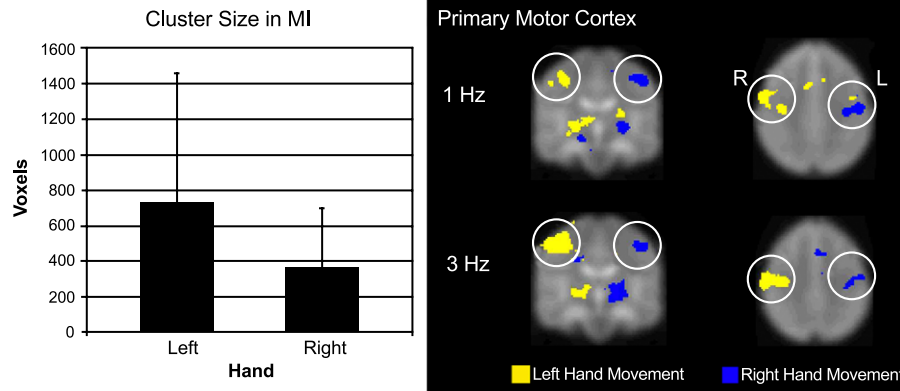


Fig. 3. Cluster size in MI during movement of right and left hands. Graph depicting the average number of voxels within contralateral primary motor cortex activated during movement of the left or right thumb at 1 and 3 Hz. Error bars represent standard deviation. On the right side of the panel, group data showing the volume of activity during flexion of the right and left thumb are depicted. Movement of the left thumb (yellow) elicits a greater volume of activity in contralateral precentral gyrus than does movement with the right thumb (blue). All images represent group data and are thresholded at  $Z > 3.69$  ( $P < 0.0001$ , uncorrected).

#### Activity within rostral and caudal MI hand areas

An examination of the movement vs. fixation contrast suggested that the most significant focus of activity in the posterior precentral gyrus was in the caudal MI area during movement of the left hand and in the rostral MI area during movement of the right hand. This was further investigated by performing paired  $t$  tests contrasting the mean difference images from the 3 Hz right and left movement tasks. Both the 3-Hz Left  $>$  Right and the 3-Hz Right  $>$  Left contrasts were computed and the peak  $Z$  score within the precentral gyrus was identified for each contrast. The location of that coordinate was plotted on the movement vs. rest map ( $Z > 3.09$ ;  $P < 0.001$ , uncorrected) (Fig. 6). This analysis confirmed the initial observation that the peak activity for right-hand movement is

in the rostral MI representation and the peak for left-hand movement is in the caudal MI area.

#### Discussion

In this study, we have demonstrated specialization of a left-lateralized corticostriatal system for the control of speeded, visually paced movement in right-handed subjects. The principal evidence supporting the existence of this regional specialization is differential activation of a medial premotor corticostriatal loop during movements of the right compared with the left hand, with the contralateral medial premotor area, thalamus, and putamen displaying rate-related modulation only during movement of the right hand. In addition, we have examined the two hand representations within the posterior precentral gyrus and have shown hemispheric differences in their patterns of activity, with movement of the right hand more strongly related to activity in the rostral representation and movement of the left hand more strongly related to activity in the caudal representation.

In the motor system, task-related signal change can be exquisitely sensitive to small variations in movement rate. Therefore, we specifically chose a basic motor task and were particularly careful to monitor the subjects' performance during data acquisition. Analysis of the kinematic data indicated that there were no significant differences in movement rate or variability for either hand, demonstrating that the subjects responded at the specified rates. It is unlikely that the differences in task-related activity seen with use of the right or left hand were due to performance differences between the hands. Analysis of the estimated interscan head motion indicated that there were no significant effects of the hand used or movement rate on head motion. As with the kinematic data, differences in associated head motion related to task properties could confound the interpretation of the functional neuroimaging data.

#### Laterality effects with categorical contrasts

##### Right- and left-hand movements

Concerning the task-related activity seen when comparing movement vs. rest conditions, our results are in accord with those

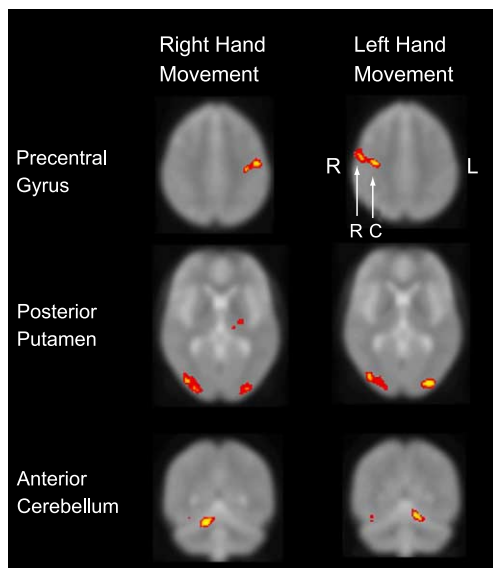


Fig. 4. SPM of rate-related activity during movement of left and right hands. Group data depicting significant ( $Z > 3.1$ ) correlation between MR signal change and asymptotic increase model for movement of the right and left hands. Both the rostral (R) and caudal (C) representations in the precentral gyrus are labeled.



Table 3  
SPM99–Talairach coordinates, correlation coefficients and Z scores for thumb flexion with the right or left hands

Region	BA	Right hand					Left hand					
		<i>x</i>	<i>y</i>	<i>z</i>	<i>r</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>r</i>	<i>Z</i>	
Anatomical label												
Right caudal precentral gyrus	4						38	−14	50	0.66	4.40	
Left caudal precentral gyrus	4	−36	−16	48	0.56	3.56						
Right rostral precentral gyrus	4						44	−8	54	0.38	2.31	
Left rostral precentral gyrus	4	−48	−16	48	0.55	3.45	−54	0	52	0.46	2.78	
Right postcentral gyrus	3,1,2						60	−22	50	0.17	1.00 <sup>a</sup>	
Left postcentral gyrus	3,1,2	−50	−16	48	0.52	3.25						
Right pre-SMA	6	6	14	58	0.43	2.63	8	10	48	−0.09	−0.51 <sup>a</sup>	
Left pre-SMA	6	−10	4	60	0.39	2.36	−4	10	60	0.05	0.27 <sup>a</sup>	
Left SMA	6	−6	−6	52	0.20	0.75 <sup>a</sup>	−12	−6	50	0.07	0.01 <sup>a</sup>	
Right occipital lobe	18	28	−94	0	0.63	4.07	26	−94	2	0.57	3.60	
Left occipital lobe	18	−22	−98	−2	0.48	2.97	−22	−94	4	0.63	4.08	
Right anterior putamen		20	4	12	0.14	0.82 <sup>a</sup>	22	−2	4	0.24	1.43 <sup>a</sup>	
Left anterior putamen		−20	4	8	0.37	2.24 <sup>a</sup>	−18	8	−2	−0.14	−0.79 <sup>a</sup>	
Right posterior putamen							26	−16	−2	0.14	0.82 <sup>a</sup>	
Left posterior putamen		−28	−14	−4	0.47	2.86						
Right thalamus							8	−14	4	−0.21	−1.23 <sup>a</sup>	
Left thalamus		−16	−18	2	0.49	3.05	−8	−18	4	0.11	0.63 <sup>a</sup>	
Right cerebellum lobule V		8	−54	−20	0.58	3.69						
Left cerebellum lobule V							−10	−54	−18	0.63	4.07	
Right cerebellum lobule VI		28	−66	−26	0.51	3.17	28	−66	−26	0.42	2.55	
Left cerebellum lobule VI		−28	−64	−24	0.39	2.37	−34	−58	−26	0.32	1.89	
Right cerebellum crus I		14	−86	−18	0.03	0.16 <sup>a</sup>						
Left cerebellum crus I							−44	−58	−32	0.27	1.60 <sup>a</sup>	

<sup>a</sup> Activation below the critical threshold.

from previous studies of finger flexion, showing task-related signal change in the contralateral primary motor cortex (Fink et al., 1997; Larsson et al., 1996; Remy et al., 1994), SMA (Fink et al., 1997; Larsson et al., 1996; Remy et al., 1994), pre-SMA (Boecker et al., 1998; Deiber et al., 1999; Larsson et al., 1996; Remy et al., 1994), primary somatosensory cortex (Fink et al., 1997; Larsson et al., 1996; Remy et al., 1994), putamen (Dettmers et al., 1995; Jenkins et al., 2000; Rijntjes et al., 1999), thalamus (Lutz et al., 2000; Rijntjes et al., 1999), and ipsilateral anterior intermediate cerebellum (Grafton et al., 1992; Mattay et al., 1998). In addition to these motor areas, bilateral task-related signal changes were identified in striate and extrastriate cortex, resulting from differences in the pacing stimulus in the movement and control conditions. Flashing visual stimuli are known to strongly activate visual cortex in a rate-related fashion (Fox and Raichle, 1984).

One way to efficiently summarize the pattern of task-related activity is by reference to various subsystems involved in the control of voluntary movement. It can be seen that movement of the right thumb activated multiple contralateral cortical and subcortical areas known to be involved in motor control. Some of these areas, including the medial premotor area, putamen, and thalamus, are part of the medial premotor corticostriatal loop (McFarland and Haber, 2000). This loop has been characterized in nonhuman primates and is thought to project from the SMA to the putamen (Nakano et al., 2000). Leaving the striatum via the globus pallidus, it projects back to the SMA by way of the thalamic motor nuclei VAp and VL. (See Nakano et al., 2000 for a detailed review of striatal thalamocortical loops.) A second system involved in the control of voluntary movement is the corticocerebellar loop, consisting of neurons projecting from the cerebellar cortex to the cerebellar nuclei and then to the contralateral thalamus, from there

to the primary motor cortex, and then back to the cerebellar cortex via cortico-pontine and ponto-cerebellar pathways (Huffman and Krubitzer, 2001; Middleton and Strick, 1997, 2000a). In the current experiment, the identified components of this network included the anterior intermediate cerebellum ipsilateral to the right hand and the thalamus and precentral gyrus contralateral to the right thumb.

The patterns of task-related activity seen with left-hand movement were similar to those observed during right-hand movement except that activation of the ipsilateral precentral gyrus was more prominent. This replicates the results of previous functional neuroimaging studies, which have identified task-related activation of the ipsilateral motor cortex, particularly during movements of the left hand (Kawashima et al., 1993; Kim et al., 1993; Mattay et al., 1998; Salmelin et al., 1995; Singh et al., 1998). Although some of these studies have reported task-related signal change in the ipsilateral premotor or primary motor cortex during movement of the right hand, such findings were not observed in the present study. Previous studies have used higher field strength magnets (Kim et al., 1993) or more complex finger-to-thumb opposition tasks (Kawashima et al., 1993; Salmelin et al., 1995; Singh et al., 1998), which may explain why those results differ from the current study.

One interpretation of the finding that ipsilateral primary motor cortex activity is more common during movement of the left hand than the right hand is that the left hemisphere assists movements controlled by the right hemisphere. If the right hemisphere were less adept at accurately controlling rapid thumb movements, as performance requirements increase, it might require the assistance of the left hemisphere. Therefore, when more complex tasks involving sequential finger movements are compared to index finger flexion tasks, one observes greater activation of the ipsilateral motor cortex (Salmelin et al., 1995). These results are consistent with an account

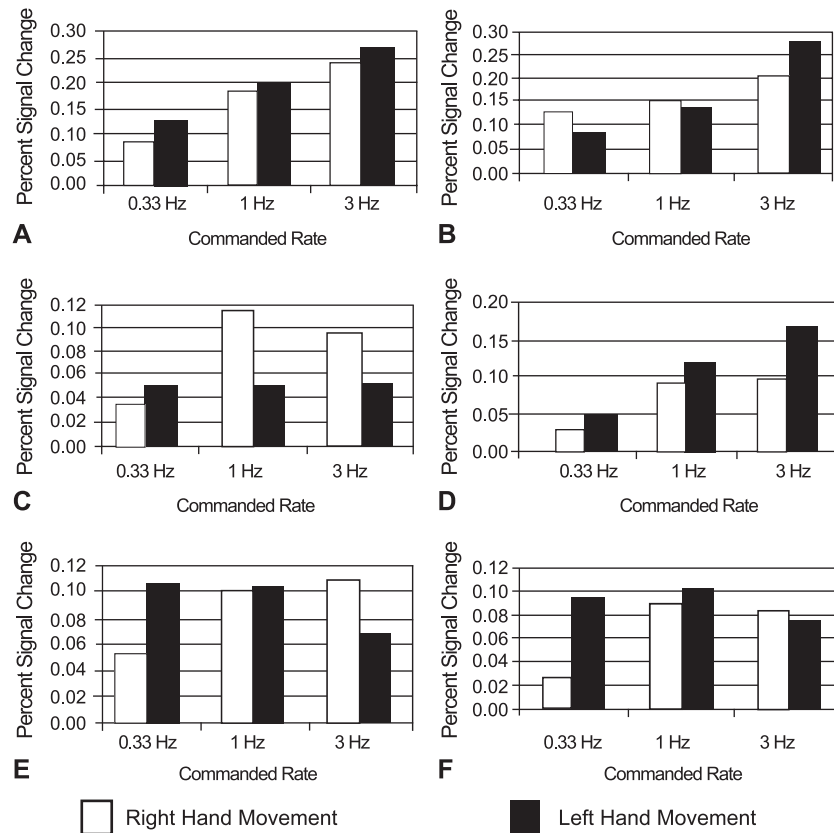


Fig. 5. Percent signal change vs. commanded rate. Graphs depicting percent signal change vs. movement rate for the *caudal* focus in the contralateral posterior precentral gyrus (A), the *rostral* focus in the posterior precentral gyrus (B), the posterior putamen (C), the ipsilateral anterior intermediate cerebellum (D), the contralateral thalamus (E), and contralateral pre-SMA (F). Movement of the right hand is shown in white bars and solid bars represent movement of the left hand. Percent signal change was computed for the voxel at which the correlation coefficient was identified, which are listed in Table 3. Note for the posterior putamen, thalamus, and pre-SMA (panels C, E, and F) that the right hand demonstrates an increase in percent signal change as requested rate increases but that the left hand does not show this relationship.

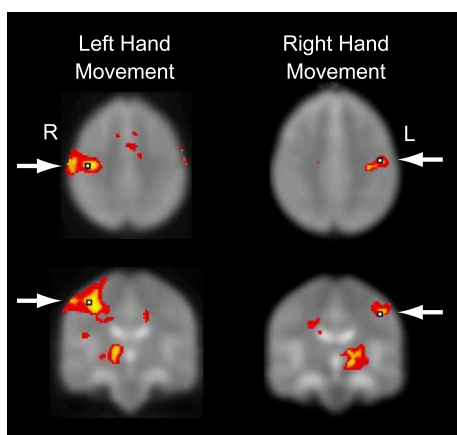


Fig. 6. Localization of the peak coordinate within the precentral gyrus during right- and left-hand movement. The peak Z score within the precentral gyrus was identified for the 3-Hz Left > Right and the 3-Hz Right > Left contrasts and the location of that coordinate was plotted as a white box surrounded by a black border on the movement vs. rest map ( $Z > 3.1$ ). The top row shows axial, and the bottom row coronal, sections through MI. Results show that peak activity for right hand movement is in the rostral MI representation and the peak for left hand movement is in the caudal MI area.

of motor system organization that includes relative left hemisphere specialization for the control of voluntary movement.

Other evidence supporting left hemisphere specialization for motor control comes from studies employing transcranial magnetic stimulation (TMS) as a means to reversibly perturb the processes involved in movement planning and execution. Using TMS to interrupt motor performance on a choice reaction time task, it was found that when TMS was applied over the right lateral premotor cortex, reaction times were increased for movements of the left, but not the right, hand. When TMS was applied over the left lateral premotor cortex, reaction times were increased for movements of the right and the left hands (Schluter et al., 1998). The authors proposed that the premotor cortex is important in the selection of visually cued movements and further that the left hemisphere is specialized for the rapid selection of action. In another study, subjects performed simple and complex movements with the left and the right hands separately. During the performance of these movements, TMS was applied to the ipsilateral motor cortex. Application of TMS to the right motor cortex resulted in timing errors during the performance of both the simple and the complex sequence. Compared with application of TMS to the right hemisphere, application of TMS to the left hemisphere resulted in an increased number of timing errors on the complex sequence. In addition, subjects continued to make timing errors after cessation

of TMS to the left hemisphere, an effect not observed during TMS stimulation of the right motor cortex (Chen et al., 1997). The authors concluded that the left motor cortex, compared with the right motor cortex, is specialized for the timing of complex ipsilateral motor sequences and further that it may be specialized for planning and implementing complex motor programs. Although these studies propose different mechanisms to explain their results, both support the general hypothesis that the left hemisphere is specialized for the control of voluntary movement.

#### *Spatial extent of activation*

The spatial extent findings depicted in Fig. 3 demonstrate another aspect of hemispheric specialization for movement control. Sequential finger-to-thumb opposition movements executed using the left hand, which may be less automatic than the same movements executed with the right hand, have been shown to recruit a larger volume of cortical tissue (Mattay et al., 1998). Therefore, one aspect of the left hemisphere specialization for movement control may involve the degree to which experience has resulted in simple movements achieving a higher degree of automaticity, and thereby reduced processing demands and a concomitantly smaller cortical spatial representation.

One important consideration in the interpretation of the spatial extent result relates to the fact that spatial autocorrelation in statistical parametric maps may result in the spatial extent and amplitude of BOLD contrast signal changes being confounded. Following low-pass spatial filtering, the activation areas are reduced in amplitude and increased in size. Hence, greater spatial extent may result from either an increase in response amplitude or an increase in the volume of gray matter involved in processing. This effect can be reduced, but not eliminated, by minimizing the degree of spatial filtering and therefore the ultimate degree of spatial autocorrelation in the statistical maps. We further addressed this problem by analyzing the peak and mean percent BOLD contrast signal change within the activation clusters and found that there were no significant differences in either average or peak percent signal change when comparing movements of the right and left hands. This lack of a significant difference in signal amplitude suggests that the difference in cluster size observed in association with left- or right-hand movements is unlikely to be an artifact resulting from statistical map smoothing.

#### *Regional specialization for the control of movement rate*

In relation to voluntary movement made using either hand, we found differential effects using categorical contrasts and measures of response amplitude or spatial extent. In addition, an effect of hand was also observed in the analysis of the relationship between response amplitude and movement rate. To quantify this relationship, changes in the BOLD contrast signal were modeled as a nonlinear function of rate using linear regression techniques. The selected asymptotic increase model is visually similar to the data from the hand representation of motor cortex in the posterior bank of the precentral gyrus (Fig. 1) and also shows the strongest correlation with BOLD contrast signal change within the precentral gyrus ( $r = 0.57$ ).

#### *Rate-related brain activity*

Analysis with the asymptotic nonlinear model described above revealed significant correlations between signal intensity and move-

ment rate. These results agree with previous studies of parametric rate variation that have identified rate-related changes in primary motor or sensorimotor cortex (Blinkenberg et al., 1996; Jancke et al., 1998b; Khushu et al., 2001; Rao et al., 1996; Sadato et al., 1996a, 1997; Schlaug et al., 1996; VanMeter et al., 1995), the SMA (Khushu et al., 2001; Sadato et al., 1996b; VanMeter et al., 1995), thalamus (VanMeter et al., 1995), and ipsilateral cerebellum (Sadato et al., 1996a; VanMeter et al., 1995). Also, Turner et al. (1998) have reported rate-related activation in the posterior globus pallidus, close to the focus identified in the posterior putamen in the current study. In addition to the areas previously identified, the current study identified rate-related changes in signal intensity in visual cortex and pre-SMA. The rate effects observed in the visual cortex are most likely due to the parametric variation in stimulus rate, as it has been shown that activity of the visual cortex varies as the visual stimulus presentation rate varies (Fox and Raichle, 1984). Other motor control studies have identified rate-related changes associated with stimulus presentation rate (Blinkenberg et al., 1996).

While movement rate-related activity has been observed in the SMA proper, immediately posterior to the pre-SMA (Khushu et al., 2001; Sadato et al., 1996b; VanMeter et al., 1995), only one previous study identified rate-related changes in the pre-SMA (Schlaug et al., 1996). The SMA is known to have reciprocal connections with the primary motor cortex and therefore would be expected to have a high degree of functional coupling, whereas the pre-SMA does not have any direct connections with MI, being directly connected with prefrontal cortical areas (Luppino et al., 1993; Matelli et al., 1993) and therefore likely to exhibit weaker functional coupling with primary motor cortex. A possible explanation for the discrepancy between this study and previous ones is that the activity identified in the current study and labeled as “pre-SMA” may represent the same activity identified in previous investigations and labeled “SMA.” The division of human SMA into two parts by a line perpendicular to the AC was suggested in 1996 (Picard and Strick, 1996) and several of the rate-related studies predate that nomenclature. Some of these earlier studies (VanMeter et al., 1995) report foci close to this border and it has recently been suggested that the border between the SMA and pre-SMA is not the AC, but is more anterior (Vorobiev et al., 1998). Therefore, possibly at least one of the foci reported in the present study as being in the pre-SMA is actually in the SMA, as the precise, cytoarchitectonically defined borders between the SMA and the pre-SMA are impossible to determine in human imaging studies.

The basal ganglia are known to process both kinematic and dynamic information concerning planned and current movements. Studies in awake behaving primates have indicated that neurons within the globus pallidus and the putamen encode information about movement parameters such as velocity, amplitude, force, and direction (DeLong, 1972, 1984; Georgopoulos et al., 1983; Liles, 1985). A linear relationship has been reported between the discharge rate of neurons within the globus pallidus and the amplitude or peak velocity of movement (Georgopoulos et al., 1983). The activity of neurons within the basal ganglia and putamen can also encode the direction of arm movements (Crutcher and DeLong, 1984; DeLong, 1972). In one such study (Crutcher and DeLong, 1984), it was shown that 76% of the neurons sampled in the putamen were sensitive to the direction of movement, with 57% of the neurons active for only one direction of movement.

The functional role of the basal ganglia in the control of movement has also been studied with functional brain imaging in

humans. Right index finger flexion is associated with task-related signal change in the putamen contralateral to the movement (Jenkins et al., 2000; Sadato et al., 1996b; Turner et al., 1998; Weeks et al., 2001). In one study, it was observed that, during right index finger movement, the contralateral putamen was active only at 0.75 and 1 Hz and not at slower or faster rates, indicating rate sensitivity within the putamen (Sadato et al., 1996b). Other studies, in which the complexity of the finger-to-thumb opposition movements has been parametrically modulated, have shown that activity within the globus pallidus increases as the complexity of the movement sequence increases (Boecker et al., 1998; Sadato et al., 1996a). The putamen has also been shown to be active during more complex tasks in which subjects signed their name, performed joystick movements, or performed complex bimanual movements (Sadato et al., 1997; Scholz et al., 2000; Turner et al., 1998). A review of functional neuroimaging results in which the basal ganglia showed task-related activity concluded that the middle putamen was active during the free selection of movements and the posterior putamen was active during prelearned and repetitive movements (Jueptner and Weiller, 1998). These studies support the contention that the cortico-striatal system is sensitive to both the rate and complexity of voluntary movement.

Rate-related changes in the posterior putamen have not previously been described during simple finger movements, although one study did describe such changes in the adjacent globus pallidus (Turner et al., 1998). However, one would expect to see rate modulation in the putamen based on the detection of rate-related activity in an anatomically linked area such as the pre-SMA. Anatomical studies using retrograde tracers in nonhuman primates have identified connections from the pre-SMA to the putamen (McFarland and Haber, 2000). Previous functional neuroimaging studies may have failed to identify rate-related changes in the posterior putamen due to limited spatial sampling, spatial resolution, or statistical power, as it is more difficult to detect activity in the basal ganglia, due to the relatively smaller change in signal intensity compared to cortical motor areas (1% vs. 3%), possibly as a result of this structure's higher iron content (Mattay and Weinberger, 1999; Scholz et al., 2000).

Lastly, a central role for the striatum in the control of variable rate movements is supported by the behavioral effects of damage to this structure. Individuals with Parkinson's disease, a neurodegenerative disorder affecting the nigrostriatal system, invariably exhibit bradykinesia, a movement disorder characterized by impairments in the execution of speeded, voluntary movement.

#### *Laterality effects*

Is there hemispheric specialization for the control of voluntary movement rate, as measured by differential parametric rate effects during movements of the right and left hands? The behavioral evidence strongly supports the superior dexterity of the right hand measured using a variety of speeded movement tasks. Studies in which right-handed volunteers were instructed to perform finger flexion as fast as possible have shown that the right hand is capable of faster movement rates than the left hand (Rousselle and Wolff, 1991) and that movement with the right hand is less variable than movement of the left hand (Klicpera et al., 1981; Wittmann et al., 2001). When subjects drew circles with either hand, the right hand was faster than the left hand (Swinnen et al., 1996). These results suggest that there is a left hemisphere advantage, and possibly a related regional functional

specialization, for the planning and execution of speeded voluntary movement.

Concerning the neural mechanisms responsible for the repeatedly observed behavioral asymmetries in manual proficiency, one previous imaging study (Jancke et al., 1998a) examined rate effects in both the right and left hands in a few subjects and found that, for both the left and right sensorimotor cortex, movement at higher rates resulted in a greater volume of task-related activity. However, there was no characterization of differences in the rate effect between the hands.

In the present study, several components of the medial premotor cortico-striatal-thalamo-cortical system, including the bilateral pre-SMA, contralateral posterior putamen, and contralateral thalamus, exhibited rate modulation during movement of the right hand, but did not exhibit rate modulation during movement of the left hand. The differential activation of the medial premotor corticostriatal motor loop in relation to visually paced movement of the right or left hand represents a robust example of hemispheric specialization for the control of voluntary movement. The left hemisphere modulates activity within this loop as a function of the movement rate, but the right hemisphere does not. Because the right hemisphere system is less skilled at controlling variable-rate movements, it becomes maximally engaged at a lower movement rate and does not increase its activity with increasing movement rate. This pattern of activity resembles the step function previously described (VanMeter et al., 1995) and not the asymptotic function used in this experiment. Percent signal change data recorded in the posterior putamen, thalamus, and pre-SMA are shown in Fig. 5 and these data support this hypothesis.

#### *Hemispheric differences in patterns of activity within MI*

Microstimulation studies in nonhuman primates have identified multiple representations of the hand in the area classically identified as the primary motor cortex (Strick and Preston, 1978). Hand and wrist movements could be elicited by stimulating two different regions within the posterior precentral gyrus, labeled the caudal and rostral hand representations (Strick and Preston, 1978). Further experiments indicated that both regions have similar efferent projections to the same motoneuron pool and that stimulation of either area was able to evoke the same movements using the same musculature (Strick and Preston, 1982a). However, differences between the two areas were identified when the types of afferent input were investigated. The caudal representation receives input from cutaneous skin receptors and is responsive to tactile feedback while the rostral representation receives input from deep joint receptors (Strick and Preston, 1982b). More recently, anatomical tracing studies have shown that each area receives the majority of its input from different subcortical structures. The caudal representation receives its primary input from the globus pallidus via nucleus VLo of the thalamus while the rostral representation receives input primarily from the cerebellum via thalamic nucleus VPLO (Holsapple et al., 1991). The human functional neuroimaging literature also provides evidence for two foci of activation within the primary motor cortex and supports the observation from nonhuman primates that each focus receives different types of afferent input (Geyer et al., 1996). Self-generated movement is associated with activation of both the rostral and caudal finger representations in the posterior precentral gyrus but a roughness discrimination task predominantly activates the caudal area (Geyer et al., 1996). The movement condition would activate both deep



joint receptors and cutaneous skin receptors when the finger encounters the response box or another finger while the roughness discrimination task preferentially activates the cutaneous skin receptors and not deep joint receptors.

These different types of afferent input and the finding that each area receives the majority of its input from a different thalamic nucleus suggest that each may be part of a different cortical motor control loop and that there may be different patterns of relative activation of these two areas depending on the nature of the motor task. Results from both the categorical and parametric contrasts identified significant activity within both the rostral and caudal representations during movement of the right and left hands. It is unlikely that these two foci represent a functional neuroimaging artifact such as draining veins because the intersubject averaging inherent in the analysis of group data would minimize such effects. Further analysis revealed that the peak task-related signal change lay within the rostral representation during movement of the right hand and within the caudal representation during movement of the left hand (Fig. 6).

One interpretation is that this differential pattern activation is due to the different nature of the movements performed with the right and left hands. As was described above, the rostral motor representation receives input from muscle afferents and joint receptors while the caudal representation receives mainly cutaneous input (Strick and Preston, 1982b, 1983). The right hand is preferentially employed for tasks that are greatly overlearned. It is possible that tasks performed automatically would not require as much cutaneous input for control and might therefore activate the rostral area to a greater extent while a task that was not automatic and relied on more sensory feedback would activate the caudal representation more strongly. The results from this study are in accord with this hypothesis. The more practiced and automatized speeded movements of the right hand activated the rostral primary motor cortex representation more than it did the caudal representation. The same task, when performed with the less practiced left hand, resulted in greater activation of the caudal motor representation.

## Conclusions

We have utilized parametric variations in movement rate to explore regional functional specialization for the control of speeded voluntary movement. By comparing movements of the right and left hands, it was possible to identify a rate-sensitive lateralized premotor corticostriatal system. Our results support the theory that the left hemisphere is specialized for the control of at least one aspect of voluntary movement, evidenced by the novel finding of rate-related activity in a premotor corticostriatal loop during movement of the right but not the left hand. Because the right hemisphere system is less skilled at controlling variable-rate movements, it becomes maximally engaged at a lower movement rate and is not further modulated with increasing movement rate. These functional imaging results extend existing accounts concerning the anatomy and physiology of the subcortical structures with which the motor cortical areas participate as part of large-scale functional systems. Dysfunction of these systems may result in anomalous manual specialization and future experiments may explore the role the medial premotor corticostriatal plays in the pathophysiology of developmental coordination disorders.

## Acknowledgments

We wish to thank John VanMeter and Karen Jones for their help with data analysis, Kimford Meador for review of an early version of the manuscript, and the National Institutes of Health for their support through grants MH12584 and HD40095.

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