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RESEARCH ARTICLE

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Inhibitory control of competing motor memories

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Abstract The ability to inhibit previously learned visuomotor associations is essential for efficient learning of novel behaviors. While the neural basis of the system that might control interactions between competing motor memories is not known, it has been demonstrated that animals with ventral and orbital prefrontal cortex (PFC) deficits have particular difficulties in learning to withhold responses to previously conditioned sensory stimuli. Here we measured regional cerebral blood flow (rCBF), using positron emission tomography, during learning of a novel motor task that required inhibition of a previously learned motor memory. Subjects (n=24) learned reaching movements in a force field (field A). After a variable time interval, some subjects (n=15) learned to reach in a field with a reversed pattern of forces (field B). When the time interval was short (10 min), learning in field B was coincident with a reactivation of regions that had become initially activated during learning in field A: the left putamen and bilaterally in the dorsolateral PFC. Behaviorally, this was accompanied with perseveration that lasted for hundreds of movements, suggesting an instantiation of the internal model for field A during learning in field B. Neither the reactivation nor the perseveration were observed in a different group of subjects that learned field B at 5.5 h. We found that the regions which significantly differentiated the two groups during learning of B were in the ventrolateral PFC (bilaterally): there were sharp decreases in rCBF here in the 5.5 group but not in the 10-min group. At 5.5 h motor learning again involved the striatum, but this time in the left caudate. Neither the caudate nor the ventral PFC had exhibited learning-related activity in field A. Instead, they showed changes in rCBF during the reversal of the learning problem when the previously acquired motor memory was successfully gated. The results demonstrate that: (1) perseveration of a competing motor memory may be linked to reactivation of the neural circuit that participated in acquiring that memory, and (2) the ventral PFC may play an important role in the inhibitory control of the competing motor memory.

Key words Motor learning and memory · Perseveration · Prefrontal cortex · Reversal learning · Basal ganglia · Human

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Introduction

Making reaching movements while holding an object involves programming descending commands based on an estimate of the mechanical dynamics of the object (Gordon et al. 1991; Gottlieb 1994; Shadmehr and Mussa-Ivaldi 1994a; Flanagan and Wing 1997). This estimate, termed an "internal model" (IM), is a motor memory which is instantiated based on the visual properties of the object (Gordon et al. 1993). An adaptive control system that needs to control many objects, each with a different mechanical property, is faced with the problem of classifying the visual or other properties of the objects along an appropriate number of dimensions and then associating each classification to a particular IM. This classification is learned through experience (Gordon et al. 1992). Therefore, the situation will arise when a cue instantiates an IM that will turn out to be inappropriate for the current task. Efficient learning of a novel IM depends on the ability to inhibit previously learned but now inappropriate visuomotor associations.

An example of this scenario is provided in a paradigm where subjects learn to make reaching movements while holding a manipulandum that is acting as a novel mechanical system. Through practice, subjects learn an IM

of the dynamics of the system, which we may refer to as IM_1 (Shadmehr and Mussa-Ivaldi 1994b). When the dynamics of the manipulandum change, previously learned cues continue to instantiate IM_1, as evidenced by the aftereffects (Shadmehr and Brashers-Krug 1997), despite the fact that it is grossly inappropriate for the current task. As a consequence of this perseveration, even after a hundred reaching movements performance continues to be significantly worse than that of naive subjects (Shadmehr et al. 1995). Therefore, we have an example where, in the case of normal individuals, the adaptive controller fails to sufficiently inhibit a previously learned but now inappropriate motor memory. The importance of the ability to do so is underscored by the finding that the perseveration detrimentally affects future recall of IM_1 (Brashers-Krug et al. 1996). Similar observations have been reported in other studies of learning multiple and potentially conflicting visuomotor associations (Bunch 1939; Lewis et al. 1949, 1951a, 1951b; Flook and McGonigle 1977). However, the inability to inhibit the previously learned visuomotor association is transient: with temporal distance between acquisition of IM_1 and the change in the dynamics of the system, aftereffects during learning of IM_2 show a reduced influence from IM_1 (Shadmehr and Brashers-Krug 1997). Accordingly, learning of IM_2 becomes efficient (Brashers-Krug et al. 1996). In this study, we wished to determine what neural system might be responsible for inhibitory control of a previously learned motor memory.

While in the case of motor skill learning this question has not been explored, there is some evidence that, in certain other tasks, control of internal interference may be dependent on the integrity of the prefrontal cortex (PFC). For example, in learning to associate pairs of words (Shimamura et al. 1995), sorting cards (Owen et al. 1993), or visual discrimination (Rolls et al. 1994; Partiot et al. 1996), prefrontal patients show a particular difficulty in inhibiting previously learned associations that are competing with the current learning. In monkeys, lesions of the ventral or orbital PFC result in a loss of inhibitory control of responses to previously conditioned sensory stimuli (Iversen and Mishkin 1970; Passingham 1972; Deuel and Mishkin 1977; Dias et al. 1996). Extrapolating from these and other results, current theories of the function of the PFC in motor control has proposed a key role for this brain structure in both acquisition of a new motor skill and control of interference from a previously learned skill (Passingham 1993; Wise et al. 1996; Fuster 1997). The task that we have studied provides an opportunity to test this theory: formation of IMs for arm movements result in a time-dependent pattern of perseveration in normal individuals. Does the PFC, in particular the ventral region, play a role in controlling the interaction of the two competing motor memories?

We performed a (positron emission tomography) PET study in which groups of subjects learned IM_2 at either 10 min after acquiring IM_1, when there was perseveration, or at 5.5 h, when subjects successfully inhibited the competing motor memory. We asked in which areas of the brain did activations during learning of IM_2 differentiate subjects that could inhibit IM_1 from those who could not.

Materials and methods

We used PET to monitor changes in regional cerebral blood flow (rCBF) as right-handed volunteers (n=24) learned an IM of reaching movements in a novel mechanical environment. Eight of the volunteers (six men, two women, aged 22.1±2.3 years) were recruited specifically for this study, while the data for 16 subjects who had recently participated in a similar study (Shadmehr and Holcomb 1997) were used as controls. The experiment was approved by the Johns Hopkins University Joint Committee on Clinical Investigation.

Participants lay in a supine position in a dimly lit, sound-attenuated room, on the gurney of a GE 4096+ whole-body tomograph. A catheter was placed in the left cubital vein for injection of the radioisotope. The novel dynamics were represented as a force field and produced by a robotic arm (Shadmehr and Mussa-Ivaldi 1994a). Subjects gripped the handle of the robot with their right hand and viewed a monitor that displayed a cursor corresponding to the handle's position. The task was to take the handle to a series of targets. Two days before the experiment, participants arrived at the lab and were instructed on the task. They were told to reach for the displayed target and that their movement time should be within 500±50 ms (targets were at 10 cm). A target randomly appeared in one of eight directions. The target turned blue if a participant reached it too late, red if they reached it too soon, and "exploded" if the reach was in time, making a distinctive sound. One second after a target was reached, the next target appeared. Subjects practiced during this pretraining session (robot motors off) for 400 targets.

On the day of the experiment, participants initially practiced the task with the robot motors turned off (during which no rCBF measures were taken). They made accurate, straight movements. We acquired rCBF measures as participants performed the task during two repetitions of five successive conditions:

1. During a null field condition, in which the robot's motors were off.
2. During a random field condition, in which the robot produced a random, nonstationary velocity-dependent force field representing an unlearnable mechanical system.
3. During an early learning condition, in which the robot produced a stationary force field that we labeled "A". This field, like all other fields considered here, was a linear function of the hand velocity vector and produced a curl pattern, i.e., it produced a force that was at all times perpendicular to the actual direction of motion of the hand. Field A represented a learnable mechanical system.
4. During a late learning condition, in which participants performed the task skillfully after further practice in field A.
5. During a perseveration condition in which some subjects (n=15) learned field B. This field was mathematically anticorrelated with field A, i.e., forces were rotated 180°. Subjects learned field B either 10 min after completion of practice in field A (n=8), or at 5.5 h (n=7).

Measures of performance and motor output

We sampled the manipulandum's joint angles and joint velocities at a rate of 100 Hz and computed hand positions and velocities. Trajectories were aligned using a velocity threshold at the onset of movement. The performance measure was the similarity between the hand trajectory in the force field and a "typical" baseline trajectory in the null field measured for each subject. This similarity was defined as a correlation between two time series of hand ve-

locity vectors (Shadmehr and Mussa-Ivaldi 1994a). A typical baseline trajectory for a subject was found by correlating each trajectory with all the other trajectories for that target direction and finding the one with the highest mean correlation. A second measure of performance was the amount that the force field perturbed the hand from a straight line trajectory to the target. This distance was measured at 200 ms into each movement.

In order to estimate the motor output during a movement, we estimated the force produced by the subject on the robot's handle. The computational technique involved mapping from the arm's trajectory to forces produced at the hand. This was done via a model of the inverse dynamics of the subject's arm (Shadmehr and Brashers-Krug 1997) and the field produced by the robot. Forces produced at the hand during a reaching movement were defined as:

$$f = M_x(\theta)\ddot{x} + V_x(\theta,\dot{\theta}) + B\dot{x}$$

where f is the force vector at the subject's hand, M_x is the Cartesian mass matrix of the subject's arm, V_x is the Coriolis and centrifugal matrix, B is the viscosity produced by the robot, θ is the subject's vector of joint angles, and x is hand position. Motor output during a scan was estimated as the integral of the force produced at the hand over the period of the scan:

$$\text{Motor output} = \int_{t_i}^{t_f} |f| \, dt$$

where t_i and t_f were the start and end times of the scan period, and $|f|$ was the magnitude of the force vector.

Image acquisition and normalization

A scan produced 15 brain image slices at a resolution of 2.0× 2.0 mm in the horizontal plane and 2.0×6.5 mm in the coronal plane. Emission scans were attenuation corrected with a transmission scan. Twenty seconds before each scan, 62 mCi of $H_2{}^{15}O$ was administered. Accumulated radioactivity in the 90 s after initiation of the scan was used as an index of rCBF. Scans were acquired at 10-min intervals. The motor task was initiated 90 s. before administration of the bolus and continued until completion of the scan. Participants practiced in the field for 6 min between scans 6 and 7 and rested between all other scans. Arterial blood was not sampled. Blood flow data reported here are changes in units of flow relative to the mean of the flow acquired for the gray matter regions of the brain. These regions were identified using an intensity threshold of 80% maximum pixel value per image. The mean flow in the gray matter was normalized to 50 ml dl^{-1} per minute.

Images were realigned and normalized with statistical parametric mapping (SPM96; Wellcome Department of Cognitive Neurology, London, UK). All PET scans were realigned to the first scan (Friston et al. 1995). A T1-weighted magnetic resonance (MR) image was coregistered to the mean PET image for each participant and then normalized into standard stereotactic space (Talairach and Tournoux 1988) using a template image from the Montreal Neurological Institute (Evans et al. 1993). The resulting transformation matrix was applied to the PET images, generating images that had a voxel size of 2.0 mm in each dimension. The normalized PET images were smoothed with an isotropic Gaussian filter, full-width at half-maximum set at 12 mm. The normalized MRI scans were then averaged across the population to generate an anatomic atlas. Activation patterns were rendered on this atlas to identify the corresponding neural structures. However, we also rendered the activation patterns on the normalized MRI of each subject in order to confirm the consistency of our atlas-based localization.

Within-subject analysis

Smoothed, normalized PET data were analyzed using SPM software. Statistical parametric maps (SPMs) were generated with a multiparticipant block design, two replications per condition and an AnCova global normalization. Images in this stage of statistical analysis were those from the first four conditions (two images per condition, eight images per subject), in which all the subjects performed the same tasks, i.e., null, random, early field A, and late field A. In the design matrix, participant, global brain activity, and motor output were the covariates of no interest and the four conditions of the task were the covariates of interest. The only exception to this was the case where we looked for regions of the brain where activation changes correlated with motor output, in which case the motor output was a covariate of interest.

Contrast vectors were of the {*0,–1,1,0*} variety where two covariates of interest were directly compared. The search volume was from z=–30 to z=60 mm and did not allow a complete view of the cerebellum. We considered regions where voxel-level Z-values were significant at a corrected P<0.05. We also considered as significant regions in the sensorimotor system that we had selected a priori, where voxel-level Z-values were larger than 3.0. These regions were the dorsolateral prefrontal cortex, primary sensorimotor cortex, premotor cortex, supplementary motor area, striatum, and the cerebellum.

Eigenimage analysis

We used SPM96 to perform eigenimage analysis. In this software, eigenimage analysis is performed only on the pixels that have been identified to significantly change with the covariates of interest, i.e., the pixels identified in the SPM(F) map. Therefore, it is important to note the design matrix that was used to generate the SPM(F) map. Our design matrix had 192 rows by 29 columns. The rows represented eight images per subject (24 subjects) and the columns were: a covariate for each of the four conditions, a covariate for each of the 24 subjects, and a covariate reflecting global brain activity for each subject. Eigenimages of the resulting SPM(F) map were calculated (Friston et al. 1993).

We used the dot product of an eigenimage with a given PET image to arrive at a scalar variable called a *component score*. This variable was computed for all scans across all conditions, resulting in a description of the change in the weighted activation of the neural network described in the eigenimage as a function of conditions of the task for each subject. ANOVA with repeated measures was used to arrive at the 95% confidence interval associated with the mean changes in the component score for each of the groups.

The significance of the results obtained from the eigenimage analysis were assessed by finding the statistical distribution of the component scores (McIntosh et al. 1996). We used a permutation approach to arrive at these distributions. The data matrix, where each row was a volumetric image (192 rows in all), was kept constant while the rows of the design matrix were randomly shuffled. In this way, the correspondence between the task covariates and the acquired scans was lost. For each reordering, singular value decomposition was performed to compute a new set of eigenimages. For each eigenimage, a corresponding component score vector was computed. The correlation coefficients between each newly generated component score vector and vectors that characterized each condition of interest in the experimental task were generated. This procedure was repeated 4000 times to arrive at a distribution. A 95% confidence interval (CI) was defined for each distribution. Using this CI, we asked whether a given eigenimage acquired from the original design matrix could be significantly associated with a component of the task performed by the subjects. The null hypothesis was rejected only if the component score was larger than that which was observed in 95% of the randomized trials.

Between-subject analysis

SPM96 software was used to perform a multistudy, multiparticipant block design with two replications per condition and an AnCova global normalization. Again we included the motor output of each subject during each scan as a confounding variable. Here, the design matrix had 240 rows (24 subjects, ten images per subject)

and 41 columns (15 conditions of interest representing three study groups, with five conditions per group, one covariate for each of the 24 subjects, and two confounding variables representing global activation for each image and motor output for each subject at each scan). This design was used to differentiate activation patterns in the group that learned field B at 5.5 h from the group that learned field B at 10 min, while taking into account the differing levels of motor output among the subjects. We were interested in finding pixels where activation changes were similar among the groups during the first four conditions of the task, but differentiated the groups during learning of field B (condition 5). We considered regions where voxel-level *Z*-values were significant at a corrected $P<0.05$.

Results

Movement kinematics

In the current study, measures of rCBF were acquired during five conditions. In all conditions, subjects made reaching movements to a pseudorandom sequence of visually presented targets. Targets were 10 cm apart. In the 1st condition (two scans), the robot's motors were off (null field) and the subjects were able to make smooth, straight reaching movements to the targets. This is shown in Fig. 1A, where the mean displacement from a straight-line trajectory in the null field was essentially zero. In the 2nd condition (two scans), robot's motors were engaged and for each movement a force field was present. However, from movement to movement the force field changed randomly. Our intention was to have a condition that differed from the previous condition in only one factor: forces were acting on the hand, but the forces were not learnable. When the random field was introduced, trajectories were significantly disturbed. However, subjects showed little improvement with practice. This is shown in the perpendicular displacement from a straight line (Fig. 1A), correlation measures (Fig. 1B), and movement length (Fig. 1C).

In the 3rd condition (two scans), a force field was again present during each reaching movement. However, the field (field A) was kept time-invariant from movement to movement. Our intention was to have a condition that was otherwise identical to the previous condition, except that the forces were learnable. During this condition, we observed rapid improvements in performance (Fig. 1). By the end of the second scan of this condition, perpendicular displacement, movement length, and correlation measures had improved by 7.3±0.7 mm, 20.8±2.3 mm, and 0.079±0.016 with respect to the mean values observed in the previous condition (random field). Previous results suggest that this improvement is due to formation of an IM for field A (Shadmehr and Mussa-Ivaldi 1994b) and that the IM

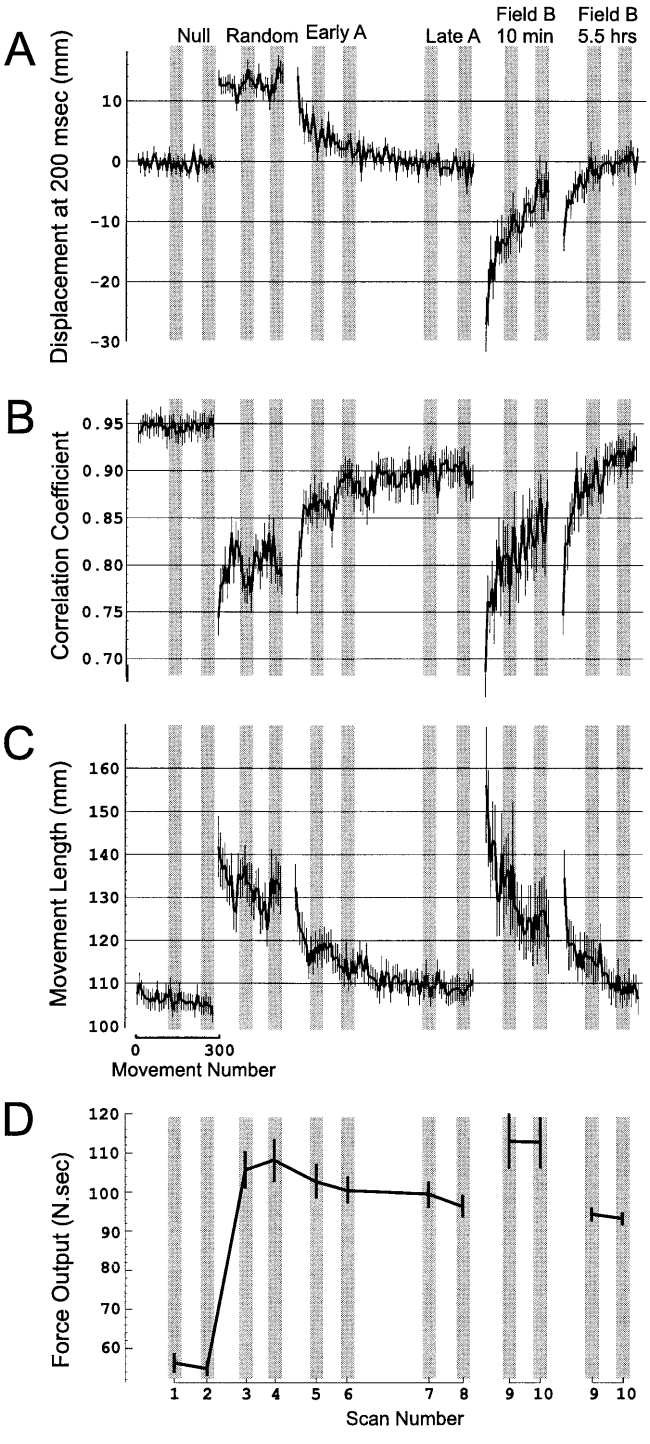

Fig. 1A–D Performance of subjects during various conditions of the imaging study. Subjects made targeted reaching movements in a force field. The conditions, null, random, early A, late A, and field B defined the type of field present and extent of training in each. We acquired two brain scans per condition. While all subjects (n=24) learned A, some subjects (n=8) learned B at 10 min after A, and some subjects (n=7) at 5.5 h. Data are mean±SE, bin size is 8. **A** Displacement from a straight-line trajectory to the target at 200 ms into the movement. In the case of random field, the mean of the absolute value of displacement is shown since the field was as likely to perturb in one direction than in the other. **B** Correlation coefficient of the movement in the field with a typical movement in the null field. The algorithm used for calculating this variable has been described elsewhere (Shadmehr and Mussa-Ivaldi 1994a). **C** Length of movements. **D** Motor output, as calculated via an integral of the total force that each subject exerted on the robot's handle over the period of the scan

may be retained for many months (Shadmehr and Brashers-Krug 1997).

After this initial period of training in field A (called "early learning"), subjects received further training (200 targets) without being scanned. During the 4th condition (two scans; called "late learning"), subjects were able to make essentially straight line movements in field A (Fig. 1C). During this condition, performance had plateaued and no significant improvements were observed in perpendicular displacement, movement length, or correlation measures.

In the 5th condition, the learning problem changed. A force field was again present for every movement, but now the field was mathematically anticorrelated to field A. This new field was called field B. We were interested in recording how the subjects responded to the change in the learning problem. Computationally, efficient learning of field B requires a gating of the memory for field A (Brashers-Krug et al. 1995). The main question was the neural correlates of this gating of a previously learned but now inappropriate motor memory.

Our approach was to record behavior and rCBFs as subjects were presented with field B at either 10 min (n=8) or 5.5 h (n=7) after completion of practice in A. The reason for measuring behavior at these two times was that we had previously observed that at 10 min subjects were not able to inhibit the memory of field A in order to learn field B (Shadmehr and Brashers-Krug 1997). The evidence for this lack of inhibition was that performance in field B displayed aftereffects for field A. However, with the passage of time since learning in field A (4–6 h), the ability to gate the memory of field A gradually improved: by 6 h, aftereffects in field B became similar to those of naive subjects.

In the current study, we again observed that subjects who learned field B at 10 min after completion of practice in field A exhibited significantly worse performance than naive subjects in field A (P<0.01, paired t-test, for each index of performance in Fig. 1). In contrast, in the group of subjects who learned field B, 5.5 h after completion of practice in field A, performance levels in B were not significantly different than early learning of A. In fact, it took nearly 300 movements for the 10-min group to reach a level of performance in field B that was shown at the onset by the 5.5 group (Fig. 1C). Taken together with our previous observations regarding the nature of the aftereffects, the behavioral evidence is consistent with the idea that at 5.5-h rCBFs were measured as training in field B took place while the memory of A was substantially gated, whereas at 10 min the same training took place while the memory of field A was not gated.

Motor output

rCBFs in the sensorimotor cortex (SMA) and the cerebellar vermis have been shown to monotonically increase with the force produced at the hand (Dettmers et al. 1996). Therefore, in a motor learning task the changing motor output is a potentially confounding variable that must be quantified. We estimated the motor output by the total force produced at the hand during various conditions (Fig. 1D). When the force field was presented in the random condition, the motor output nearly doubled from the null condition. When the force field became learnable, motor output modestly declined from the levels observed in the random field. A comparison of the motor output in the last two scans of learning field A versus random field showed a decline of 8.2±3.3 N.s (paired t-test, P<0.05). Motor output significantly increased when field B was presented at 10 min (P<0.01), but was not significantly different than the late A condition when it was presented at 5.5 h.

Eigenimage analysis

We wished to explore the neural correlates of perseveration. Because the behavioral data suggested that at 10 min learning of field B took place with an IM appropriate for field A, we hypothesized that the learning of field B at 10 min might be coincident with a re-engagement of the neural circuits that had become activated during learning of field A. We had a relatively large sample of 24 subjects that had learned field A. Therefore, a strong test was to initially identify the network that was engaged during learning of field A and then determine how the rCBF in this network changed when the subjects had to learn field B. Accordingly, the eight scans acquired during the first 4 conditions were used to identify a network where rCBF changes correlated with learning of field A. We then asked how the activation in this functional network changed during the 5th condition, i.e., when the force field was reversed.

The field of view of our PET instrument was 10 cm, requiring a compromise regarding the regions of the brain from which data was recorded. In order to view most of the frontal lobe, we were able to view only the anterior regions of the cerebellum. The superior-inferior boundaries of the regions of the brain from which data were acquired are shown in Fig. 2.

The initial eight scans (representing the first 4 conditions, i.e., null, random, early A, and late A) for the

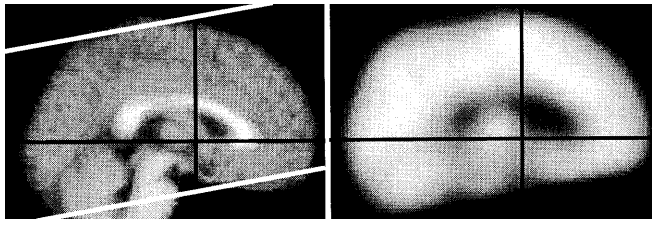

Fig. 2 The rostrocaudal extent of the regions of the brain from which regional cerebral blood flow data was acquired. The *left image* is the mean normalized MR image of our 24 subjects. The *right image* is the mean normalized PET image of the same subjects. The approximate boundary of the PET data set is marked on the MR image

24 subjects were analyzed using a principal component analysis (Friston et al. 1993). This choice is based on the idea that an image represents a measure of rCBF from thousands of independent variables, each a location in the brain. By employing principal component analysis, we hoped to find a small subspace spanned by a set of orthogonal eigenimages where projections of the original data could be effectively studied. If these few eigenimages were found to reproduce most of the variation in all of the original variables, and if these eigenimages vectors were interpretable, then the eigenimages could be used to give a much simpler description of the data than the original variables.

Computing the eigenimages amounts to calculating the eigenvectors of the covariance matrix of the data set. A common practice for deciding on the number of principal components to keep is to compare the eigenvalues of the covariance matrix with the mean of the diagonal elements of the covariance matrix (Jolliffe 1986). If the *n*th largest eigenvalue is smaller than this mean, then one keeps the first *n*–1 principal components. Based on this criterion, the first three eigenimages were found significant. Together, these images represented 80% of the variance in the data.

The first eigenimage

The first eigenimage accounted for 51% of the variance in the data. The positive-weighted pixels of this image identified a region in the left superior temporal gyrus. Activation in this region showed a sharp decline from the null to the random condition (Z=4.65, peak at –56,–48,10), and did not show any further significant changes during other conditions. The negative-weighted pixels of the first eigenimage identified a region in the right cingulate gyrus (10,40,6). Activation in this region showed a sharp increase from the first scan of the null to the second scan of this condition, and showed no further significant changes. These variations did not correlate with motor performance or learning of the task, and did not differentiate the groups. Instead, they appeared to represent rapid, within session changes that were limited to the very first scans and did not play a role in learning of the IM of the fields. In a recent PET study, it was also reported that there were deactivations in the temporal areas independent of task conditions, i.e., changes that related to passage of time alone (Rajah et al. 1998).

The second eigenimage: left sensorimotor cortex

The second eigenimage accounted for 15% of the variance in the data. The positive-weighted pixels of this eigenimage, shown in Fig. 3A, had their largest value in a region centered at the left sensorimotor cortex (peak pixel at –56,–34,46). An eigenimage can be interpreted as a functional connectivity map (Friston et al. 1993), and the projection of each subject's data onto this map, called a

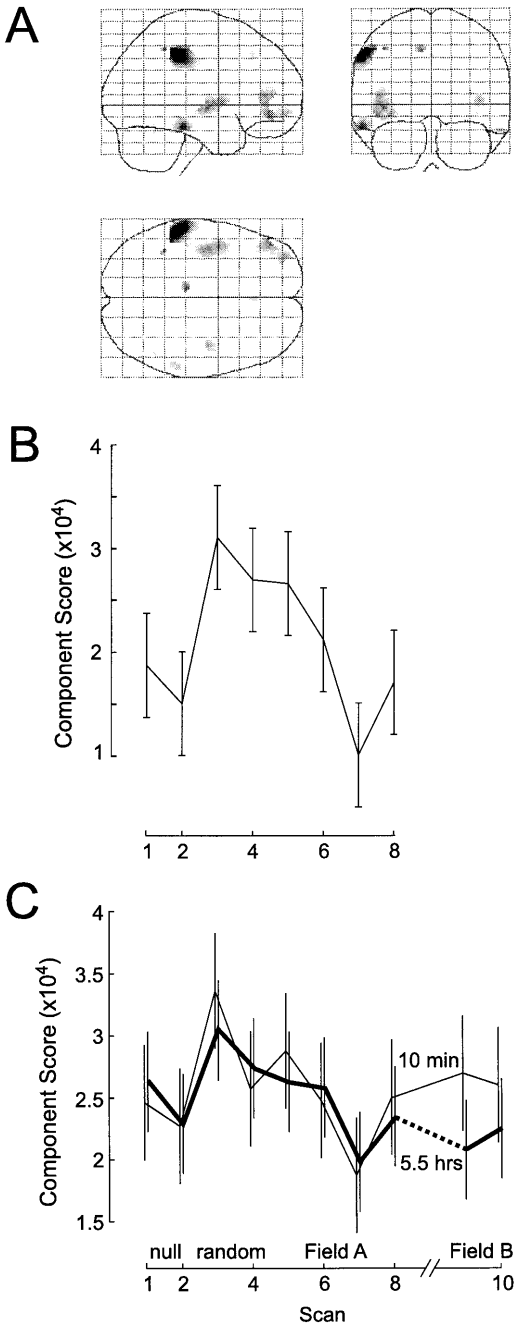

Fig. 3A–C The second eigenimage of the cerebral blood flow data collected over the first eight scans, i.e., during null, random, early learning A, and late learning A conditions, from all 24 subjects. **A** The positive-weighted component of the second eigenimage, with the *darker intensity* reflecting larger weights. The area with the highest intensity is at the left sensorimotor cortex, peak at –56,–34,46. **B** Projections of each subject's data via the weights defined in **A**, resulting in a scalar that represents the degree of activation in all the regions as a function of scans. Data are mean±95% confidence interval. **C** Degree of the activation in the subpopulations that learned field B at 10 min and at 5.5 h. Data are mean±95% confidence interval. The *heavy line* is the data for the group that learned field B at 5.5 h

component score, represents the degree of activation of the regions highlighted by the eigenimage during various conditions of the experiment. The component score for the entire population (n=24, mean±95% CIM) is shown in Fig. 3B. It sharply increased from null to random condition and then gradually declined to baseline levels as the subjects learned the field. Motor output also sharply increased from the null to the random condition (Fig. 1D). However, it showed only modest declines as the field was learned. Therefore, the component score, which was dominated by the left sensorimotor cortex, appeared to show a larger decline than was expected from the relatively small changes in motor output during learning of the field.

When subjects learned field B at 10 min after completion of practice in A, their motor output was significantly higher than subjects who learned the same field at 5.5 h (Fig. 1D). Accordingly, the component score showed a difference between the groups according to when field B was learned (Fig. 3C): those who learned field B at 10 min tended to have larger activations (as reflected by their component scores) than those who learned B at 5.5 h (t-test, P<0.01).

Within-subject statistical analysis (multisubject design with one replication per subject and contrast –1,1,0,0) confirmed that, from the null to the random condition, the most significant changes in rCBF occurred in the left sensorimotor cortex: there was a significant increase in the activation of the left sensorimotor cortex when subjects were moving against a random force field (Z=4.12, peak at –58,–30,46). The peak identified by this technique was within 4.5 mm of the peak of the second eigenimage. rCBF changes for a 6-mm cube centered at this location are plotted in Fig. 4. The SPM is plotted on an "average brain". This brain is the mean of the normalized MR images of our 24 subjects. The SPM is also plotted on a "typical brain," which is the MRI of a typical subject in our sample.

While rCBF in the left sensorimotor cortex sharply increased from the null to the random condition, it declined to levels of the null field condition as the force field was learned. This occurred despite the fact that, during learning of the field, force production was nearly 2 times higher than in the null field (Fig. 1D). Therefore, activation changes in the left sensorimotor cortex appeared to reflect two processes: first, the changing levels of force production in the task and, second, a process of habituation as the field was learned.

In order to statistically test the idea that the rCBFs in the sensorimotor cortex declined more during learning than would have been expected from the reductions in motor output, we performed a within-subject comparison of the random and late learning scans while assigning the motor output of each subject to a confounding variable. We found a significant decrease in the left sensorimotor cortex (Z=3.44, peak at –60,–34,42) from the random to the late learning of A condition. This suggests that with extended practice in the force field, activations in the sensorimotor cortex declined significantly more than would have been expected from changes in motor output.

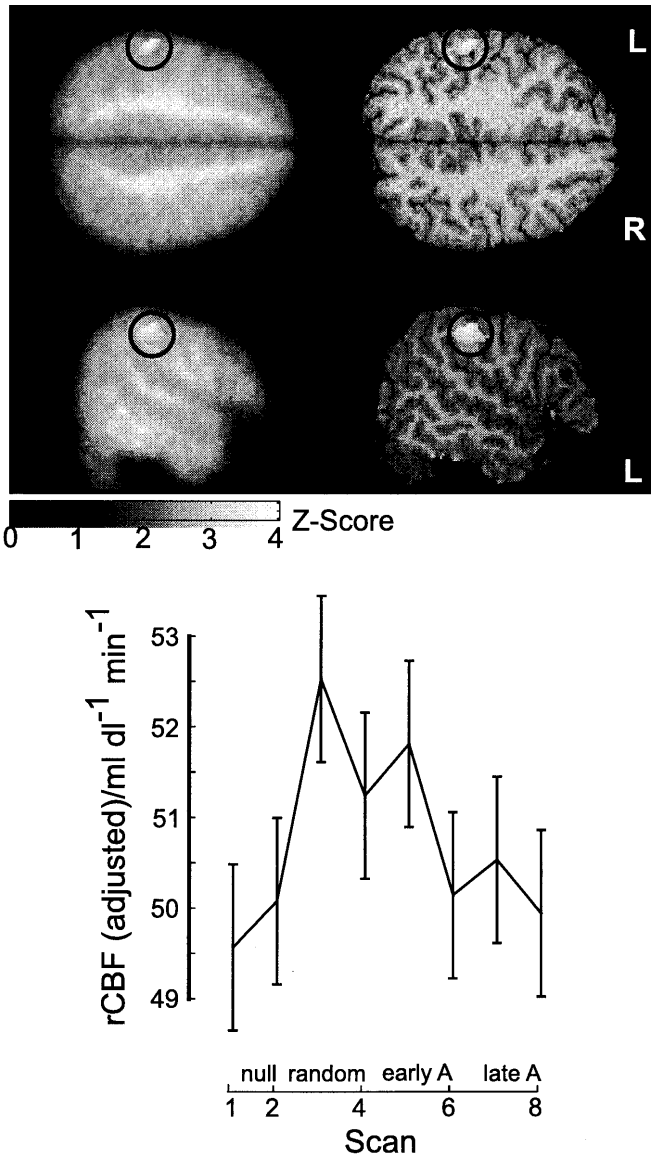

Fig. 4 Activation regions in the left sensorimotor cortex when subjects were presented with a random force field. A statistical parametric map (SPM) was generated by comparing images during the null field condition with that of random. We found that the peak increase was in the left sensorimotor cortex (Z=4.12, peak location at –58,–30,46, BA 4). This corresponded exactly to the peak location in the second eigenimage (Fig. 3A). The SPM is plotted on a mean MR image computed for our population sample (n=24), as well as on the MR image of a typical subject in our study. Regional cerebral blood flow data are shown as mean±95% confidence interval for a 6-mm cube centered on the peak location

The third eigenimage

The third eigenimage accounted for 14% of the variance in the data. The positive-weighted pixels of this eigenimage are shown in Fig. 5A. The region with the largest

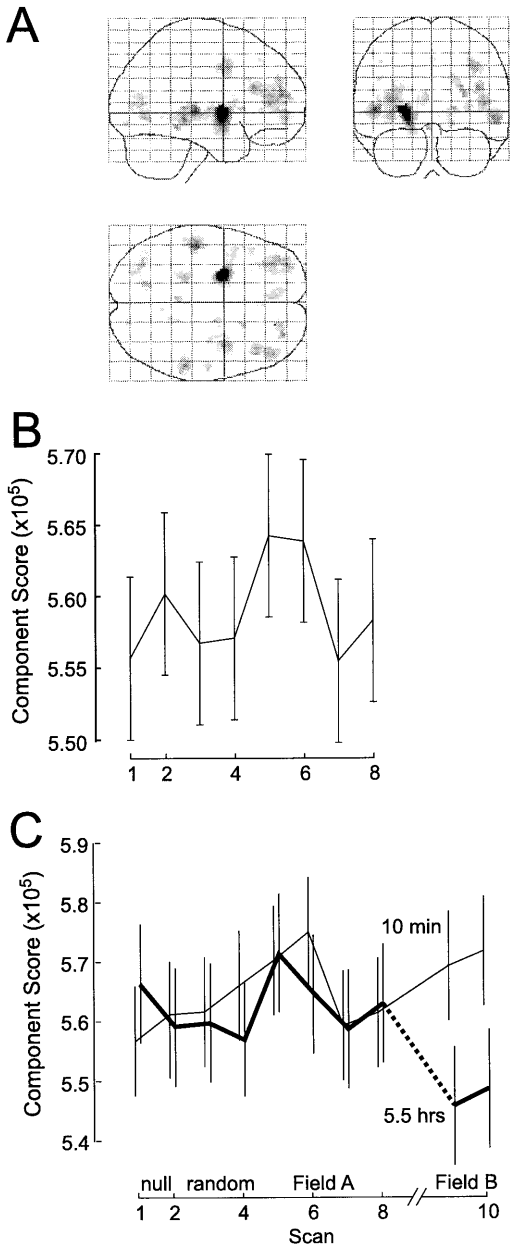

Fig. 5A–C The third eigenimage of the regional cerebral blood flow data collected over the first eight scans, i.e., during null, random, early learning A, and late learning A conditions from all 24 subjects. **A** The positive-weighted component of the third eigenimage, with the *darker intensity* reflecting larger weights. The area with the highest intensity is in the left putamen, peak at –24,0,2. **B** Projections of each subject's data via the weights defined in **A**, resulting in a scalar that represents the degree of activation in all the regions as a function of scans. Data are mean±95% confidence interval. **C** Degree of the activation in the subpopulations that learned field B at 10 min and at 5.5 h. Data are mean±95% confidence interval. The *heavy line* is the data for the group that learned field B at 5.5 h

weight was centered in the left putamen (peak pixel at –24,0,2). Other regions in this eigenimage included portions of the PFC (bilaterally) and the left superior temporal gyrus. Changes in the activations of the regions described by this eigenimage are visualized via the changes in the component scores in Fig. 5B. The component score showed an increase from baseline levels only when the field became learnable.

We quantified this apparent covariance with the learnability of the task via a correlation between the component score and changes in the task (as specified by a vector that was zero for each condition except the condition for which the task became learnable). The correlation coefficient was 0.781. To assess whether this apparently high degree of covariance was statistically significant, we performed a permutation analysis. In this procedure, singular value decomposition was applied 4000 times to the covariance matrix that resulted from a random shuffling of the rows of the matrix of image sequences, resulting in a random correspondence between the design matrix and the imaging data (McIntosh et al. 1996). For each of the 4000 sets of eigenimages, a new component score was generated and correlated with the task vector. The resulting distribution had a mean of 0.0052 and SD of 0.376. The correlation that we had obtained from the eigenimage of Fig. 5 was significant at a level of $P<0.01$. Furthermore, activation changes in the regions of the brain identified by this eigenimage did not appear to be related to motor output. This is demonstrated by the fact that while motor output nearly doubled from the null to the random condition, no significant increases were observed in the component scores. Indeed, the correlation coefficient between these two variables was –0.38 ($P>0.4$). Therefore, activation changes in the regions identified in this eigenimage, as represented by a component score, were significantly correlated with motor learning.

We next asked how the component score for the regions in the third eigenimage changed when subjects attempted to learn field B. Note that the eigenimages were calculated from data that did not include the scans for learning of field B, providing a strong test of the idea that perseveration, i.e., the inability to gate the motor memory of field A in order to learn B, should be accompanied with reactivation of regions that were activated in learning of field A, i.e., the PFC and striatal regions of Fig. 5A. The activations of these regions, as measured by the component score of the two groups of subjects, are plotted in Fig. 5C. We found that the component scores were comparable across the groups during learning of field A. However, the regions were reactivated only when field B was learned at 10 min (paired comparisons of mean component scores in B with respect to late learning, $P<0.05$), whereas the component scored showed a decline when field B was learned at 5.5 h ($P<0.01$).

Parametric maps of within-subject subtractions

How do these results compare with a standard within-subject subtraction analysis? In order to identify regions of the brain that participated in learning of field A, we compared images acquired during the random field con-

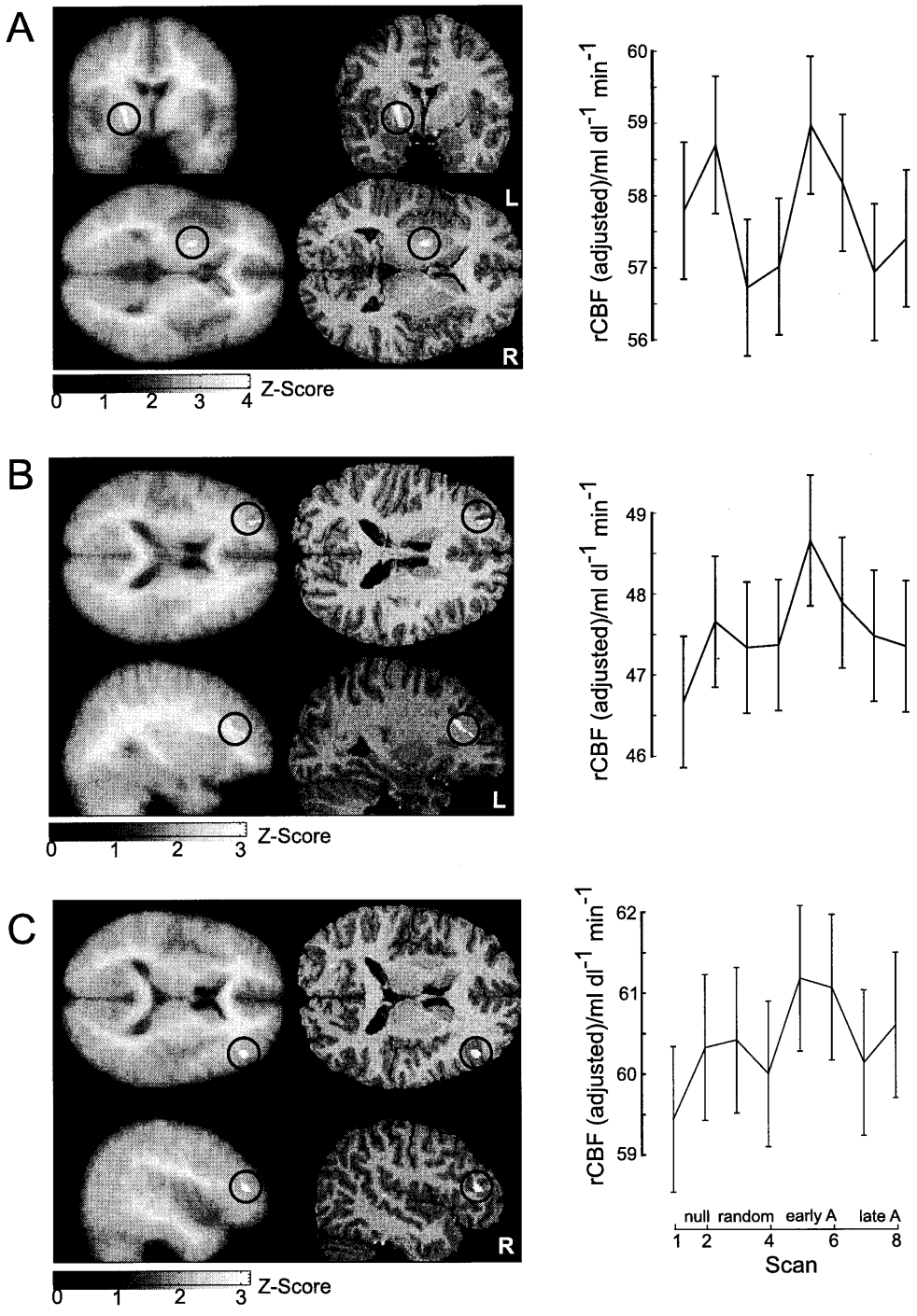

Fig. 6A–C Activation regions in the areas of the left putamen (**A**), left dorsolateral prefrontal cortex (PFC) (**B**), and right dorsolateral PFC (**C**) that showed learning-related activity. These regions are plotted on a mean MR image computed for our population sample (n=24), as well as on the MR image of a typical subject in our study. Regional cerebral blood flow data are mean±95% confidence interval and are shown for a 6-mm cube centered on the peak location. The SPMs are for a contrast vector that reflected within condition improvement in performance, i.e., learning, as defined by displacement from a straight-line trajectory to the target (Fig. 1A). The region with the highest correlation had its peak in the left putamen (Z=3.96, peak at –22,–2,0). This peak was 3.5 mm from the peak of the third eigenimage (Fig. 3A). The regions with the second and third highest correlation measures were in the right dorsolateral PFC (Z=3.26, peak at 46,40,10, BA 46) and left dorsolateral PFC (Z=3.14, –32,36,16, BA 46)

dition with the images acquired during the early learning of A condition. The motor output for each subject was accounted for as a confounding variable. The comparison showed that, when the force field became learnable, there was a significant increase in the left putamen (Z=3.87, peak at –22,–2,0), as well as the right (Z=3.57, peak at 40,28,20, BA 46) and left dorsolateral PFC (Z=3.23, peak at –26,46,22, BA 46). The location of the peak in the striatum as identified by this subtraction analysis was within 3.5 mm of the peak location in the 3rd eigenimage.

The putamen was again highlighted when we specifically searched for pixels where activation changes correlated with a measure of learning (while again keeping the motor output as a confounding variable). This measure was the amount that the performance improved within each scan period, as defined by the displacement from a straight-line trajectory. This function was largest early in learning of field A, and decreased as the subjects learned the task. The regions with the highest correlation to this measure were the left putamen (Z=4.01, peak at –22,–2,0), and the right (Z=3.19, peaks at 42,26,22 and

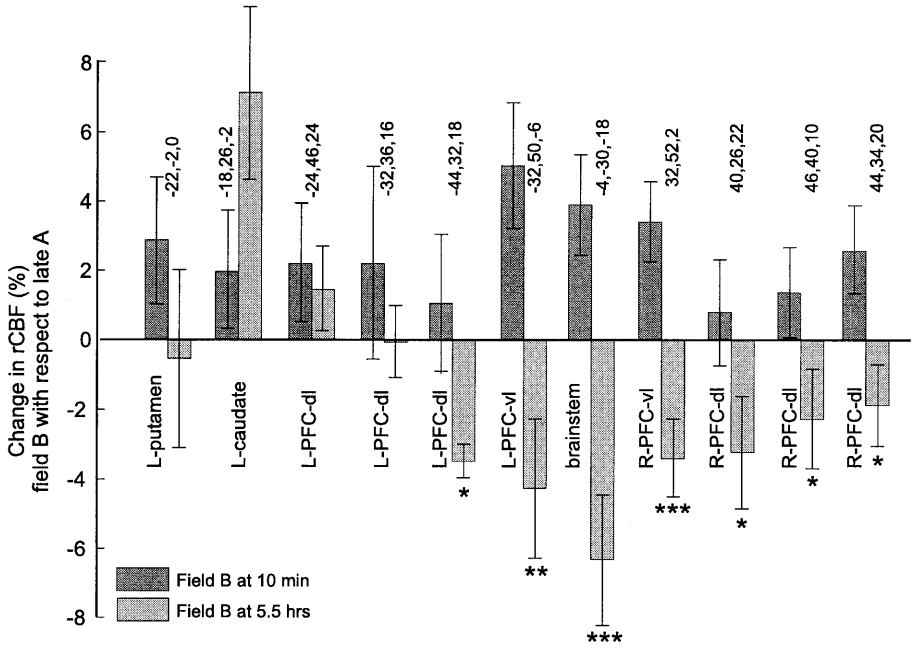

Fig. 7 Regional cerebral blood flow (rCBF) changes from the late learning A condition to learning of field B condition for the two subject groups. Data are represented as percentage change from the rCBF measured during late A and are mean±SE for each subject group. The data shown are for peaks in the left striatum, dorsolateral PFC (bilateral), ventral PFC (bilateral), and the brainstem (probably the midbrain region). *P<0.05, **P<0.01, ***P<0.001, t-test of the comparison of the means of the two subject groups

46,40,10, both in BA 46) and left (Z=3.00, peak at –32,36,16, BA 46) dorsolateral PFC. The extent and intensity of the SPMs in the left putamen and the dorsolateral PFC are plotted in Fig. 6. SPMs are plotted on a mean brain and a typical brain. Also plotted are the rCBFs associated with a 6-mm cube centered on the peak pixel of each SPM.

While the motor output nearly doubled from the null to the random condition, rCBF in these areas did not increase. In fact, the putamen showed a sharp decrease from the null condition when the random force field was presented. There was a significant rCBF increase with respect to the random condition once the field became learnable. With extensive practice, rCBFs of the peaks in the putamen and the dorsolateral PFC declined from levels recorded during early learning. Therefore, both the eigenimage analysis and the subtraction analysis indicated that, when subjects were reaching in a force field, learning of the field was coincident with activation of a system which included regions of the dorsolateral PFC (bilaterally) and the left putamen.

rCBF changes in the PFC and striatum during learning of field B: within-subject comparisons

Because a component score is a weighted sum of activation patterns for all pixels of the eigenimage, it provides a global measure of activity in a number of regions but does not imply consistent local changes for each region in the image. In the left putamen and dorsolateral PFC, were there consistent increases in rCBF at 10 min but decreases at 5.5 h? In Fig. 7, the rCBFs of the peak pixels in the SPMs associated with the putamen and the dorsolateral PFC are illustrated as percentage change (within-subject) from the late learning condition of A to learning of field B in the two groups. In general, during learning of field B, the 10-min group showed a trend toward reactivation in the putamen and the PFC. It is unlikely that this increase in rCBF was related to the increase in motor output: activation in these regions did not increase when the motor output had nearly doubled from the null to the random condition. However, in the 5.5-h group the change in rCBF in the putamen was smaller but not significantly different than in the 10-min group (Fig. 7). Therefore, in the left putamen where rCBF changes were related to learning of field A, we found no significant difference between groups during learning of field B.

In contrast, in the regions of the dorsolateral PFC that had exhibited learning related activity in field A, we found a significant difference between the two groups during learning of field B (P<0.05, t-test): the 10-min group tended to show a reactivation in the dorsolateral PFC, while the 5.5 h group displayed a decreased activation. Therefore, in the PFC and striatal regions that became active during learning of field A, the main difference between the two groups during learning of field B was in the PFC.

At 5.5 h, motor learning once again involved the striatum; however, this time more significantly in the caudate: a comparison of the random to the learning B condition showed a significant increase in the left caudate (Z=3.93, peak at –18,26,–2). Change in rCBF in the left caudate with respect to late A is shown in Fig. 7 for both groups. The increase observed in the 5.5-h group was larger but not significantly different than that which we observed in the 10-min group. In summary, while we found no significant difference between the two groups in the striatum during learning of field B, the 10-min group tended to show larger increases in the putamen, while the 5.5-h group tended to show larger increases in the caudate.

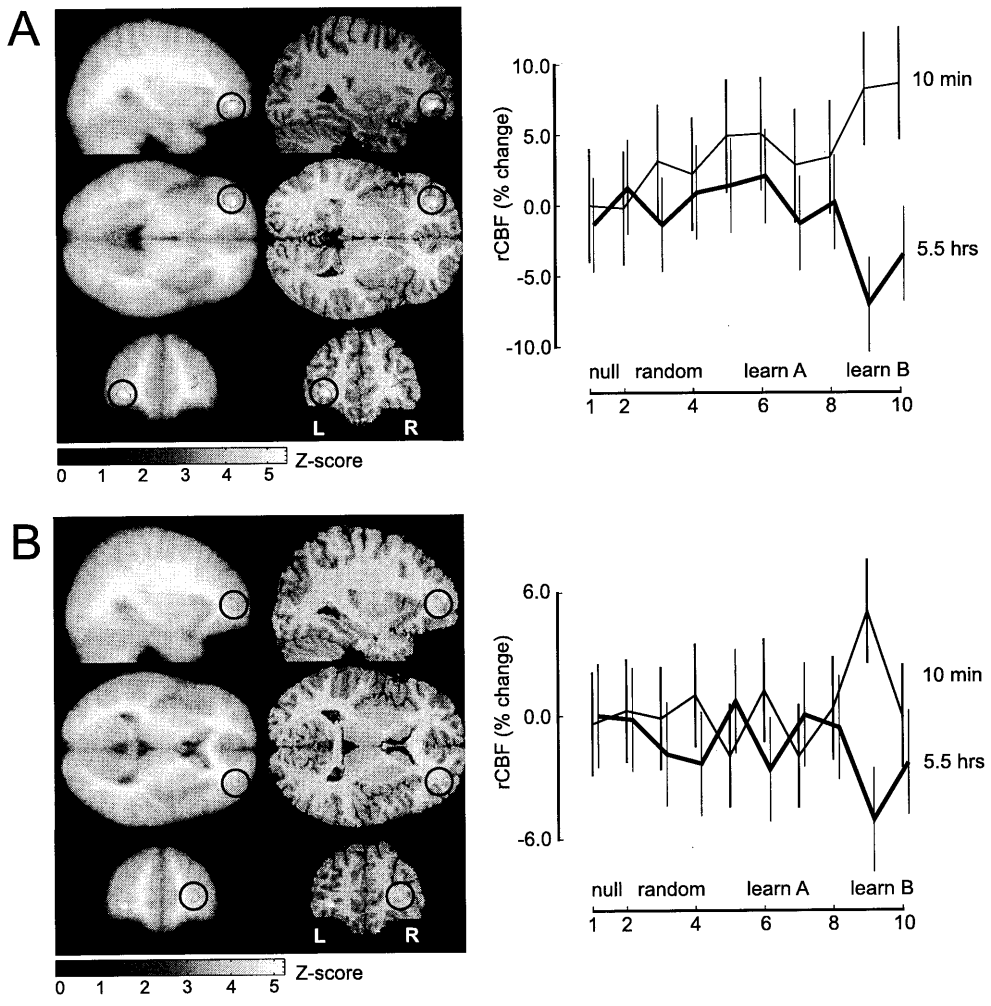

Fig. 8A, B Regions that differed in their activation levels between the 10-min and 5.5-h groups during learning of field B. In a statistical test, we searched for voxels where activity changes were similar in the two groups during the learning of field A, but differed when field B was presented. Graphs are the mean±95% confidence interval for the rCBF in a 6-mm cube surrounding the peak in each region for each group and are normalized with respect to the rCBF measured in the first two scans. The regions of activation are plotted on the mean normalized MR image for the population of subjects in this study, as well as on the MR image of a typical subject. **A** Left ventrolateral PFC, BA 10/47, peak at –32,50,–6, *Z*=5.45. **B** Right ventrolateral PFC, BA 10, peak at 32,52,2, *Z*=4.17

Between-subject comparisons during learning of field B

Activation patterns in which regions of the brain differentiated the two groups of subjects during learning of field B? To answer this question, we initially performed a multisubject, multistudy protocol, while again accounting for the variability of motor output of each subject as a confound. This is particularly crucial because the motor output of the 10-min group in field B was significantly more than in the 5.5-h group (Fig. 1D).

In this test, we wished to identify regions of the brain where activation levels were similar in the groups during the first 4 conditions of the experiment but significantly differed during learning of field B. Statistical analysis identified three regions: the left and right ventrolateral PFC (*Z*=5.53, peak at –32,50,-6, BA 10; *Z*=4.13, peak at 32,52,2, BA 10), and the brainstem (*Z*=5.39, peak at –4,–30,–18). No significant differences were found in the basal ganglia. Because the extent of the activation in the brainstem was very large (250 pixels, approximately a cube of size 12.6 mm in each dimension), its center of activation could not be reliably identified. It appeared that the activated region was typically at the rostrocaudal level of the cerebral peduncles and therefore probably in the midbrain. We did not perform further analysis on the rCBF changes in the brainstem.

In order to guard against false positives that can arise from between-subject anatomical variability, we also examined within-subject changes in the two groups. In this analysis, we compared late A with learning of field B. In the group that learned field B at 5.5 h, we found decreases in rCBF in the brainstem (*Z*=4.17, peak at –4,-30,–18) and ventrolateral PFC bilaterally (*Z*=3.23, peak at 34,50,–2, BA 10; *Z*=3.09, peak at –40,56,–4, BA 10). In comparison, in the group that learned field B at 10 min, we found a significant reduction only in the right caudate (*Z*=3.60, peak at 8,12,–2). In the 10-min group there were no regions in the frontal lobe or the brainstem that showed a significant reduction. This suggests that the differing activations in the ventral PFC in the between-subject comparisons were not due to uncompensated anatomical variability in the normalized brain of the subjects. Instead, the rCBF differences were probably due to the differences in task conditions.

The behavior during learning of field B differed between the groups in at least two ways. First, the 10-min group had significantly more trouble learning field B than the 5.5-h group (Fig. 1A). Our previous work had

suggested that, at 10 min, subjects were unable to gate the motor memory of field A in order to learn B (Shadmehr and Brashers-Krug 1997). In effect, subjects were learning field B with an IM that was appropriate for A (as evidenced by their aftereffects). Second, the 10-min group had significantly higher motor output. The motor output was at a level that was slightly higher than that recorded during the random field. To what extent did the rCBF changes in the ventral PFC reflect this second factor? To approach this question, we asked how the activation patterns in the ventral PFC changed during the first 4 conditions. Were these regions only involved when the subjects attempted to learn the reversal task, or did they also show learning-related or motor output-related change in rCBF when the subjects learned field A? In Fig. 8, the ventral PFC regions are plotted on the mean and typical MR images of our subjects. The rCBF patterns in a 6-mm cube surrounding the peak of intensity in each of the statistical parametric maps are also plotted. During the first eight scans, activation patterns in the ventral PFC did not significantly correlate with learning of field A, nor did they correlate with the changes in motor output. Instead, activation in these regions differentiated the groups in the last two scans according to when field B was presented. We saw a sharp decline in the ventral PFC when subjects trained in field B at 5.5 h, but an increase when they trained at 10 min. The rCBF changes in the brainstem region were nearly identical to those recorded from the ventrolateral PFC in each subject group.

Specificity of results to inhibition of a previously learned motor memory

To what extent is the reduction of rCBFs in the ventral PFC at 5.5 h related to the ability to control perseveration, i.e., inhibit a previously learned motor memory, as opposed to the passage of time alone? In other words, would performance of any motor task at 5.5 h be accompanied with a similar level of reduction in rCBFs of the ventral PFC? To approach this question, we re-examined the data from a different group of subjects (n=9) who had learned the sequence of null, random, and then field A in the initial session, and then returned at 5.5 h to be tested again in field A (Shadmehr and Holcomb 1997). If during learning of B at 5.5 h the reductions in the rCBFs of the ventral PFC were specific to gating of the motor memory for A, then we should not observe similar changes in this control group of subjects.

We performed a between-subject statistical test in order to find regions of the brain where activation changes were similar in the three groups of subjects during the first eight scans, but differentiated the group that learned field B at 5.5 h from the other two groups in the final two scans. Differences in motor output were considered a confounding variable. We again found significant differences in the left and right ventrolateral PFC (Z=4.17, peak at –32,48,-2, BA 10; Z=4.09, peak at 32,50,4, BA 10), as well as in the brainstem (Z=3.67, peak at –6, –26,–18).

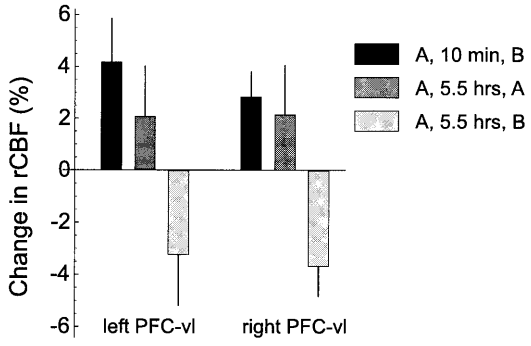

Fig. 9 Within-subject rCBF changes from the 4th condition (late learning of field A) to the 5th condition (learning of field B at either 10 min or 5.5 h, or recall of field A at 5.5 h) for the brain regions where activation changes differentiated the 5.5-h B group from the two other groups. The peaks in the left and right ventrolateral PFC are at –32,48,–2 (Z=4.17, BA 10) and 32,50,4 (Z=4.09, BA 10), respectively

In Fig. 9 we have plotted the within-subject change in the rCBFs of the ventrolateral PFC from condition 4 (late learning A) to condition 5 (learning of field B at either 10 min or 5.5 h, or recall of A at 5.5 h). We found a reduction in the activation of the ventrolateral PFC only if subjects needed to and were able to successfully gate the motor memory of field A. Both the recall of the previously learned motor memory of field A at 5.5 h and the perseveration of that memory at 10 min tended to be coincident with increased rCBFs in the ventrolateral PFC.

Discussion

Successful suppression of competing tendencies is central to the function of an adaptive control system that must live in an unstructured environment. For the case of the visuomotor transformations involved in reaching movements, the neural basis of the system that controls interactions between competing motor memories is not known. However, it is known that lesions in the ventral convexity of the PFC result in significant increases in perseveration when the stimulus-reward pairing of visual (Butter 1969; Rolls et al. 1994; Dias et al. 1996) or tactile stimuli (Deuel and Mishkin 1977) are reversed. Broadly stated, an animal with a ventral PFC lesion has difficulty liberating itself from cued behavior that is well established but, at the moment, inappropriate.

In the current task, subjects reach to a visual target while holding a novel mechanical system. After hundreds of movements, they learn to produce a complex pattern of muscle activations (Shadmehr and Thoroughman 1998) so that the resulting motion is a smooth trajectory of the hand. The term “internal model” (IM), a system for predicting behavior of a controlled process, has been used to computationally account for the changes in the patterns of motor output (Shadmehr et al.

1995). The nature of this learning is computationally similar to the problem of associating the visual appearance of an object to its mechanical properties: an empty bottle of milk painted white will instantiate an IM (of an inertial force field) that is used to generate a pattern of efferent commands. Here, the robot generates the novel dynamics, and perhaps its visual appearance serves as a cue that instantiates the IM months after the initial practice in the task (Shadmehr and Brashers-Krug 1997).

The problem, however, is that visual cues may be deceiving, as is the case with the painted milk bottle, or when the force field produced by the robot reverses. In this circumstance, the tendency to instantiate the now inappropriate IM needs to be gated in order to learn a new motor response. When this does not occur, there is perseveration: aftereffects in field B are appropriate for field A (Shadmehr and Brashers-Krug 1997), and performance after hundreds of movements continues to be worse than that which is observed in naive subjects (Fig. 1A). However, perseveration is strongest immediately after training in field A (Brashers-Krug et al. 1996). Within 4–6 h, the brain appears to gain the ability to gate the inappropriate IM, and perseveration reduces to near zero levels. Behavioral data suggests that this process is gradual (Brashers-Krug et al. 1996). Here we find evidence that: (1) perseveration in field B is coincident with reactivation of brain regions that were associated with learning of the IM for field A; and (2) that the rCBFs in the ventrolateral PFC differentiate the subjects that can successfully inhibit a recently learned IM from a group that cannot.

Motor output and the sensorimotor cortex: evidence for habituation

It has been observed that rCBF changes in certain parts of the motor system, including the primary motor cortex (M1), supplementary motor area, and the cerebellar vermis, increase monotonically with the level of force produced by the muscles of the hand and the arm (Dettmers et al. 1995). During motor skill learning, motor output is likely to decrease as movements become more accurate. While this is an inevitable consequence of skill learning, motor output is a variable that can confound comparison of brain scans. To overcome this limitation, we used an inverse dynamics model of the human arm to estimate the pattern of forces produced at the hand during each movement. This model has been shown to be a reasonable predictor of actual forces (Shadmehr and Brashers-Krug 1997). Motor output was estimated as the integral of the forces produced during each scan period. We found that motor output doubled from null to the random field condition and then declined by about 10% as the field became learnable and the subjects extensively practiced in it. As would be expected, we found a significant increase in the rCBFs of the left sensorimotor cortex when the motor output doubled. However, with extended practice in the field, the rCBFs returned to levels observed in the null field condition (Fig. 4). When motor output was accounted for as a confounding variable, the activations in the sensorimotor cortex significantly declined during learning.

A previous functional MRI (fMRI) study had observed activation decreases in M1 during a 30-min practice period of a motor task (sequence of finger movements), even though motor output was kept constant (Karni et al. 1995). Intriguingly, this initial decline was replaced with an eventual expansion of areas of activation when the task was practiced over many weeks. By accounting for changes in motor output, our results demonstrate that, for reaching movements, the initial stage of learning is also accompanied by declining rCBF in the sensorimotor cortex.

Acquisition of the IM of field A

We had previously reported that learning of reaching movements in novel force fields was coincident with increased rCBF bilaterally in the dorsolateral PFC (Shadmehr and Holcomb 1997). Here, with an increased number of subjects (n=24), we found that motor learning was associated with rCBF changes in the dorsolateral PFC and the left putamen. Within-subject activation changes in the putamen and the PFC were found to be significantly correlated with improvements in performance during each condition of the task. Eigenimage analysis suggested that PFC and putamen were engaged when the task became learnable. A permutation analysis confirmed that the variations in the component scores of the eigenimage were significantly correlated with learning. The increase in the activation in the PFC and putamen could not have been due to changes in motor output, because a doubling of the motor output from the null to the random condition did not result in corresponding changes in rCBFs of these regions.

The area of left striatum associated with learning of field A is in the middle anterior portions of the putamen (Fig. 6A). In the monkey, these regions receive projections from the motor areas of the frontal cortex (Flaherty and Graybiel 1994; Inase et al. 1996; Takada et al. 1998), but not the PFC (Selemon and Goldman-Rakic 1985). Therefore, the areas identified by the third eigenimage were functionally related in this task but not directly connected. Indeed, while the activation changes in the PFC (Figs. 6B and 6 C) and the putamen (Fig. 6A) showed increases when the field became learnable, only the putamen showed a sharp decline from the null condition when the field was introduced but was unlearnable. This suggests that the PFC and the putamen may have been involved in different aspects of the motor learning problem.

The left putamen and learning of field A

Because rCBF changes reflect changing activity of afferent fibers (Kadekaro et al. 1985) and a major input to the

putamen is from the sensorimotor cortex, a component of the activation changes seen in the putamen might reflect changes in motor output. However, a sharp reduction was observed in the putamen when subjects were making arm movements in the random field, i.e., at a time when motor output had doubled with respect to null but the field was unlearnable. Therefore, rCBF changes in this region did not appear to reflect changing motor output. A previous report has also found that rCBFs in the basal ganglia are not significantly correlated with motor output (Dettmers et al. 1995).

A second possibility is that the activation changes in the putamen partially reflect the changing reward conditions of the task. In the random field, little reward was provided to the subjects because almost no movement arrived at the target in time. It has been shown that dopaminergic cells of the substantia nigra characteristically respond to predictability of reward (Schultz et al. 1997) and that expectation of reward modulates activity of cells in the striatum during a visuomotor task (Kawagoe et al. 1998). The reducted activations in the putamen during the random field are consistent with this view.

Once the force field became learnable, rCBF increased in the putamen. It is known that behavioral conditioning leads to increased responsiveness in striatal interneurons (Aosaki et al. 1994a; Aosaki et al. 1994b; Aosaki et al. 1995; Carelli et al. 1997) and that dopamine is released in the striatum during learning of a video game (Koepp et al. 1998). Indeed, a number of functional imaging studies have reported increased activations in the striatum during motor learning (Grafton et al. 1995; Doyon et al. 1996; Jueptner et al. 1997b; Jueptner et al. 1997a). This has suggested a role for the nigrostriatal pathway in reinforcing appropriate motor actions (Graybiel et al. 1994; Houk and Wise 1995). However, this interpretation is complicated by the fact that, as the task was highly practiced, rCBFs once again declined. A recent report found that the increased responsiveness of cells in the putamen during initial stages of learning of a sensorimotor association significantly diminished once the task was highly practiced (Carelli et al. 1997). Our results agree with this and suggest that the changes in the putamen are particularly strong in the initial stages of learning novel reaching movements.

PFC and motor attention during learning of field A

We found that activations in the dorsolateral PFC increased only when the task became learnable. With extensive practice, these activations returned to baseline levels. What role might the PFC play in motor learning? One suggestion is motor attention (Passingham 1996), while another is a role in acquiring declarative knowledge of the solution to the motor problem (Doyon et al. 1996; Hazeltine et al. 1997), i.e., becoming consciously aware of the appropriate motor response.

The PFC has been implicated in acquiring declarative strategies in a motor task. For example, in a finger-tapping task with a hidden sequence, changes in PFC are correlated with gaining conscious awareness of the sequence (Doyon et al. 1996; Hazeltine et al. 1997), and disruption of the PFC prevents learning of the sequence (Pascual-Leone et al. 1996). For reaching movements, however, it seems unlikely that acquiring a declarative strategy is related to the improvement in performance: H.M. and other amnesic subjects with profound disabilities in storing declarative memories learn this motor skill normally and show long-term recall (Shadmehr et al. 1998). Therefore, conscious awareness of a strategy or acquiring declarative memories is not necessary for learning of reaching movements. While this does not rule out formation of declarative strategies in normal individuals, our postexperiment interviews have not identified a likely candidate. In general, subjects claim that their performance improved because the forces produced by the robot were turned down or turned off completely. In fact, the field was time-invariant.

An alternate explanation is to posit a link between activations in the PFC and motor attention. While the neural basis of attention for skill learning is not known, it is reasonable to assume that attentional requirements of a task may be inversely related to how "automatic" the task is. For example, subjects can perform a second task (e.g., verb generation) better if they are in the later stages of learning a motor task (sequence of finger movements) as compared to the early stages of learning the task (Nissen and Bullemer 1987; Passingham 1996). In this case, the verbal and motor tasks were performed concurrently. The difficulty in performing the two tasks is seen as a problem in divided attention (Duncan 1995). Because verb generation normally engages the PFC (Raichle et al. 1994), there may be less attentional resources available during early motor learning when PFC is also engaged, resulting in interference.

This suggests that learning a novel motor task requires attention, and that as the motor task becomes well practiced, attentional requirements decrease. Numerous functional imaging studies have shown increased rCBFs in the PFC during the initial stages of learning (Lang et al. 1988; Seitz et al. 1990; Jenkins et al. 1994; Imamura et al. 1996; Jueptner et al. 1997b). These activations tend to decline with extended practice (Passingham 1996) and can increase again if subjects are instructed to "pay attention" by thinking about their next movement (Jueptner et al. 1997b). Taken together, it is possible that the increased rCBFs in the dorsolateral PFC were related to attentional requirements of learning the novel task. However, further experiments in a concurrent dual-task paradigm are needed to shed light on this question.

Neural correlates of perseveration

After the subjects practiced in field A, the force field was rotated by 180^{o} (field B). Visual stimuli that were learned to be associated with a pattern of motor output were now counterproductive and would not be rewarded.

Instead, the subjects had to reverse the direction of the learned forces in response to the same visual stimuli.

Eigenimage and subtraction analysis had identified regions in the PFC and putamen where activation changes appeared to relate to learning of field A. During learning of field B at 10 min, these regions tended to be reactivated. Because activations in these regions had not correlated with motor output during the first 4 conditions, it is unlikely that the observed increase in the 5th condition was related to the relative increase in motor output. Instead, we suggest that the reactivation was related to perseveration. Aftereffects suggest that at 10 min learning of field B took place with an instantiated memory of field A (Shadmehr and Brashers-Krug 1997), and that this competition detrimentally affected long-term memory of A (Brashers-Krug et al. 1996). Two recent reports have also found that, when performing one task competed with subsequent learning of another, they were likely to have overlapping regions of activation in the brain (Passingham 1996; Klingberg and Roland 1997). The current report, to our knowledge, is the first to show that perseveration of motor memory is coincident with reactivation of at least some of the regions that were involved in acquisition of that memory. These regions include the dorsolateral PFC (bilaterally) and the left putamen.

Inhibitory control of a competing motor memory

What neural system contributed to learning of field B at 5.5 h? Within-subject analysis found that learning of field B was coincident with an increase in the left caudate, a region that had not shown significant changes during learning of field A. Using between-subject analysis and corrected *P*-values, we found that in the putamen the 5.5-h group showed smaller but not significantly different changes than in the 10-min group, while in the caudate the 10-min group showed smaller but not significantly different changes than in the 5.5-h group. This hinted at an increased role for the caudate when learning of field B was accompanied by successful control of perseveration. Because there are extensive projections to the caudate from the PFC (Selemon and Goldman-Rakic 1985), we expected to find differences between the groups in the PFC. Indeed, between-subject analysis found very significant differences between the groups in the ventral PFC (bilaterally). During the first 4 conditions of the task, there were no differences between the groups in these regions and activity here did not correlate with motor learning. However, during learning of field B, these regions showed increases at 10 min, but decreases at 5.5 h. Within-subject analysis comparing late A with field B confirmed this finding.

Are the changes in the ventral PFC related to control of perseveration, or would performance of any motor task at 5.5 h also show a similar decline? We found that if at 5.5 h the motor task did not involve a reversal, then the declines in the ventral PFC were not present. When subjects were asked to reach in field A at 5.5 h, they tended to show increases in the ventral PFC (Fig. 9). Between-subject analysis confirmed that activations in the ventral PFC differentiated the 5.5-h B group from both the 5.5-h A and the 10-min B groups. Therefore, decreased rCBFs in the ventral PFC were observed only when subjects were able to successfully inhibit a competing motor memory.

We did not find increased activation in the dorsolateral PFC during learning of field B at 5.5 h, despite the fact that in of itself this was new learning. It is difficult to reconcile this with the idea of attention to action during early phases of motor learning. However, a current theory of prefrontal function differentiates between the dorsolateral and the ventral regions based on the need to shift attention within or between dimensions of the task (Wise et al. 1996). Learning to suppress the influence of a previously acquired stimulus-reward association may be specific to the ventral aspects (Dias et al. 1996). It is known that lesions in the ventral PFC result in significant increases in perseveration of a previously learned but now inappropriate association (Butter 1969; Deuel and Mishkin 1977). Neuronal activity during reversals of visually associated go/no-go (Sasaki and Gemba 1986; Watanabe 1986) and delayed antisaccade tasks (Funahashi et al. 1993) in the PFC have suggested a function related to inhibition of motor actions. In humans, damage to the PFC impairs the ability to inhibit attentional and motor responses demanded by previously learned associations in reversal tasks (Verin et al. 1993; Owen et al. 1993; Shimamura et al. 1995). This inhibitory control is probably mediated through the caudate: for reaching movements, animals with left caudate lesions have a particular difficulty when they need to learn to withhold the conditioned movement upon presentation of a stimulus (Aldridge et al. 1997). Therefore, a critical role for the ventral PFC may be in the inhibitory control of previously learned actions for the purpose of new learning (Passingham 1993; Wise et al. 1996; Fuster 1997). Our results provide evidence that in normal individuals there may be a link between successful inhibition of a competing motor memory and activation change in the ventral PFC.

Why is exercise of this inhibitory control dependent on time since completion of practice in field A? In psychology, interference between pairs of tasks is often described in a framework of attention (Duncan 1995): the more attention that is required in performing task 1, the more difficult it might be to concurrently perform task 2. In this framework, attention to action is defined as a commodity that is consumed only when a task is being performed, and interference is a function of attentional resources available. In somewhat of a contrast to this framework, our result suggests that interference is a phenomenon that continues to develop after practice in a motor task ends, and that it is perhaps related to the consolidation period of motor memory. Therefore, while new learning may require attention, it is possible that its influence on the PFC, in particular the ventral aspects, is

not limited to the period during which learning took place.

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