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Differential Cortical and Subcortical Activations in Learning Rotations and Gains for Reaching: A PET Study

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Krakauer, John W., Maria-Felice Ghilardi, Marc Mentis, Anna Barnes, Milana Veytsman, David Eidelberg, and Claude Ghez. Differential cortical and subcortical activations in learning rotations and gains for reaching: a PET study. *J Neurophysiol* 91: 924–933, 2004. First published October 1, 2003; 10.1152/jn.00675.2003. Previous studies suggest that horizontal reaching movements are planned vectorially with independent specification of direction and extent. The transformation from visual to hand-centered coordinates requires the learning of a task-specific reference frame and scaling factor. We studied learning of a novel reference frame by imposing a screen-cursor rotation and learning of a scaling factor by imposing a novel gain. Previous work demonstrates that rotation and gain learning have different time courses and patterns of generalization. Here we used PET to identify and compare brain areas activated during rotation and gain learning, with a baseline motor-execution task as the subtracted control. Previous work has shown that the time courses of rotation and gain adaptation have a short rapid phase followed by a longer slow phase. We therefore also sought to compare activations associated with the rapid and slower phases of adaptation. We isolated the rapid phase by alternating opposite values of the rotation or gain every 16 movements. The rapid phase of rotation adaptation activated the preSMA. More complete adaptation to the rotation activated right ventral premotor cortex, right posterior parietal cortex, and the left lateral cerebellum. The rapid phase of gain learning only activated subcortical structures: bilateral putamen and left cerebellum. More complete gain learning failed to show any significant activation. We conclude that the time course of rotation adaptation is paralleled by a frontoparietal shift in activated cortical regions. In contrast, early gain adaptation involves only subcortical structures, which we suggest reflects a more automatic process of contextual recalibration of a scaling factor.

INTRODUCTION

Psychophysical studies suggest that visually guided reaching movements in the horizontal plane are planned as vectors with independent specification of direction and extent through feedforward mechanisms (Bock 1992; Gordon et al. 1994; Vindras and Viviani 1998). This implies that subjects can access a reference axis and a scaling factor specific to the task. More recently, we described the time courses of adaptation to extent and directional errors, induced by screen-cursor rotations and gain changes, respectively (Krakauer et al. 2000b; Pine et al. 1996). The time courses of adaptation to both rotations and gain changes were consistently better fit by double- rather than single-exponential functions, suggesting the presence of an initial rapid and a later slower phase of learning in both cases.

More important, there were marked differences in the effect of target number on the time course and degree of generalization of rotation and gain adaptation. Increasing the number of training directions from one to 8 for rotation proportionately reduced the rate of initial adaptation and adaptation was less complete at the end of the slower phase. Generalization to unexplored directions occurred only with more extended practice in multiple target directions. In contrast, subjects adapted to a new gain at the same rapid rate when training with one or multiple target distances, suggesting acquisition of a scaling factor for the whole workspace. This was supported by the finding that after training to a single target, subjects were able to generalize learning of a new gain to previously unvisited distances and directions.

These psychophysical data raise the possibility of separate anatomical substrates for the storage and processing of directional and extent errors needed for adapting to rotational and gain transformations. Previous work by our group and by others have shown that rotation adaptation activates right posterior parietal cortex (Ghilardi et al. 2000; Inoue et al. 2000) and cerebellum (Imamizu et al. 2000). We are not aware of any imaging studies of gain adaptation for reaching movements. Similarly, the presence of 2 phases of learning suggests differences in the fast and slow processing of directional and extent errors that might be paralleled by differences in brain activation over time. This possibility is supported by imaging studies that have shown modulation and shift in brain regions activated during the time course of motor learning (Inoue et al. 1997; Sakai et al. 1998). Such shifts have been proposed to reflect the transitions from learning simple stimulus–response associations to learning of sequences (Sakai et al. 1999), from novelty to automaticity (Doyon et al. 1996; Krebs et al. 1998; Petersen et al. 1998) or from working memory to consolidation (Shadmehr and Holcomb 1997).

In this paper we used PET to investigate the brain regions involved in rotation learning and to compare these regions to those involved in gain learning. Additionally, we compared activations associated with the rapid decrement in error during the first phase to more complete adaptation when learning is allowed to proceed through the second phase. To keep subjects in the rapid phase we alternated opposite values of the rotational or gain transformations every 16 movements. Some of these results were published previously in abstract form (Krakauer et al. 2000a).

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METHODS

Subjects

Twelve neurologically normal right-handed male subjects (ages 24–29 yr) volunteered for the study. All were naïve to the purpose of the experiment, signed an institutionally approved consent form, and were paid to participate. They all underwent MRI imaging to exclude any brain abnormalities.

Apparatus

Subjects underwent brain scanning while performing 2 sets of 5 motor tasks during blocks of 96 movements each. Basic task requirements are described in detail in previous publications (Ghilardi et al. 2000; Nakamura et al. 2001). In brief, all tasks required subjects to move a handheld cursor with their right hand on a 18 × 12-in. digitizing tablet (Numonics Corporation, Model 2200), while their hand and target locations were displayed on a 15-in. computer screen. A computer controlled the experiment, generated screen displays, and acquired kinematic data from the digitizing tablet at 200 Hz. On the day before PET scanning, all subjects had a session of training to become familiar with the setup and to achieve stable levels of accuracy (95% hits in 2-cm-diameter targets at a distance of 4.2 cm) in the motor reference task (CONTROL; see following text).

General procedure for motor tasks

For all tasks, subjects were required to move a cursor out and back in one uninterrupted movement from a central starting position to one of 8 radially arrayed circular targets. Targets, displayed on the vertical computer screen, were 45° apart and 4.2 cm from the center. At the start of a trial block, a series of 3 tones were sounded at 1 s intervals to provide the required tempo of the movements to follow. With the 4th and subsequent tones, successive targets turned black every second in synchrony with a tone in a predictable counterclockwise order beginning at the 3 o'clock position. Subjects were instructed to reverse sharply and in synchrony with the tone. Subjects then had to pause briefly in the starting position before moving to the next target. The specific motor tasks were the following. *1*) CONTROL. This was the control task as described above with a 1:1 relation between tablet and screen distance and rightward motion of the hand moved the cursor to the right and upward motion of the hand moved the cursor upward on the screen. *2*) GAIN. The tablet-to-screen gain was changed to 1:1.5 for one scan and 1:0.5 for the other. The former required subjects to make 2.8 cm movements and the latter 8.4 cm movements to displace the screen cursor 4.2 cm. The order of the 2 GAIN scans was randomized across subjects. These 2 gains were chosen so that the mean gain for the 2 scans combined was 1 as for the 2 control scans. *3*) GAIN*alt*. The gain was alternated between 1:1.5 and 1:0.5 every 16 movements. This was done to keep subjects in the rapid phase of gain adaptation throughout the scanning period. *4*) ROT. The direction of cursor movement relative to the direction of the hand on the tablet was rotated 30° clockwise (CW) for one scan and 30° counterclockwise (CCW) for the other. The order of the 2 ROT scans was randomized across subjects. CW and CCW rotations were chosen so that the mean angle of rotation for the 2 scans was 0°, as in the 2 control scans. *5*) ROT*alt*. The cursor rotation was alternated between 30°CW and 30°CCW every 16 movements. Because successive opposite rotations interfere with consolidation (Krakauer et al. 1999), subjects remained in the rapid phase of learning throughout the scan period.

Subjects performed two 96 s scans of each task. The scans were performed in 2 sets of task blocks and the task order within each set was pseudo-random. The 2 ROT*alt* scans were always performed as the last 2 scans of the 2nd task block for each subject. This was done to prevent practice or interference effects of either of the 2 ROT scans on performance in the 2 ROT*alt* scans, given that in previous work we showed that a second exposure to the same rotation leads to savings in performance. Savings is prevented, however, if a rotation is followed by a counterrotation (Krakauer et al. 1999), as was done here. Thus the 2 ROT conditions interfered with each other before the ROT*alt* conditions were experienced. This precaution was not taken for the GAIN*alt* scans because gain learning is so fast and savings is negligible. Between adaptation conditions, subjects were brought back to baseline performance by doing 96 s of CONTROL.

Psychophysical data analysis

As described in previous publications (Ghilardi et al. 2000; Nakamura et al. 2001), for the outward phase of each movement we computed movement time, movement extent, and the directional error. The directional error for each movement was defined as the difference between the direction of the target from the initial hand position and the direction of the position of the hand at the peak outward velocity from the same initial position. Averages and SE values of means were generated for each successive movement across all subjects.

Additionally, mean velocity and mean directional error for each cycle of 8 movements was calculated (mean peak velocity per cycle = V_{pk}; mean directional error at the peak velocity per cycle = $DirErrV_{pk}$).

Rotation adaptation was calculated as a percentage

$$100 \times \left(1 - \frac{DirErrV_{pk}}{\pm 30°}\right)$$

Decreases and increases in gain result initially in hypometric and hypermetric movements, respectively, as well as corresponding changes in velocity. However, the changes in velocity more closely approximate adaptation in feedforward control signals as extent can partly be corrected through updating (Messier and Kalaska 1999). Thus to assess the time course of gain adaptation we followed changes in peak velocity rather than in movement extent as in previous studies (Krakauer et al. 2000b). To compare rescaling across subjects the peak velocity was normalized (V_{pkN}) for each subject. This was done by dividing the peak velocity per movement in the 2 GAIN or GAIN*alt* tasks by the mean peak velocity across all movements in the 2 CONTROL scans.

Gain adaptation was calculated as a percentage (where the error in gain learning would be the expected value of V_{pkN} minus the actual V_{pkN} achieved)

$$100 \times \left[1 - \frac{V_{pkN}(Expected) - V_{pkN}(Gain)}{V_{pkN}(Expected) - V_{pkN}(Control)}\right]$$

To assess the rate of adaptation in the different conditions we calculated the incremental error reduction for each cycle of 8 movements as a percentage change in directional error or peak velocity (called "Error" in the formulae below) compared with learning at the end of the previous rotation or gain change. This was also done for the ROT and GAIN conditions even though there was no change in the imposed rotation or gain every 2 cycles. The denominator was the directional error (rotation) or normalized peak velocity (gain) in the second cycle of the previous 2-cycle alternation ($Error_{cycle2prev}$). Thus the adaptation in cycle 1, after the rotation or gain is changed, would be

$$\frac{100 \times (Error_{cycle2prev} - Error_{cycle1})}{Error_{cycle2prev}}$$

and the adaptation in cycle 2 of the alternation would be

$$\frac{100 \times (Error_{cycle1} - Error_{cycle2})}{Error_{cycle2prev}}$$

These equations capture adaptation to both imposed rotation and gain and to the aftereffect in the alternating tasks. Thus a subject might substantially reduce error caused by the aftereffect but not learn the imposed transformation. This would be reflected in a large incremen-

tal error reduction but low adaptation. Mean adaptation and incremental error reduction across subjects was then calculated for each scan pair. Differences between conditions were assessed using 2-tailed *t*-tests.

PET

IMAGE ACQUISITION. PET studies were performed in 3D mode using the GE Advance tomograph at North Shore University Hospital, Manhasset, NY. This 8-ring bismuth germanate scanner provided 35 2D image planes with an axial field of view of 14.5 cm and transaxial resolution of 4.2 mm [full width at half the maximum (FWHM)] in all directions. Ethical permission for these studies was obtained from the Institutional Review Board of North Shore University Hospital. Written consent was obtained from each subject after detailed explanation of the procedures.

In each PET session, subjects were positioned in the scanner using the Laitinen stereoadapter (Hariz and Eriksson 1986) (Sandstrom Trade and Technology, Welland, Ontario, Canada) with 3D laser alignment with reference to the orbitomeatal line. To minimize repositioning errors, we used identical stereoadapter and laser settings in all imaging sessions. Each subject was scanned in 2 sets of task blocks. Each set consisted of 5 task blocks presented in pseudorandomized order (ROT, ROT*alt*, GAIN, GAIN*alt*, and CONTROL). The ROT*alt* condition was always performed last so that the 2 ROT scans had interfered with each other and so neither one could exert a savings effect on ROT*alt*. Motor tasks were performed with the dominant right arm and an intravenous catheter was placed in the left arm for administration of $H_2{}^{15}O$. Relative cerebral blood flow (rCBF) was estimated using a modification of the slow bolus method of Silbersweig et al. (1993), in which 10 mCi of $H_2{}^{15}O$ in 4 ml saline was injected by automatic pump in 16 s (15 ml/min) followed by a manual 3-ml saline flush. Using this injection protocol, there was a time delay of about 17 s before onset of brain radioactivity, and the time from onset to peak count rate was 45–50 s. PET data acquisition began at the time of radioactivity arrival (about 10 s after the start of the motor task) in the brain and continued for 80 s. The interval between successive $H_2{}^{15}O$ administrations was 10 min to allow for the decay of radioactivity.

IMAGE ANALYSIS. Data processing was performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (MATLAB6R12, Mathworks, MA).

All the scans were spatially standardized to the PET CBF template provided with SPM99 using the nonlinear spatial standardization facility with $7 \times 8 \times 7$ basis functions and resliced with voxel size $2 \times 2 \times 2$ mm (Ashburner et al. 2000). All spatially standardized scans were smoothed using a 10-mm FWHM isotropic Gaussian spatial filter before the voxel-wise statistical analysis (Friston et al. 1996). The 2 repeated scans of each condition were averaged using the Mean Images tool within SPM99, an option that accounts for differences in global activity by proportionally scaling each image to its global mean before averaging the individual voxel activity.

To identify changes in rCBF associated with the main effects of task, we used the SPM99 statistics option Multi-subject: conditions and covariates. The main effect of task was investigated using the contrast [1 −1] for each of the 4 task conditions (ROT, ROT*alt*, GAIN, GAIN*alt*) with respect to the CONTROL condition. In separate analyses, to identify areas associated with linear increases in rCBF across similar task conditions (Turner et al. 1998) a linear weighted contrast [−1 0 1] was used. This was done to identify those regions previously identified by the subtraction analysis where the change in blood flow is linearly related to the change in level of adaptation [e.g. (CONTROL, ROT, ROT*alt*) and (CONTROL, GAIN, GAIN*alt*); see Figs. 5 and 7].

Subtraction results were displayed at $P < 0.001$, height uncorrected and $P < 0.05$, extent corrected for multiple statistical comparisons. In addition, to characterize smaller activations occurring specifically within motor execution areas, we created a motor-execution mask (Fukuda et al. 2001; Nakamura et al. 2001; Turner et al. 1998) from an independent population of 12 right-handed normal subjects who performed the CONTROL task under identical conditions to those of the current study. This mask was made by subtracting a sensory (visual/nonmovement) reference task (Ghilardi et al. 2000) from the CONTROL task and thresholding the resulting SPM(t) map at $P < 0.05$, extent corrected. Thus for comparisons using the mask, changes in rCBF were accepted at the $P < 0.05$ extent uncorrected threshold, within the predefined anatomical reference mask that includes: the left primary sensorimotor cortex (BA3, 2, 1, and 4), premotor cortex and SMA (BA6), posterior cingulate (BA23), parietal (BA5, 7, 40), and visual areas (BA7, 18) as well as the subcortical areas of the left putamen, globus pallidus, and thalamus.

The anatomical locations of significant clusters represented in the SPM(t) image were determined using the Talairach and Tournoux Atlas (Tailarach and Tournoux 1988), after converting the calculated SPM99 coordinates into Talairach coordinate space (http://www.mrccbu.cam.ac.uk/Imaging/MNI/Tailarachdifferences).

RESULTS

Psychophysics

In the control condition, subjects moved their right hand out and back with straight paths and sharp reversals and both movement segments had unimodal velocity profiles with minima at the outermost point in the paths. These trajectory characteristics were unchanged during the adaptation conditions. Specifically, during both rotation conditions there was no increased curvature or directional updates. In the gain conditions, outward velocity profiles remained unimodal without apparent submovements. The mean movement extent and peak outward velocity were somewhat greater, and movement time smaller (<20% difference) for the 4 adaptation conditions compared with CONTROL (Table 1). However, there was no significant difference in these kinematic parameters across the adaptation conditions (averaged for both scans of each condition). Subjects had 96 learning trials in the ROT and GAIN conditions and, on average, achieved >70% learning.

Although the slope of the initial phase of 30°CW adaptation was steeper than that for 30°CCW there was no significant difference in the degree of adaptation achieved in the last 2 cycles of 30°CW and 30°CCW (*t*-test, $P = 0.11$). During ROT*alt* (Fig. 1*C*), it can be seen that the shapes of the learning curves are similar to those of the initial rapid phase of the respective ROT tasks (Fig. 1, *A* and *B*) but that learning in the slow phase is incomplete. It is also apparent that adaptation during the second 2 cycles of the CW or CCW rotation in the ROT*alt* conditions is no faster than during the first 2 cycles. This indicates that the alternation of opposite rotations prevented savings in performance on 2nd exposure to the same rotation. Thus at each alternation in ROT*alt*, subjects were indeed in a

TABLE 1. *Movement time, movement extent, and peak velocity averaged across subjects for each of the five scanning tasks*

Task	Movement Time ms	Movement Extent cm	Peak Velocity cm/s
GAIN	282.6 ± 17.4	6.55 ± 0.4	38.7 ± 2.1
GAIN*alt*	283.9 ± 06.4	5.24 ± 0.1	41.1 ± 1.2
CONTROL	289.9 ± 09.8	5.12 ± 0.5	33.8 ± 1.3
ROT*alt*	260.6 ± 06.6	5.57 ± 0.1	40.4 ± 1.4
ROT	277.4 ± 09.6	5.49 ± 0.1	37.6 ± 1.2

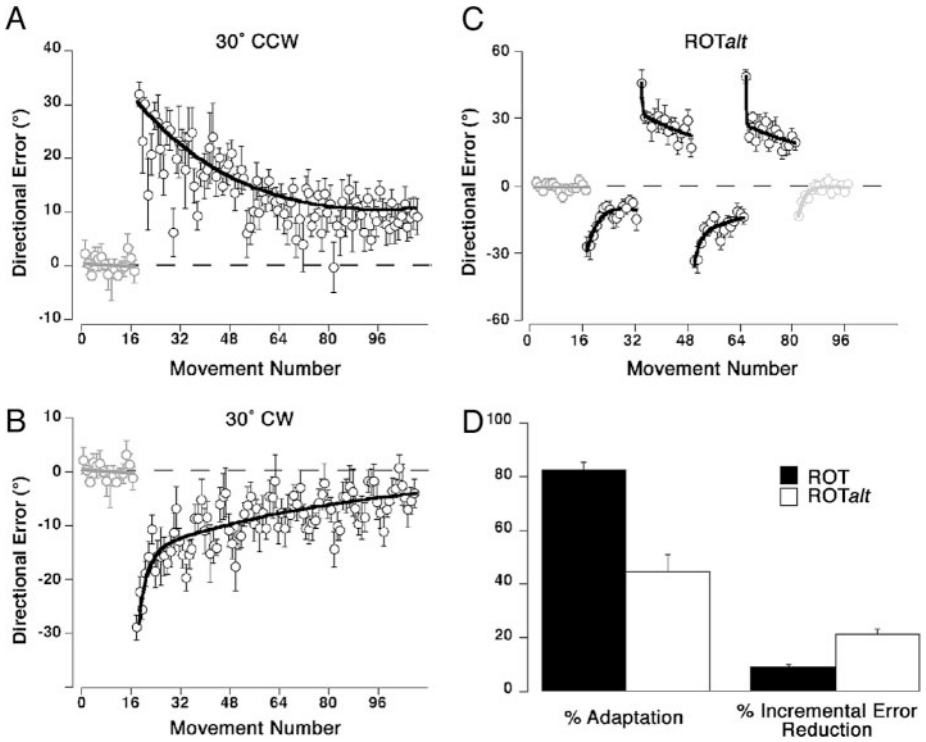

FIG. 1. Learning ROT (group data, $n = 12$) was measured by progressive reduction in the directional error at the peak velocity. First 16 movements are at rotation 0°. Rotation learning curve for *A*: CCW rotation of 30° and *B*: CW rotation of 30°. *C*: learning ROT*alt* (group data, $n = 10$) was measured by progressive reduction in the directional error at the peak velocity. First and last 16 movements are at rotation 0°. Rotation alternated between 30°CCW and 30°CW rotations every 16 movements, beginning with CW. In the first 16 movements, subjects adapted as they did at the beginning of ROT but then the aftereffects slowed learning in subsequent segments of 16 movements. There was no significant difference by *t*-test between the coefficients of the first exponential in the ROT and ROT*alt* conditions (excluding the 1st movement). *D*: incremental error reduction and adaptation in ROT and ROT*alt* (group data). Bar charts show the mean percentage adaptation and error reduction over the 96 movements of the scanning period. There was significantly less adaptation in each 16 movement segment of ROT*alt* compared with adaptation at the end of ROT (*t*-test, $P < 0.001$). There was significantly more incremental error reduction in the ROT*alt* condition (*t*-test, $P < 0.001$).

similar state as the early phase of the ROT task. Figure 1*D* shows that in ROT*alt* the overall percentage adaptation was less than that in ROT but the mean incremental error reduction was greater.

In GAIN, with a transition from a gain of 1 to 1.5, movement extents were initially hypermetric, and for a gain of 0.5, hypometric, but were adjusted within about 8 movements (see the dashed curves in Fig. 2, *A* and *B*). Peak velocities showed parallel changes. As can be seen in Fig. 2*B*, when gain was increased, peak velocity was reduced in proportion to the reduction in movement extent. However, when gain was decreased and larger movements were required, the increase in velocity was less than proportional (Fig. 2*A*), most likely reflecting saturation of the velocity displacement relationship. Nevertheless, changes in peak velocity and movement extent reached plateau at a similar point in time, indicating that no further learning occurred after the peak velocity was rescaled. In GAIN*alt*, peak velocity also reached plateau within 8 movements (Fig. 2*C*). In GAIN*alt*, as compared with GAIN, subjects spent more scan time reducing errors from movement to movement but less time in the adapted state (Fig. 2*D*).

Alternating the direction of the rotation in ROT*alt* prevented substantial adaptation from occurring in each alternating phase. Nevertheless, subjects reduced errors as much as in the gain

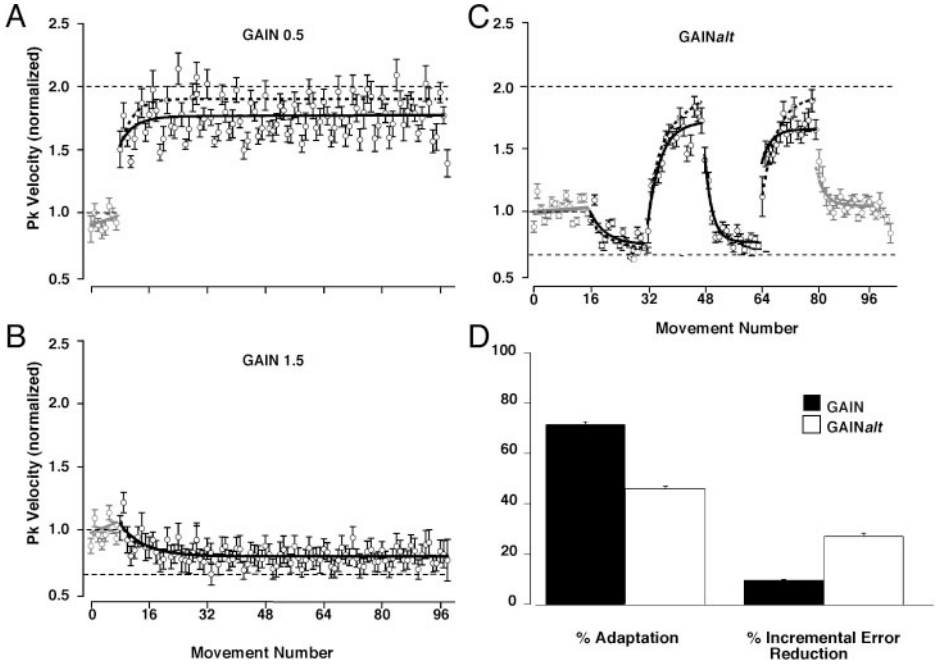

FIG. 2. Learning GAIN (group data, $n = 12$) was measured by progressive adjustment of normalized peak velocity. First 16 movements are at gain 1. *A*: gain learning curve for gain of 1:0.5. *B*: gain learning curve for gain of 1:1.5. For both gains, subjects adapted their movement extents (dashed line) within 8 movements. This was reflected in their peak velocities (black line and points) reaching the 2nd exponential in approximately the same number of movements. *C*: learning GAIN*alt* (group data, $n = 12$). First and last 16 movements are at gain 1. Gain alternated between 1.5 and 0.5 every 16 movements beginning with 1.5. Movement extent (dashed lines) and peak velocity (continuous line and points) reached the 2nd exponential in each 16-movement segment. *D*: incremental error reduction and adaptation in GAIN and GAIN*alt* (group data, $n = 10$). Bar charts show the mean percentage adaptation and error reduction per cycle over the 96 movements of the scanning period. There was significantly more adaptation per cycle in the GAIN condition. Conversely, there was significantly more incremental error reduction in the GAIN*alt* condition (*t*-test, $P < 0.001$).

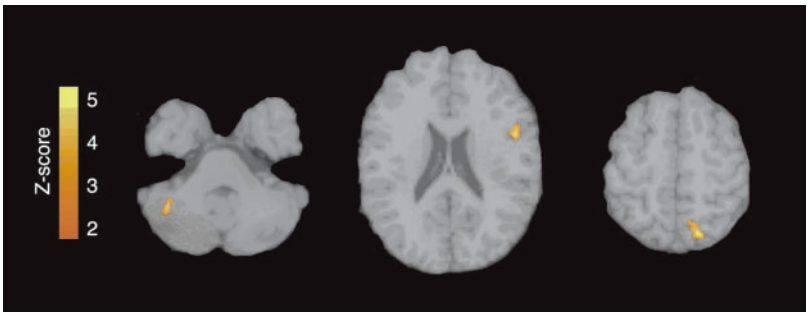

FIG. 3. Brain areas associated with ROT learning (ROT > CONTROL; Z-map thresholded at $P < 0.001$ height uncorrected; $P < 0.05$ spatial extent corrected). Significant activations were found in left lateral cerebellum, right ventral premotor cortex (BA6), and right posterior parietal cortex (BA7).

alternation task. This occurred because gain adaptation was much faster than rotation adaptation, with the 2nd cycle of each alternation already at plateau without further appreciable error reduction. In contrast, error reduction continued into the 2nd cycle for rotation adaptation.

Imaging of rotation learning

To identify areas associated with the learning of a rotated reference frame, we subtracted mean ROT images from mean CONTROL images. This revealed significant activations in the right posterior parietal cortex, right ventral premotor (PMv) cortex, and in the left lateral cerebellum (see Fig. 3 and Table 2). To identify areas associated more specifically with the rapid phase of error reduction, we subtracted mean ROT*alt* from mean CONTROL images (see Fig. 4 and Table 2). This revealed significant activation only in the preSMA. We did not find any significant additional activations within the execution-related mask (see METHODS) even at the lower threshold of $P < 0.05$ (extent, uncorrected).

Although the ROT–CONTROL comparison did not show significant preSMA activation, a weighted linear contrast analysis revealed that the preSMA activation was maximal in ROT*alt*, intermediate in ROT, and lowest in CONTROL (Fig. 5*B*). A reordering of the linear contrast revealed that the rCBF increase in the right posterior parietal cortex identified in the initial subtraction between CONTROL and ROT increased progressively from CONTROL to ROT*alt* to ROT (Fig. 5*B*). Thus as rotation learning progressed, preSMA activation decreased and posterior parietal activation increased. We did not find a significant linear trend in the right PMv or left lateral cerebellum. A direct comparison of ROT and ROT*alt* did not yield significant activations, given that the percentage change in rCBF between these 2 tasks was small, presumably because these tasks share regions of activation, as suggested by the linear contrast analysis.

TABLE 2. *Tailarach coordinates and Z-scores for significant activations*

Task	Area	X, Y, Z Coordinates	z-Value
ROT	Left cerebellum	−42, −58, −34	4.58
	Right PMv	52, 6, 16	4.39
	Right posterior parietal cortex	18, −70, 58	4.03
ROT*alt*	Right preSMA	6, 22, 52	3.96
GAIN*alt*	Left putamen/insula	−36, −2, −8	3.32
	Left cerebellum	−22, −58, −40	3.54
	Right putamen	30, −4, 4	3.43

PMv, ventral premotor cortex; SMA, supplementary premotor area.

Imaging of gain learning

A preliminary investigation of the data showed that neither GAIN − CONTROL nor the GAIN*alt* − CONTROL subtractions showed significant activation at $P < 0.05$ (extent, corrected for multiple statistical comparisons), which would seem to indicate that these tasks are using the same regions already activated by the CONTROL task. Support for this possibility comes from a recent PET study investigating the effect of movement velocity on rCBF, which showed activation in a subset of cortical and subcortical regions activated during movement execution (Turner et al. 1998). Thus given that gain adaptation involves modulating movement velocity to a given target distance, we hypothesized that neural changes may be confined to subregions of the previously identified CONTROL network. To test this hypothesis, we looked for activation only within a CONTROL mask (see METHODS; also see Fukuda et al. 2001). We found no significant activation inside the mask for the GAIN − CONTROL subtraction. However, the GAIN*alt* − CONTROL subtraction, inside the CONTROL mask, showed significant activations in the left insula/putamen, left medial cerebellum, and right putamen (see Fig. 6 and Table 2). Thus the rapid phase of gain adaptation was associated with activation in a subset of the motor areas activated in the CONTROL task. Subtraction images showed no significant additional activation late in the performance at the new gain, unlike the cortical activation seen in ROT. However, weighted linear contrasts did show that GAIN caused intermediate levels of activation in the medial cerebellum and right putamen (Fig. 7). This supports the idea that the rapid process of gain adaptation occurring throughout GAIN*alt* also occurred at the beginning of the GAIN task.

DISCUSSION

In this study we used $H_2{}^{15}O$ PET to identify the brain regions responsible for the learning of reference axes and new

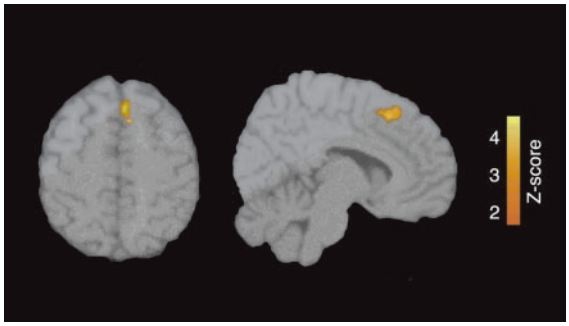

FIG. 4. Brain areas associated with ROT*alt* learning (ROT*alt* > CONTROL; Z-map thresholded at $P < 0.001$ height uncorrected, $P < 0.05$ spatial extent corrected). Only significant activation was in the preSMA (BA6).

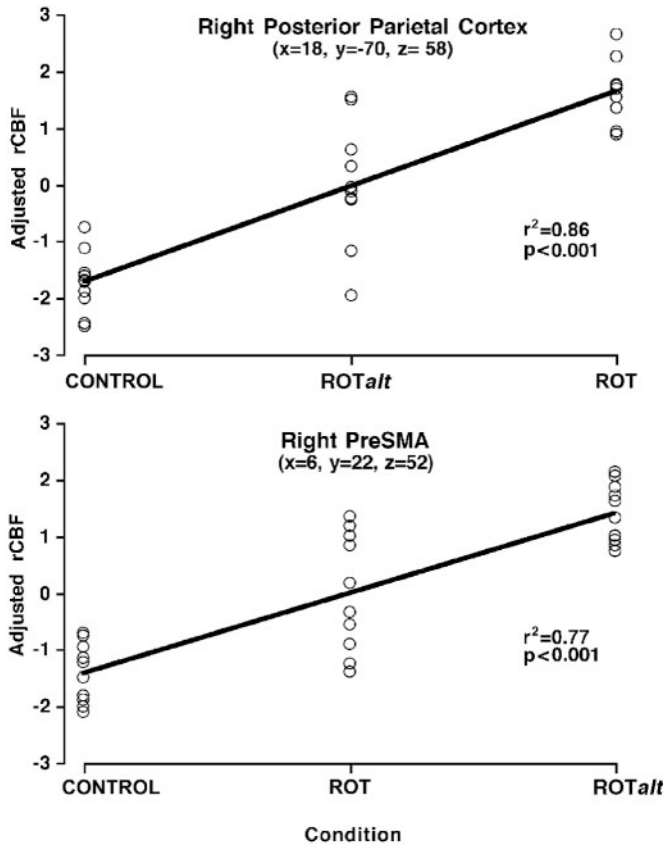

FIG. 5. *A*: relationship between mean rCBF in the posterior parietal cortex for the 2 rotation learning conditions. There is a significant linear trend ($P < 0.005$) with greatest activation in ROT. *B*: relationship between mean rCBF in the preSMA for the 2 rotation learning conditions. There is a significant linear trend ($P < 0.005$) with greatest activation in ROT*alt*.

scaling factors in motor planning by examining adaptation to variant gains and rotations in a visuomotor task. During adaptation, trajectories did not show apparent corrections, indicating that movements remained under feed forward control and that adaptation involved learning new visuospatial models.

We sought to determine whether different regions are involved in the early rapid phase of adaptation compared with the later slower phase of adaptation. To maintain subjects in the early rapid phase of adaptation we alternated the rotation or the gain every 2 cycles. This procedure was successful in keeping subjects in the more rapid phase of adaptation for both the gain and rotation transformations throughout the scan. Our previous work and that of others suggests that alternating perturbations should interfere with savings and consolidation of any learning that occurs during the previous 2 cycles (Krakauer et al. 1999; Wigmore et al. 2002). This is supported by the psychophysical results in the current study, which did not show improved performance the second time the same rotation or gain was experienced in the alternation tasks (see Figs. 1*C* and 2*C*). Thus at each alternation, subjects adapted as though performing the rotation or gain for the first time. In rotation learning, the regions activated were principally cortical for both rapid and slow learning phases. In contrast, we found that the rapid phase of gain learning involves subcortical components of a previously identified motor execution network. Operating at a new gain caused no significant activation outside of the baseline execution network.

The number of individual movements was constant across conditions but there were small but significant differences (up to about 20%) in peak velocity and movement extent in the learning conditions compared with CONTROL (Table 1). Turner et al. (2003) examined the activation patterns associated with different near constant velocities and different extents using a single degree of freedom tracking task. To keep visual input the same under the different velocity conditions, subjects were adapted to different gains before scanning. The authors found a linear relationship between movement velocity and extent and rCBF in bilateral basal ganglia and the ipsilateral cerebellum. It is unlikely, however, that differences in velocity or movement extent account for our findings: In the 2 gain tasks, a pattern of subcortical activation, somewhat similar to that found by Turner et al. (2003), was found only in GAIN*alt*, even though the peak velocity was higher in GAIN; the opposite result would have been predicted if the changes were attributed to a dependency on velocity. Moreover, the average movement velocity was almost identical in the rotation and gain conditions, whereas the activation patterns were distinctly different. Thus the activation differences in our study are more likely to reflect processes associated with adaptation. Interestingly, we obtained contralateral rather than ipsilateral cerebellar activation in GAIN*alt*. This is consistent with studies that have shown that gain adaptation generalizes (Bock 1992; Krakauer et al. 2000b) and is not specific to the trained limb (Vindras and Viviani 2002), whereas the control of velocity would be expected to be effector-dependent.

Learning a rotated reference frame

We investigated the rapid phase of rotation adaptation using the ROT*alt* task, in which the direction of the rotation changed sign every 2 cycles, and found significant activation only in the preSMA. This same area is activated early in motor sequence learning (Hikosaka et al. 1996, 1998) and seems to relate to learning visuomotor associations for individual sequence ele-

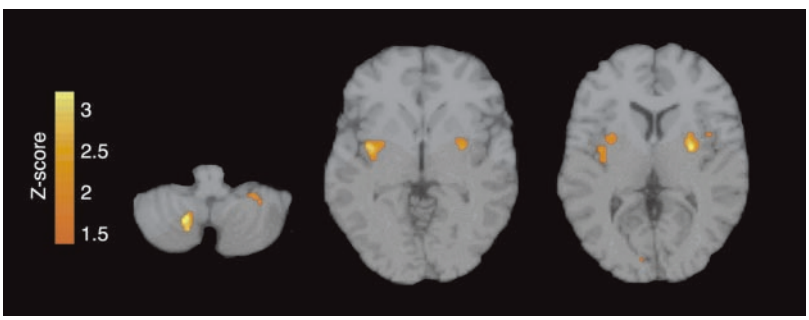

FIG. 6. Brain areas associated with GAIN*alt* learning (GAIN*alt* > CONTROL within the CONTROL mask; Z-maps were thresholded at $P < 0.01$ height uncorrected, $P < 0.05$ spatial extent corrected). Significant activations were found in the left medial cerebellum, left posterior putamen, and right insular/posterior putamen.

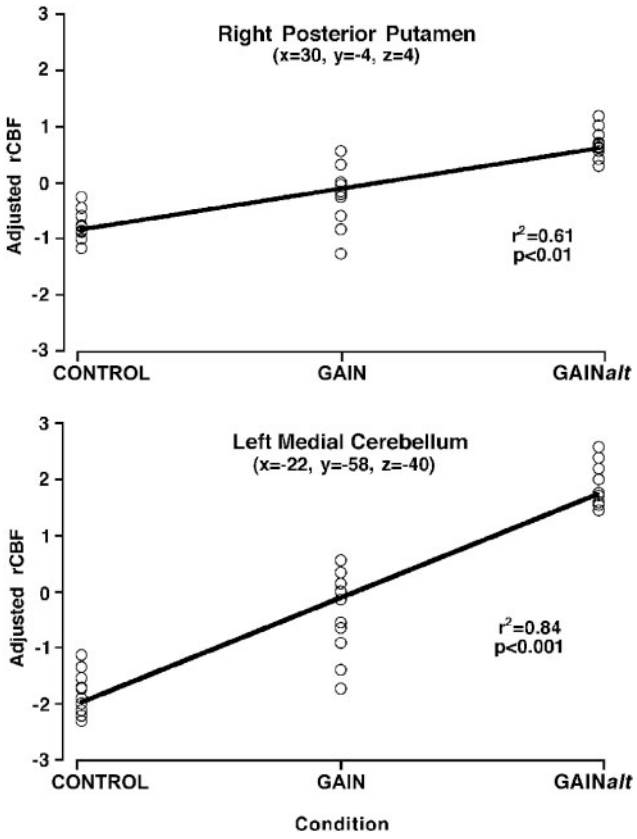

FIG. 7. *A*: relationship between mean rCBF in the right posterior putamen for the 2 gain learning conditions. There is a significant linear trend ($P < 0.01$) with greatest activation in GAIN*alt*. *B*: relationship between mean rCBF in the left medial cerebellum for the 2 gain learning conditions. There is a significant linear trend ($P < 0.005$) with greatest activation in GAIN*alt*.

ments (Sakai et al. 1999). In a previous study of rotation adaptation to 8 targets, we found that for at least the first 18 visits to any particular target the rate of adaptation was the same as training to a single target (Krakauer et al. 2000b). This suggested that learning of a cursor rotation with multiple targets is target direction–specific in the early phase and generalizes to intermediate directions only in later cycles. It is therefore plausible that alternating the sign of the rotation every 16 movements erased the previously stored elements and prevented target direction–specific responses from being combined into a new spatial map. Recent studies provide evidence for a role of the preSMA in working memory (Petit et al. 1998) and more specifically in coding a change in direction of an upcoming movement (Matsuzaka and Tanji 1996). Thus activation of the preSMA seen in our task could reflect the temporary storage of target direction-specific responses during rotation learning.

With more complete adaptation to the rotation, we found significant activation in the right PMv, right posterior parietal cortex, and left inferolateral cerebellum. Although we did not find significant preSMA activation in the ROT–CONTROL contrast, the weighted linear contrast did show that preSMA activation was higher in ROT than in CONTROL. This supports the idea that the preSMA activation reflects the process of rapid error reduction common to both ROT*alt* and ROT, rather than the process of interference that occurs only in ROT*alt*. There was less activation of the preSMA during the ROT task because this was dominated by the second slower phase of rotation adaptation.

Thus moving from the early to the late phase of rotation adaptation is associated with a reduction in preSMA activation and a transition to novel areas of activation. A similar shift in areas of brain activation with increasing practice in a task was previously demonstrated in several imaging studies (Doyon et al. 1996; Inoue et al. 2000; Krebs et al. 1998; Petersen et al. 1998; Sakai et al. 1998; Shadmehr and Holcomb 1997; van Mier et al. 1998). We found significant activation in PMv, an area reported to represent visual targets in arm-centered coordinates (Graziano et al. 1997). Unexpectedly, the PMv activation was ipsilateral to the moving limb. However, recent studies in monkeys have shown that PMv activation can be effector independent in preparation to reach a target (Hoshi and Tanji 2002) and for other forms of visuomotor transformation (Fogassi et al. 2001). The right PMv activation seen in our study could thus have resulted from cortico-cortical input from the activated right posterior parietal cortex.

We also found significant left lateral cerebellar activation, an area connected to right PMv, and close to the posterior superior fissure, an area associated with late learning (hours) of a novel rotational transformation in a recent fMRI study (Imamizu et al. 2000). Finally, we obtained activation in the right posterior parietal cortex, as previously shown (Ghilardi et al. 2000; Inoue et al. 1997, 2000). Interestingly, of the 3 regions activated during the ROT task only the posterior parietal cortex showed a linear increase in activation from CONTROL to ROT*alt* to ROT. This may imply that the new map is stored in the cerebellum or premotor cortex and the parietal cortex is involved in a more general visuospatial computation. Such a role for the posterior parietal cortex in integrating sensory information with motor output is supported by other imaging studies that have implicated posterior parietal cortex as a site for the representation of motor sequences (Sakai et al. 1998) and for internal models of limb dynamics (Shadmehr and Holcomb 1997). The right-sided posterior parietal activation found in our study contrasts with recent studies that have implicated the left posterior parietal lobe in "on-line" trajectory corrections (Desmurget et al. 1999, 2001). The absence of significant left-sided parietal activation and subjects' straight hand paths support the conclusion that such corrections did not play a significant role in the adaptive process studied here.

Further experiments will be required to determine whether the transition from activation in preSMA to 3 anatomically connected areas, previously shown to be involved with visuomotor transformations and storage and retrieval of internal representations, is attributed to a generalization process that combines target direction–specific information into a new rotated reference frame, to consolidation, or to some other process over time.

Interestingly, the cortical activations were ipsilateral and the cerebellar activation contralateral to the right arm. Other studies of motor learning have shown similar activation of regions that are not directly connected to the effector (Imamizu et al. 2000; Inoue et al. 2000; van Mier et al. 1998). A possible concern with these studies is that activations in the contralateral hemisphere may not reach significance because they are already close to maximally active in the control task so that further learning-related increments are small and remain undetected. We do not think this explains the laterality of our

activations for 3 reasons: First, we demonstrated increased activation in left-sided structures with sequence learning but not for rotation learning in another PET study that compared these 2 conditions (Ghilardi et al. 2000). Second, we did not find any additional rotation learning-related activation within the baseline execution-related mask. Third, the literature consistently reports a right hemispheric specialization for computing spatial coordinate relationships (Dong et al. 2000; Harris et al. 2000; Vallar et al. 1999), processes that are likely to be similar to the rotation in extrinsic space required by ROT. Thus we conclude that there is hemispheric specialization for particular aspects of motor learning that is accessible to either arm.

Learning a scaling factor

In the gain conditions of the current study, subjects rescaled their peak velocity within about a cycle after the perturbation. They then maintained the new scaling factor for the remainder of the block. Thus for most of the GAIN task, adaptation was at an asymptotic level, a level also reached by the 2nd cycle of each alternation in GAIN*alt*. This may explain why our initial image analysis did not reveal a significant activation in either of the 2 GAIN tasks, compared with control, because for significant portions of the scans subjects were at a steady gain just as they were in the control task. We therefore hypothesized that gain adaptation may be a process that occurs within regions activated by the CONTROL task and created a mask. Further support for this hypothesis comes from recent studies that show that modulation in the velocity of movements occurs in subregions of the basic motor execution network (Turner et al. 1998, 2003).

The GAIN − CONTROL subtraction image showed no significant activations even with a priori defined regions using the mask. However, the GAIN*alt* − CONTROL subtraction showed subcortical activation with significant basal ganglia and cerebellar activation. The basal ganglia activation was in the right posterior putamen and left insula/putamen. The posterior putamen receives input from motor areas (Hoover and Strick 1993), is somatotopically organized (Crutcher and DeLong 1984), and contains neurons with visual receptive fields that are in register with their arm tactile receptive fields, coding the adjacent space in hand- and arm-centered coordinates (Graziano and Gross 1993). Recent animal and imaging studies have implicated the sensorimotor striatum in the later phases of procedural learning when behavior becomes automatic (Doyon et al. 1996; Jog et al. 1999; Jueptner et al. 1997a,b; Miyachi et al. 1997). The other subcortical site activated was the left medial cerebellum. Studies have also implicated the cerebellum in late learning and automatization (Doyon et al. 1997, 1998; Miyachi et al. 1997). The amount of error correction in GAIN*alt* was greater than that in ROT (compare Fig. 1*D* and Fig. 2*D*) and yet no cortical activation was seen in GAIN*alt*. Thus differences in activation between rotation and gain tasks are not likely to have resulted from differences in the difficulty of learning the 2 types of transformation. Our psychophysical studies show fundamental differences in generalization for these 2 types of transformation (Krakauer et al. 2000b), suggesting that the activation differences we see are attributable to categorical differences in the way directional and extent errors are processed during adaptation.

A weighted linear contrast analysis revealed that the same areas activated in GAIN*alt* were also activated but to a lesser degree in GAIN, suggesting that these areas reduce their activation as adaptation proceeds. Our results differ from those in the learning studies already cited because we found significant cerebellar and putaminal activation in the early rather than late phases of learning. However, a series of single-unit recording studies in monkeys adapting to a novel gain found that changes in climbing fiber discharge occurred transiently over the period that velocity was rescaled and not once adaptation was complete (Ojakangas and Ebner 1992, 1994). The authors concluded that the climbing fiber system is involved in calibration of movement velocity. Thus our finding of subcortical activation early rather than late during gain adaptation may be because recalibration is an overlearned process. In this framework, the error induced by the gain change is recognized as a contextual cue that triggers recall of the already acquired calibration process and so activates structures associated with late rather than early learning. A recent model makes just such a distinction between using sensory information for contextual switching of internal models versus using the sensory information to learn a new internal model (Wolpert and Kawato 1998). This interpretation is also consistent with recent suggestions that the striatum and cerebellum are involved in context switching (Bischoff-Grethe et al. 2002; Houk and Wise 1995; Laforce and Doyon 2001; Peigneux et al. 2000). Finally, recent studies have implicated the cerebellum (Desmurget et al. 1998, 2000) and the basal ganglia (MacAskill et al. 2002) in a form of saccadic adaptation, analagous to a gain change, suggesting interesting similarities to our results. A tentative scheme might be that the putamen is involved in context switching and the cerebellum is involved in adaptive rescaling of the movement velocity. This division is similar to one proposed for implicit sequence learning (Exner et al. 2002). The bilateral subcortical activation might help explain why gain adaptation transfers readily across limbs (Vindras and Viviani 2002).

In conclusion, our PET study provides insight into why gain and rotation adaptation show such distinct differences at the psychophysical level (Krakauer et al. 2000b). Rotation adaptation involves learning a new reference frame that requires recruitment of novel cortical regions. In contrast, gain adaptation transiently recruits subcortical regions within the motor execution network, consistent with the contextual recall of an already acquired recalibration procedure. The different activations both for initial rapid reductions in direction and extent errors and for later more complete rotation and gain learning imply a separation in the processing of extent and direction errors. This is consistent with vectorial planning for horizontal reaching movements. In addition, the activation differences between the early and later phases provide further imaging evidence that adaptation to new spatial mappings may consist of 2 distinct and successive processes (Desmurget et al. 2000; Imamizu et al. 2000; Redding and Wallace 2001).

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