Anatomy of Motor Learning. I. Frontal Cortex and Attention to Action

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[1]Wellcome Department of Cognitive Neurology, Institute of Neurology, London WC1N 3BG; [2]Medical Research Council Cyclotron Unit, Hammersmith Hospital, London W12 0HS; [3]Department of Experimental Psychology, University of Oxford, Oxford OX1 3UD, United Kingdom; [4]Department of Neurology, University Clinics Essen, 45122 Essen; and [5]Neurology Clinic, D-40225 Dusseldorf, Germany

Jueptner, M., K. M. Stephan, C. D. Frith, D. J. Brooks, R.S.J. Frackowiak, and R. E. Passingham. Anatomy of motor learning. I. Frontal cortex and attention to action. *J. Neurophysiol.* 77: 1313–1324, 1997. We used positron emission tomography to study new learning and automatic performance in normal volunteers. Subjects learned sequences of eight finger movements by trial and error. In a previous experiment we showed that the prefrontal cortex was activated during new learning but not during automatic performance. The aim of the present experiment was to see what areas could be reactivated if the subjects performed the prelearned sequence but were required to pay attention to what they were doing. Scans were carried out under four conditions. In the first the subjects performed a prelearned sequence of eight key presses; this sequence was learned before scanning and was practiced until it had become overlearned, so that the subjects were able to perform it automatically. In the second condition the subjects learned a new sequence during scanning. In a third condition the subjects performed the prelearned sequence, but they were required to attend to what they were doing; they were instructed to think about the next movement. The fourth condition was a baseline condition. As in the earlier study, the dorsal prefrontal cortex and anterior cingulate area 32 were activated during new learning, but not during automatic performance. The left dorsal prefrontal cortex and the right anterior cingulate cortex were reactivated when subjects paid attention to the performance of the prelearned sequence compared with automatic performance of the same task. It is suggested that the critical feature was that the subjects were required to attend to the preparation of their responses. However, the dorsal prefrontal cortex and the anterior cingulate cortex were activated more when the subjects learned a new sequence than they were when subjects simply paid attention to a prelearned sequence. New learning differs from the attention condition in that the subjects generated moves, monitored the outcomes, and remembered the responses that had been successful. All these are nonroutine operations to which the subjects must attend. Further analysis is needed to specify which are the nonroutine operations that require the involvement of the dorsal prefrontal and anterior cingulate cortex.

INTRODUCTION

We have previously identified the cortical and subcortical areas involved in the learning of motor sequences by trial and error (Jenkins et al. 1994). The tasks required the subjects to learn a sequence of finger movements that was eight moves long. On each trial subjects moved a finger, and the computer gave auditory feedback to tell the subjects whether that was the correct move at that point in the sequence.

We compared new learning of sequences with automatic performance of a sequence that was overlearned before scanning. This sequence was practiced until the subjects could perform it without the need to pay attention to what they were doing. The evidence was that the subjects could hold a conversation or repeat five digits back at the same time as performing the motor task. More recently, Passingham (1996) has provided a more formal demonstration that the sequence learning task becomes automatic; in an experiment with Watkins, Passingham showed that when the task had become overlearned, subjects could perform the verb generation task at the same time with little interference. The advantage of being able to perform a motor task automatically is that one can direct one's attention elsewhere.

Raichle et al. (1994) have also reported that there is a decrease in the activation of the prefrontal cortex as subjects repeatedly supply the same verbs in response to a list of nouns. Raichle et al. also showed that the activation of the prefrontal cortex increased again when the subjects were provided with a *new* list of nouns from which to generate verbs.

The aim of the present experiment was to see what areas would be reactivated if the subjects were required to perform the *same* sequence that they could perform automatically, but were required to attend again to its performance. Automatic performance allows us direct our attention to a more demanding or important task while running off a less important one without thinking (Shaffer 1975); but we can also attend to actions we might otherwise perform without thinking. For example, although we do not usually attend to walking, we walk cautiously on a slippery surface, attending to what we are doing. The hypothesis is that the prefrontal cortex is involved in attention to action.

The subjects were therefore tested on a prelearned sequence as in the study by Jenkins et al. (1994). In the attention (ATT) condition the subjects were tested on the prelearned sequence, but were asked to think about the next movement they were going to make. In this condition the subjects performed the same sequence but the instructions were altered. A comparison could then be made between the activations when the subjects performed the prelearned sequence and the activations when subjects were required to attend to what they were doing. For comparison, subjects were also tested while they learned new sequences.

The study also differs from the earlier study by Jenkins et al. (1994) in that we used a more sensitive method. This was achieved in several ways. First, we used a camera with higher intrinsic resolution, with the use of 31 rings of detectors instead of 15. Furthermore, we used a more sensitive

method for the detection of radioactivity. We scanned in "3-D mode," in which the interplane septa are retracted during the scans (Townsend 1991).

We also improved the methods for anatomic localization. All images were corrected for involuntary movement artifacts between scans (Woods et al. 1992). Finally, the foci of significant change were coregistered onto a group magnetic resonance imaging (MRI) scan so as to increase the amount of anatomic information derived from the scans.

METHODS

Subjects

The subjects were 12 normal male volunteers with a mean age of 25.5 yr (range 21–37 yr). All were strongly right-handed as measured by the Edinburgh MRC Handedness Inventory (Oldfield 1971). None of these subjects had a history of neurological or psychiatric disease, and none took any medication. Each subject gave informed written consent. Ethical approval for the experiments was given by the Ethics Committee of the Royal Postgraduate Medical School of the Hammersmith Hospital. Permission to administer radioactive $H_2^{15}O$ was given by the Administration of Radioactive Substances Advisory Committee of the Department of Health, UK.

Experimental design

Twelve sequential measurements of regional cerebral blood flow (rCBF) were performed for each subject with the use of $H_2^{15}O$ as a tracer; this reflects neuronal synaptic activity (Jueptner and Weiller 1995). The scans were performed under four different conditions with three runs per condition.

The new learning (NEW) condition involved learning a new sequence of key presses. The sequence was eight moves long and was learned by trial and error. The movements were paced by a tone at a frequency of one every 3 s. Correct identification of a movement was rewarded immediately by a high-pitched tone, and incorrect movements were followed immediately by a low-pitched tone.

The subject first tried to identify the first move in the sequence. At each pacing tone the subject tried a finger, and this continued until the subject was given feedback that the movement was correct. The subject then tried to identify the second key press, again by trial and error, and then the third key press, and so on until the subject had correctly identified the sequence of eight movements. The end of the sequence was signified by three short high-pitched tones. The subject then returned to the beginning of the sequence and continued to perform the task in the same way.

In each NEW condition, subjects were given new sequences. The sequences were identical for all subjects. If a subject learned the sequence to criterion (no errors in 1 run-through), a further new sequence was presented so as to continue the process of motor learning.

Approximately 90 min before scanning, subjects learned a standard sequence in the same way as described above. This was the prelearned sequence (PRE) condition. The subjects continued to perform the task until they made no errors. After a rest period of 2 min, subjects continued to rehearse the same sequence for 3.5 min followed by another rest of 2 min. A sum of 10 trials was completed, each consisting of 3.5 min of rehearsal and 2 min of rest.

The automaticity of the motor task was assessed in the last trial. Subjects were asked to repeat five- or six-digit strings presented at a rate of one every second. Subjects had to repeat the strings immediately and in the same order. A more formal demonstration

that the prelearned sequence has become automatic is given by Passingham (1996) (see DISCUSSION).

Immediately before scanning, subjects performed two further trials of the prelearned sequence while lying on the scanner couch. This ensured that subjects were able to perform the sequence in this situation. During scanning, the same sequence was used for all three runs of this condition.

In the third condition, subjects performed the prelearned sequence. However, immediately before scanning, subjects were asked to "think of the next movement" once they finished the previous one. This meant that the subjects had to pay attention to the prelearned sequence (ATT condition). Again, the same standard prelearned sequence was used for all three runs of this condition.

During the baseline (BASE) condition the computer generated a sequence of pacing and feedback tones at the appropriate frequency to control for auditory input. The subjects rested without making any finger movements.

The scans were performed in a darkened room with the subjects lying supine with eyes closed. Head position was maintained by a football helmet internally coated with air cells to fit the individual's head. A chin strap was used to further reduce involuntary head movements during the scans.

The pacing and feedback tones were produced by an Amiga computer. Tones were sufficiently different to be easily distinguished by all subjects. The computer monitored the the key presses, errors, number of omissions (failure to depress a key within 3 s after the pacing tone), and response times (reaction time plus movement time).

The task was performed on a keypad with four keys with the use of the fingers of the right hand: I = index, M = middle, R = ring, L = little. The following sequences were used: PRE and ATT, RILMLRIM; NEW1, IRLRLMIM; NEW2, MIRLRMRI; NEW3, ILMIMRML.

The tasks were performed in the following order: BASE, PRE, PRE, PRE, ATT, ATT, ATT, BASE, NEW, NEW, NEW, BASE. This order was chosen to avoid any interference between new sequence learning and the performance of the prelearned sequence. It is a problem with this ordering of the conditions that it assumes that the baseline is stable across scans. We confirmed that the baseline was stable by reading the values at the peak coordinates for prefrontal, cingulate, premotor, and parietal cortex. Thus for the right dorsal prefrontal cortex the rCBF values for the baseline were 48.2, 49.7, and 48.8.

Data acquisition

The positron emission tomography (PET) scans were performed with the use of a CTI/Siemens 953B PET scanner (CTI, Knoxville, TN) with removable septa. The scanner collects data from 31 rings of crystal detectors, giving an axial field of view of 10.65 cm. To examine the whole brain, thus visualizing effects in all cortical and subcortical structures, we scanned six subjects high (including the vertex) and six subjects low (including the bottom of the cerebellum). Thus we were able to image the entire cerebral volume, including the whole of the cerebellum.

The complete data set extended from 52 mm below the intercommissural (AC-PC) plane to 72 mm above it. Where the data sets for the subjects scanned high and low overlapped, the data for the high set for six subjects were used. This is true, for example, for the data for the basal ganglia.

The distribution of cerebral radioactivity was recorded for 90 s, in 3-D mode, i.e., with the scanner interplane septa retracted (Townsend et al. 1991). Radioactivity was administered as a bolus injection of $H_2^{15}O$ through a venous line in the left arm. Emission data were corrected for attenuation by the tissues of the head with the use of a transmission scan ($^{68}Ga/^{68}Ge$ sources), which was

performed before the activation scans. The PET data were reconstructed into 31 planes with the use of a Hanning filter with a cutoff frequency of 0.5 cycles/s. The resolution of the resulting images was $8.5 \times 8.5 \times 6.0$ mm at full width half maximum (Spinks et al. 1992). The reconstructed images contained 128×128 pixels, each 2.05×2.05 mm.

During each scan, 3 ml of radiolabeled water were applied containing 11 mCi of ^{15}O. PET scans were collected over a period of 90 s; the paradigm was started 30 s before data acquisition and continued for 2 min.

For anatomic reference, T1-weighted MRI scans were obtained from six subjects on a 1-T Picker HPQ Vista system with the use of a radiofrequency spoiled volume acquisition with the following parameters: repeat time 24 ms, echo time 6 ms; nonselective excitation with a flip angle of 35°; field of view in plane 25×25 cm; 192×256 in plane matrix with 128 secondary phase encoding steps oversampled to 256; resolution $1.3 \times 1.3 \times 1.5$ mm; total imaging time 20 min.

Data analysis

All calculations were performed on Sparc computers (SUN Microsystems, Mountain View, CA) with the use of the interactive image display software ANALYZE (Biodynamic Research Unit, Mayo Clinic, Rochester, MN) and SPM software for image analysis and matrix operations (MRC Cyclotron Unit, Hammersmith Hospital, London, UK) in the Matlab environment (Mathworks, Sherborn, MA).

The attenuation corrected data were interpolated to 43 slices. Each slice was displayed in a 128×128 pixel format, with a pixel size of $\sim 2 \times 2 \times 2.5$ mm. The scans were corrected for involuntary movement artifacts with the use of realignment to the first corrected image (Woods et al. 1992).

All images were then reoriented to the AC-PC line and transformed into the standard anatomic space (Talairach and Tournoux 1988). This resulted in 26 planes parallel to the AC-PC line with an interplanar distance of 4 mm (Friston et al. 1989). The PET images were filtered with a low-pass Gaussian filter (10 pixels at full width half maximum) to increase the signal-to-noise ratio (Friston et al. 1990).

Differences in global blood flow between subjects and conditions were removed by analysis of covariance (ANCOVA) with global flow as the confounding variable (Friston et al. 1990). The data for the three scans for a particular condition were treated as independent samples; however, we used a blocked ANCOVA to account for subject effects, therein modeling intrasubject correlations. Blood flow changes between the conditions were assessed with the use of t statistics with appropriate weighting of the adjusted condition-specific values (Friston et al. 1991).

The results are presented as sets of spatially distributed z values that constitute statistical parametric (SPM{t}) maps. SPM{t} maps identify the site of areas of statistically significant blood flow change occurring as a result of the differences in relative perfusion between task conditions. The results were thresholded to a value of $P < 0.001$ (Friston et al. 1991). Furthermore, the SPM{t} maps were inspected for trends, i.e., increases of rCBF at a lower threshold ($P < 0.01$). All results are reported in the same order throughout this publication: significant increases of rCBF are presented in the prefrontal cortex, cingulate cortex, premotor cortex, parietal cortex, insula, basal ganglia, thalamus, and cerebellum. To assess the significance of attention in the NEW conditions, we performed the following comparisons: NEW versus PRE, NEW versus BASE, ATT versus PRE, ATT versus BASE, NEW versus ATT.

The MRI scans were all aligned parallel to the AC-PC line and transformed into the standard anatomic space of the atlas of Talairach and Tournoux (1988). The scans were then averaged so as to provide a mean MRI scan in which there were sufficient details to identify major anatomic landmarks. The blurring in the mean MRI scan reflects the variability in position of anatomic structures for this group of individuals. This average MRI scan served as a template onto which the average PET data were coregistered for localization of activations. This procedure allowed us to report activated foci in terms of Talairach and Tournoux coordinates as well as by reference to anatomic structures. The foci of maximal change in rCBF were identified for each area with the use of the Talairach and Tournoux coordinates (Talairach and Tournoux 1988). The results are shown in transverse sections with the left side of the image being the left side of the brain.

RESULTS

Task performance

At the end of the prelearning period (trial 10 before scanning) all subjects were tested on repeating back digits while performing the PRE task. All were able to repeat back six digits without making errors. During scanning, none of these subjects made omissions during any of the tasks; thus the number of key presses was identical for all subjects and all conditions.

During the NEW condition, four subjects managed to learn two of three sequences completely within the time of scanning, i.e., they were able to perform the new sequence without any errors before the end of the scan. Six subjects learned one sequence completely, whereas two subjects failed to reach criterion on any of the three sequences before the end of the scan. The mean errors for new learning were 8.1 on trial 1, 3.8 on trial 2 and 1.8 on trial 3. The total number of errors (incorrect choice of finger movement) for the PRE task was 14 over all the subjects, that is, 0.9% of all key presses in the entire PET study. The total number of errors for the ATT condition was nine, that is, 0.6% of all key presses. There was no significant difference between the number of errors in these two tasks (PRE vs. ATT) ($t = 1.1$, df $= 11$, $P = 0.295$, paired t-test).

The mean response time for the NEW condition in the scanner was 716 ± 130 (SD) ms, with a mean of 751 ms on trial 1, 698 ms on trial 2, and 657 ms on trial 3. The mean response time was 425 ± 103 ms for the PRE condition and 533 ± 117 ms when subjects attended to their movements (ATT). The response times differed significantly for all three comparisons (paired t-tests): NEW versus PRE ($t = 6.2$, df $= 11$, $P = 0.000$); ATT versus PRE ($t = 4.4$, df $= 11$, $P = 0.001$); NEW versus ATT ($t = 4.8$, df $= 11$, $P = 0.001$). Comparing the results with those of the companion paper (Jueptner et al. 1997) it will be seen that the time for the ATT condition was not significantly different from the time for the free selection (FREE) condition in which subjects decided on every trial which move to make (ATT $= 533$ ms, FREE $= 517$ ms), and the time for the PRE condition was not significantly different from the time when subjects simply repeated the same response on every trial (REP condition) (PRE $= 425$ ms, REP $= 430$ ms).

NEW versus PRE

Table 1 lists the areas in which there was more activation ($P < 0.001$) in new learning than in performance of the PRE task. In this and all other tables the term ''peak activa-

TABLE 1. *Comparison of NEW vs. PRE: foci of significant (P < 0.001) increases of rCBF in NEW*

Area Activated	Extent of Area Activated (Relative to AC-PC Plane), mm	Talairach Coordinates of Peak Activation	z Score of Peak Activation	Increase in Normalized rCBF, %
Prefrontal cortex				
Areas 10, 46, 9 (L)	−4 to +40	−28, 42, 20	5.50	3.46
Areas 10, 46, 9 (R)	−8 to +40	38, 24, 28	6.68	5.30
Cingulate cortex				
Areas 24, 32 (R)	+4 to +40	2, 20, 28	4.05	7.04
Area 32 (L)	+4 to +44	−2, 14, 44	6.11	3.34
Premotor cortex				
Area 6 (L)	+52 to +64	−18, −8, 60	4.97	3.42
Area 6 (R)	+48 to +68	28, 4, 52	7.15	5.78
Parietal cortex				
Areas 7, 40 (R)	+28 to +52	40, −54, 44	5.93	5.82
Insula (L)	+16 to +20	−30, −16, 20	3.17	2.87
Insula (R)	−8 to +16	30, 26, 12	6.05	4.08
Basal ganglia				
Caudate nucl. (L)	0 to +24	−24, 22, 0	3.98	3.52
Caudate nucl. (R)	+4 to +24	16, 20, 8	6.06	3.83
GP (L)	−4 to +4	14, 0, 4	3.47	2.17
GP (R)	0 to +4	14, 6, 4	3.28	2.70
Thalamus				
Dorsomedial (L)	+4 to +16	−8, −26, 4	4.72	2.65
Dorsomedial (R)	+8 to +16	8, −20, 12	5.21	3.32
Ventroanterior (L)	+8 to +12	−10, −2, 8	3.64	2.67
Ventroanterior (R)	+12	4, −2, 12	3.76	2.55
Cerebellum				
Vermis	−32 to −24	4, −62, −32	3.99	2.14
Nuclei (L)	−32 to −28	−26, −56, −32	3.97	2.43
Hemisphere (L)	−36 to −32	−40, −48, −32	3.83	2.93
Hemisphere (R)	−36 to −32	54, −48, −32	3.67	4.06

NEW, new learning; PRE, prelearned sequence; rCBF, regional cerebral blood flow; AC-PC, intercommissural; L, left; R, right; GP, globus pallidus.

tion'' refers to the activation that was statistically most robust.

Significant relative increases of rCBF at this level were found in prefrontal areas bilaterally (Brodmann areas 10, 46, and 9), medial frontal area 32 bilaterally, and the right anterior cingulate area 24. Further activations were detected in premotor cortex bilaterally, right parietal cortex (Brodmann areas 7 and 40), and the insula bilaterally.

Significant activations were found in the following subcortical areas: caudate nucleus, including the more ventral part of the striatum, and globus pallidus bilaterally; dorsomedial and ventroanterior thalamus bilaterally; cerebellar hemispheres bilaterally, and cerebellar vermis and nuclei.

The following trends were found, that is, increases of rCBF at a lower significance level ($P < 0.01$): left parietal cortex area 7 (maximum z score 2.36), left parietal cortex area 40 (maximum z score 2.42), and right pulvinar nucleus of the thalamus (maximum z score 2.73).

Figure 1, *top rows* in *A* and *B,* shows the SPM{t} maps for prefrontal and cingulate cortex (*A*) ($P < 0.001$) and for premotor and parietal cortex (*B*). Figure 2, *top rows* in *A* and *B,* shows the SPM{t} maps for the basal ganglia (*A*) and cerebellum (*B*). Figure 3 shows the increases of normalized blood flow for selected brain areas. In the figures showing SPM{t} maps, the white area shows the extent of the activated areas. These areas result from a group analysis with secondary smoothing of the data, and they can therefore merge across different subregions of the cortex, for example the prefrontal and premotor cortex. However, a subregion is not taken to be significantly activated unless the analysis

gives a significant peak within that area. The coordinates of these peaks are given in the tables.

ATT versus PRE

Table 2 shows the areas in which there was more activation ($P < 0.001$) when subjects performed the ATT task compared with the PRE task. The following cortical areas showed significant increases of rCBF at this level: left prefrontal cortex (Brodmann areas 46 and 9) and right anterior cingulate cortex (areas 32, 24). No further significant increases of rCBF were found in cortical areas.

There were no significant activations in subcortical areas in this comparison at a threshold of $P < 0.001$. The following trends were found, that is, increases of rCBF at a lower significance level ($P < 0.01$): right anterior supplementary motor area (SMA) (maximum z score 2.65), left sensorimotor cortex (maximum z score 3.08), right somatosensory cortex (maximum z score 2.87), left insula (maximum z score 3.03), right insula (maximum z score 2.83), right caudate nucleus (maximum z score 3.08), left cerebellar hemisphere (maximum z score 2.59), cerebellar vermis (maximum z score 2.56), and left cerebellar nuclei (maximum z score 2.59).

Figure 1, *bottom rows* in *A* and *B,* shows the SPM{t} maps for the prefrontal and anterior cingulate cortex (*A*) and premotor and parietal cortex (*B*). Figure 2, *bottom rows* in *A* and *B,* shows the SPM{t} maps for the basal ganglia (*A*) and cerebellum (*B*). Figure 4 shows the increases of normalized blood flow.
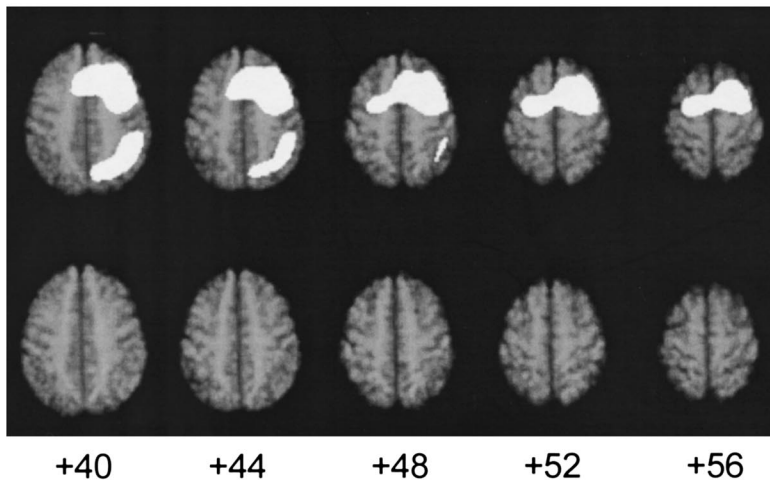
A

+20 +24 +28 +32 +36
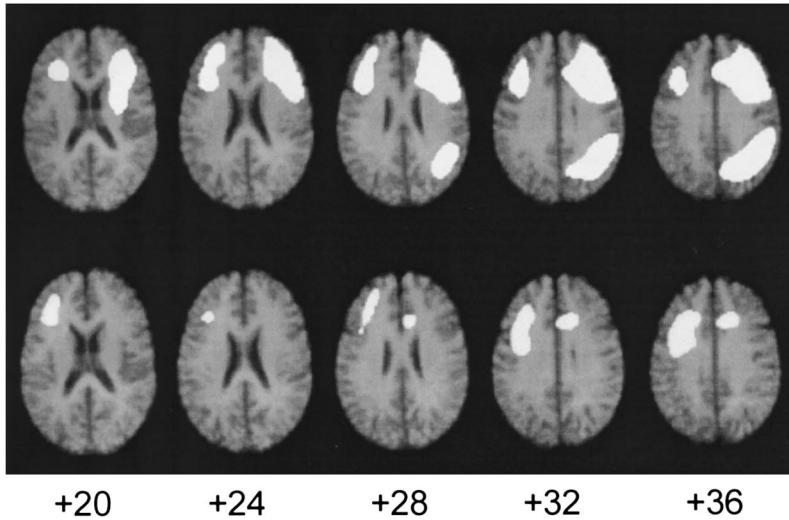
FIG. 1. *Top rows* in *A* and *B*: statistical parametric (SPM{t}) maps of significant increases of regional cerebral blood flow (rCBF) in the new learning (NEW) condition compared with the automatic performance of the prelearned sequence (PRE condition). *Bottom rows* in *A* and *B*: SPM{t} maps of significant increases of rCBF in the attention (ATT) condition compared with the prelearned sequence. *A*: prefrontal, anterior cingulate, and parietal cortex were activated in the NEW task (NEW vs. PRE). When subjects attended to their actions (ATT vs. PRE), prefrontal and anterior cingulate cortex were activated. *B, top row*: significant increases of rCBF in premotor and parietal cortex with new learning (NEW vs. PRE). *B, bottom row*: absence of significant increases of rCBF when subjects attended to their actions compared with the automatic performance of the same task (ATT vs. PRE). In Figs. 1 and 2, the white area shows the extent of the activated areas. These areas result from a group analysis with secondary smoothing of the data, and they can therefore merge across different subregions of the cortex. However, a subregion is not taken to be significantly activated unless the analysis gave a significant peak within that area. The coordinates of these peaks are given in the tables.

B

+40 +44 +48 +52 +56

NEW versus ATT

Table 3 shows the areas in which there was more activation ($P < 0.001$) in new learning than in the ATT task. The following areas showed significant increase in rCBF at that level: prefrontal cortex (Brodmann areas 10, 46 and 9), anterior cingulate area 32, and premotor cortex bilaterally; right parietal cortex (areas 7 and 40); and right insula.

Increases of rCBF were found in the following subcortical areas: caudate nucleus, including the ventral striatum, and dorsomedial thalamus bilaterally, right ventroanterior thalamus, and cerebellar vermis.

The following trends were found, that is, increases of rCBF at a lower significance level ($P < 0.01$): left parietal cortex area 7 (maximum z score 2.96), left parietal cortex area 40 (maximum z score 2.72), and right pulvinar nucleus of the thalami (maximum z score 2.44).

NEW versus BASE

Table 4 lists the areas in which there was activation ($P < 0.001$) comparing the NEW condition with the BASE condition. There were increases of rCBF at that level in the following areas: prefrontal areas bilaterally (Brodmann areas 10, 46 and 9) and anterior cingulate cortex bilaterally (areas 32, 24). Further activations were detected in the premotor cortex, SMA bilaterally, left primary motor cortex, parietal cortex (Brodmann areas 7 and 40) bilaterally, and right insula.

Significant activations were found in the following subcortical areas: right caudate nucleus, putamen and globus pallidus bilaterally; dorsomedial and ventroanterior thalamus bilaterally; cerebellar hemispheres bilaterally, cerebellar vermis, and left nuclei.

PRE versus BASE

Table 5 shows the areas in which there was more activation ($P < 0.001$) in the PRE than in the BASE task. The following areas showed a significant increase in rCBF at that significance level: left cingulate areas 23 and 24, left SMA, left posterior premotor cortex, left motor cortex, and
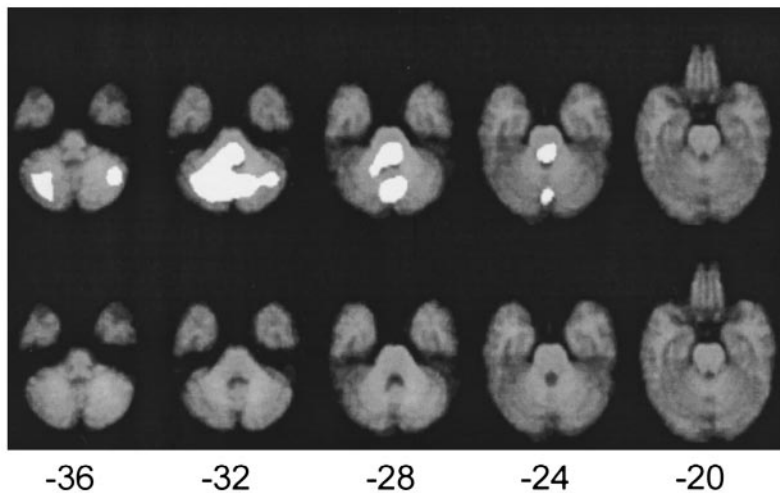
A

-4   0   +4   +8   +12

B

-36   -32   -28   -24   -20
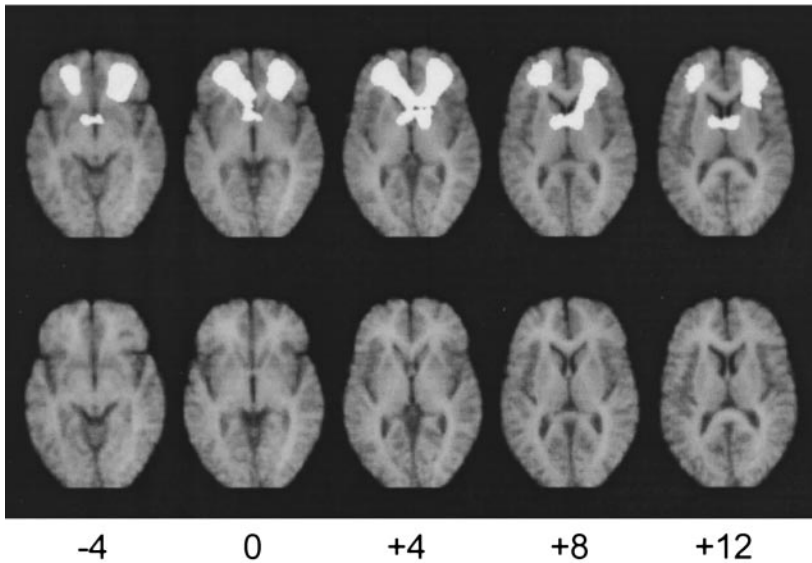
FIG. 2. *Top rows* in *A* and *B*: SPM{t} maps of significant increases of rCBF in the NEW condition compared with the automatic performance of the prelearned sequence. *Bottom rows* in *A* and *B*: SPM{t} maps of significant increases of rCBF in the ATT condition compared with the prelearned sequence. *A, top row*: significant increases of rCBF in the basal ganglia with new learning (NEW vs. PRE). *A, bottom row*: activation in the basal ganglia did not reach the high level of significance ($P < 0.001$) when subjects attended to their actions compared with the automatic performance of the same task (ATT vs. PRE). However, there was a trend in the caudate nucleus (z score = 3.08); this is not shown in this figure. *B, top row*: significant increases of rCBF in the cerebellar hemispheres, nuclei, and vermis with new learning (NEW vs. PRE). *B, bottom row*: absence of significant increases of rCBF when subjects attended to their actions compared with the automatic performance of the same task (ATT vs. PRE).

left parietal cortex (areas 7 and 40). There were additional significant increases of rCBF in subcortical brain areas, that is, the left posterior putamen, cerebellar hemisphere bilaterally, right nuclei, and cerebellar vermis.

The following trends were found, that is, increases of rCBF at a lower significance level ($P < 0.01$): right inferior parietal cortex area 40 (maximum z score 2.79), right posterior SMA (maximum z score 2.46), left insula (maximum z score 2.64), right putamen (maximum z score 2.98), and left anterior thalamus (maximum z score 3.06).

ATT versus BASE

Table 6 shows the areas in which there was more activation ($P < 0.001$) during the ATT task than in the BASE condition. The following areas showed a significant increase in rCBF at that significance level: anterior cingulate (areas 32, 24) bilaterally, left SMA, and lateral premotor, sensorimotor, and parietal cortices bilaterally.

Significant activations were found in the following subcortical areas: left putamen and globus pallidus, cerebellar hemispheres bilaterally, cerebellar nuclei, and vermis.

The following trends were found, that is, increases of rCBF at a lower significance level ($P < 0.01$): left insula (maximum z score 2.58) and right pulvinar nucleus (maximum z score 2.47).

DISCUSSION

New learning and automatic performance

We compared rCBF in the NEW condition with the automatic performance of a prelearned sequence (NEW vs. PRE). As in the earlier study (Jenkins et al. 1994), the dorsal prefrontal cortex and anterior cingulate area 32 were extensively activated in new learning (NEW vs. PRE, NEW vs. BASE) but not during automatic performance (PRE vs. BASE). Activity in the prefrontal cortex was, if anything,
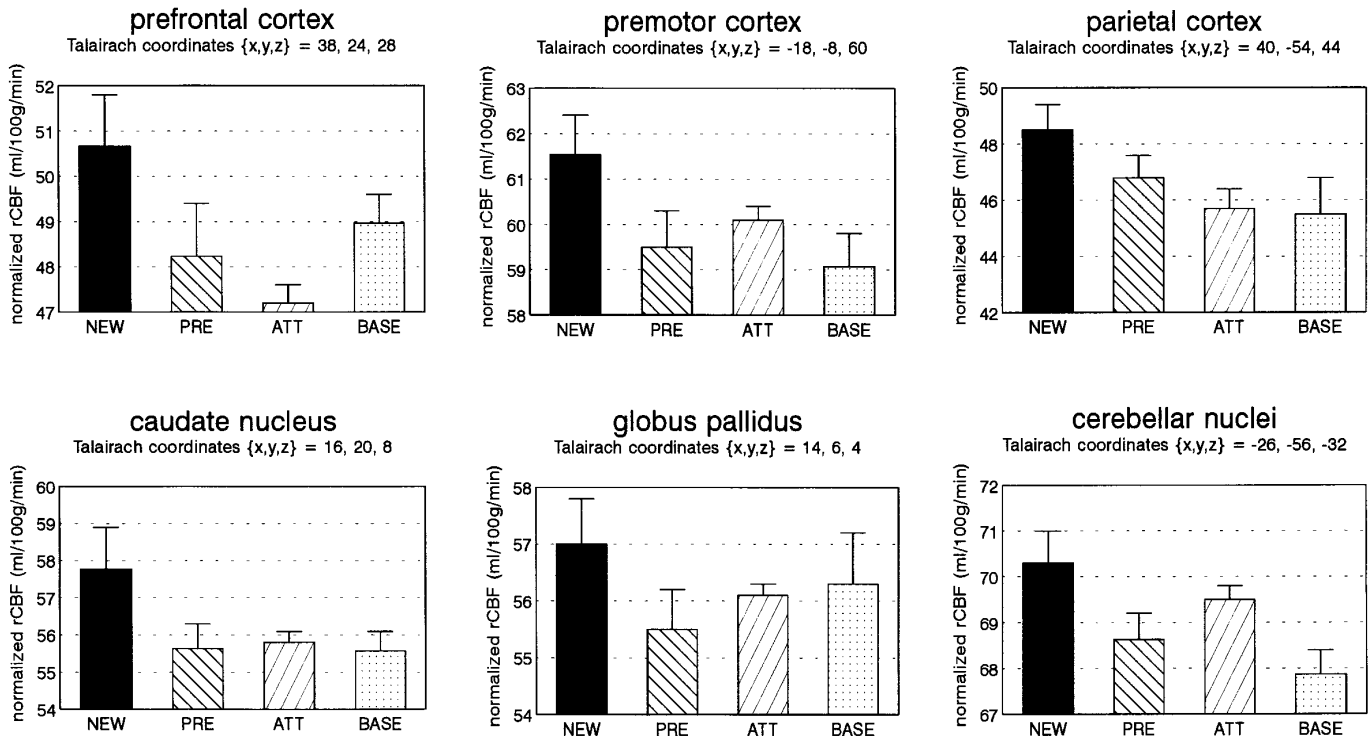
FIG. 3. Graphs illustrating changes of rCBF across 3 conditions: *1*) NEW condition; *2*) PRE condition; *3*) baseline reference (BASE) condition. The rCBF for the ATT condition at that coordinate is also included. The mean normalized rCBF values and SE are given for the peak activation (specified in terms of Talairach coordinates). Bars: SE.

TABLE 2. *Comparison of ATT vs. PRE: foci of significant (P < 0.001) increases of rCBF in ATT*

Area Activated	Extent of Area Activated (Relative to PC-PC Plane), mm	Talairach Coordinates of Peak Activation	z Score of Peak Activation	Increase in Normalized rCBF, %
Prefrontal cortex				
Areas 46, 9 (L)	+16 to +32	−30, 22, 20	3.92	3.53
Cingulate cortex				
Areas 24, 32 (R)	+28 to +36	18, 10, 28	3.41	4.96

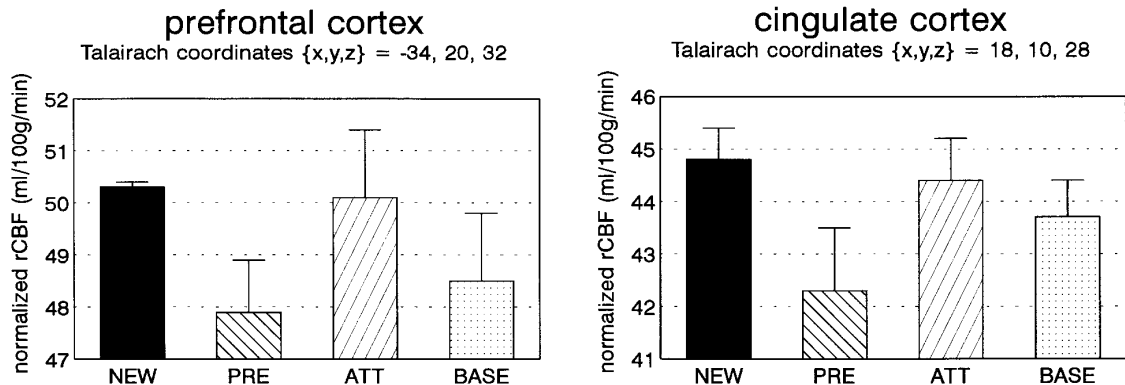ATT, attention task; for other abbreviations see Table 1.

FIG. 4. Graphs illustrating changes of rCBF across 3 conditions: *1*) ATT condition; *2*) PRE condition; *3*) BASE condition. The rCBF for the NEW condition at that coordinate is also included. The mean normalized rCBF values and SE are given for the peak activation (specified in terms of Talairach coordinates). Bars: SE.

depressed compared with the BASE condition during performance of the PRE task (Fig. 3).

The study differs from the earlier one (Jenkins et al. 1994) in that we used a more sensitive method and improved the methods for anatomic localization. Given the higher sensitivity, we found that there was activity in the region of the

TABLE 3. *Comparison of NEW vs. ATT: foci of significant (P < 0.001) increases of rCBF in NEW*

Area Activated	Extent of Area Activated (Relative to AC-PC Plane), mm	Talairach Coordinates of Peak Activation	z-Score of Peak Activation	Increase in Normalized rCBF, %
Prefrontal cortex				
Areas 10, 46, 9 (L)	−4 to +36	−30, 40, 20	4.66	2.83
Areas 10, 46, 9 (R)	0 to +40	34, 28, 28	7.02	5.50
Cingulate cortex				
Area 32 (L)	0 to +44	−2, 16, 44	5.28	2.93
Area 32 (R)	−8 to +40	18, 34, −4	5.74	5.11
Premotor cortex				
Area 6 (L)	+56 to +64	−22, −6, 60	4.05	2.59
Area 6 (R)	+44 to +64	24, 4, 56	6.85	5.62
Parietal cortex				
Areas 7, 40 (R)	+32 to +52	38, −50, 36	6.57	5.38
Insula (R)	−8 to +20	30, 20, 12	6.38	3.82
Basal ganglia				
Caudate nucl. (L)	+4	−6, 18, 4	3.41	2.26
Caudate nucl. (R)	+4 to +16	10, 4, 12	4.03	3.13
Thalamus				
Dorsomedial (L)	0 to +8	−4, −22, 8	5.25	3.43
Dorsomedial (R)	+12 to +16	6, −20, 12	5.05	3.41
Ventroanterior (R)	+4 to +8	6, −4, 8	4.09	3.11
Cerebellum				
Vermis	−32 to −28	2, −62, −32	4.20	2.29

For abbreviations see Tables 1 and 2.

TABLE 4. *Comparison of NEW vs. BASE: foci of significant (P < 0.001) increases of rCBF in NEW*

Area Activated	Extent of Area Activated (Relative to AC-PC Plane), mm	Talairach Coordinates of Peak Activation	z Score of Peak Activation	Increase in Normalized rCBF, %
Prefrontal cortex				
Areas 10, 46, 9 (L)	+8 to +28	−28, 44, 8	4.09	3.50
Areas 10, 46, 9 (R)	−4 to +40	32, 30, 28	6.93	5.76
Cingulate cortex				
Areas 24, 32 (L)	+28 to +36	−6, 4, 32	3.32	2.62
Areas 24, 32 (R)	−4 to +40	10, 16, 36	5.28	2.85
Premotor cortex				
Area 6 (L)	+48 to +64	−28, −14, 64	5.33	6.13
Area 6 (R)	+32 to +68	18, −4, 60	7.84	5.97
SMA				
Area 6 (L)	+52 to +68	−4, −4, 52	6.20	4.15
Area 6 (R)	+64	4, −10, 64	5.60	4.22
Motor cortex				
Area 4 (L)	+36 to +56	−32, −26, 52	6.69	6.79
Parietal cortex				
Areas 7, 40 (L)	+40 to +48	−34, −32, 48	6.63	6.36
Areas 7, 40 (R)	+28 to +56	30, −58, 40	6.85	5.45
Insula (R)	0 to + 20	28, 14, 12	6.98	4.06
Basal ganglia				
Caudate nucl. (R)	+8 to +16	12, 10, 16	3.68	2.73
Putamen (L)	+4 to +8	−22, 14, 4	3.24	1.96
Putamen (R)	−4 to +8	22, 12, 8	6.75	3.89
GP (L)	0 to +4	−16, −6, 0	4.75	2.23
GP (R)	0 to +4	18, −2, 0	3.27	1.41
Thalamus				
dm,va (L)	+0 to +16	−8, −24, 0	6.04	3.59
dm,va (R)	+4 to +12	6, −24, 12	6.43	4.07
Cerebellum				
Vermis	−36 to −16	14, −58, −32	6.08	3.12
Nuclei (L)	−28 to −24	6, −60, −24	6.68	3.25
Hemisphere (L)	−40 to −24	−28, −58, −32	5.66	3.80
Hemisphere (R)	−40 to −24	24, −56, −28	5.01	3.59

BASE, baseline condition; SMA, supplementary motor area; dm, dorsomedial; va, ventroanterior; for other abbreviations see Table 1.

TABLE 5. *Comparison of PRE vs. BASE: foci of significant (P < 0.001) increases of rCBF in PRE*

Area Activated	Extent of Area Activated (Relative to AC-PC Plane), mm	Talairach Coordinates of Peak Activation	z Score of Peak Activation	Increase in Normalized rCBF, %
Cingulate cortex				
Areas 23, 24 (L)	+24 to +36	−20, −38, 28	4.45	2.97
SMA				
Area 6 (L)	+52 to +68	−2, −16, 64	3.66	2.75
Premotor cortex				
Area 6 (L)	+52 to +56	−14, −20, 56	4.20	3.28
Motor cortex				
Area 4 (L)	+40 to +64	−20, −32, 48	5.95	3.96
Parietal cortex				
Areas 7, 40 (L)	+32 to +56	−22, −34, 44	5.69	4.07
Basal ganglia				
Putamen (L)	−4 to +8	−24, −10, 0	4.86	2.41
Cerebellum				
Vermis	−32 to −16	2, −62, −20	5.27	2.52
Nuclei (R)	−24 to −20	10, −52, −24	6.23	2.87
Hemisphere (L)	−28 to −20	−32, −54, −28	3.53	2.10
Hemisphere (R)	−36 to −20	18, −54, −36	3.50	4.62

For abbreviations see Tables 1 and 4.

dorsomedial nucleus during new learning (NEW vs. PRE, NEW vs. BASE) but not during automatic performance (PRE vs. BASE). The dorsomedial thalamic nucleus is heavily and reciprocally interconnected with the prefrontal cortex (Giguere and Goldman-Rakic 1988; Tobias 1975). The loop connecting the dorsomedial nucleus and the dorsal prefrontal cortex may be involved in the process by which information is held in working memory.

The results also differ from those of the earlier study in that we found that there was more activity in the caudate nucleus and globus pallidus when subjects learned new se-

quences compared with performance of the prelearned sequence (NEW vs. PRE, NEW vs. BASE). When the task was performed automatically, there was activation posteriorly in the putamen but no activation in the caudate nucleus (PRE vs. BASE).

Other PET studies have also reported changes in the activation of the basal ganglia during motor learning. Roland et al. (1991) scanned subjects while the subjects practiced a complex sequence of finger movements. The sequence was taught before scanning, and scans were then taken early in practice, when learning was advanced, and when the perfor-

TABLE 6. *Comparison of ATT vs. BASE: foci of significant (P < 0.001) increases of rCBF in ATT*

Area Activated	Extent of Area Activated (Relative to AC-PC Plane), mm	Talairach Coordinates of Peak Activation	z Score of Peak Activation	Increase in Normalized rCBF, %
Cingulate cortex				
Area 24/32 (L)	+12 to +44	−8, −18, 44	5.70	3.81
Area 24 (R)	+24 to +32	2, −2, 32	4.51	3.40
SMA				
Area 6 (L)	+48 to +72	−8, −18, 60	6.15	4.83
Premotor cortex				
Area 6 (L)	+56 to +64	−14, −20, 56	6.54	5.23
Area 6 (R)	+44 to +64	24, −12, 52	3.69	3.06
Motor cortex				
Area 4 (L)	+36 to +64	−34, −32, 48	7.35	7.48
Area 4 (R)	+32 to +44	44, −22, 40	3.12	1.92
Parietal cortex				
Areas 7, 40 (L)	+28 to +44	−36, −30, 44	7.36	7.13
Areas 7, 40 (R)	+36 to +56	18, −66, 48	3.76	2.69
Insula (R)	+12 to +16	30, 4, 12	3.26	1.57
Basal ganglia				
Putamen (L)	+4 to +12	−24, −6, 4	4.94	2.74
GP (L)	−4 to 0	−20, −4, 0	5.36	2.36
Cerebellum				
Hemisphere (L)	−40 to −28	−30, −54, −36	4.61	3.12
Hemisphere (R)	−44 to −36	20, −54, −36	4.01	3.15
Nuclei (L)	−32 to −28	−28, −56, −32	3.96	2.46
Nuclei (R)	−32 to −24	14, −48, −24	6.86	3.06
Vermis	−32 to −8	10, −50, −20	6.95	3.46

For abbreviations see Tables 1, 2, and 4.

mance was skilled. Activity in the lentiform nucleus was depressed early in practice, and less so as the task became more skilled.

Grafton et al. (1992, 1994) reported an increase in the activity of the putamen when subjects learned a visual tracking task. In Grafton et al. (1994) it was also shown that the activity in the putamen was related to learning on day 2.

The present study differs in two respects. First, the rate of movements was controlled by a pacing tone. In the studies mentioned above the rate of movement was not controlled. Although in the studies by Grafton et al. (1992, 1994) the target moved at a constant rate, this is not evidence that the subjects made the movements at a constant rate.

The present study also differs in that the scans were taken while the subjects learned what to do. In the studies by Roland et al. (1991) and Grafton et al. (1992, 1994) the subjects knew what to do, and were scanned at different stages of practice. In the present study the subjects learned which moves to make.

Grafton et al. (1995) studied the serial reaction time task, in which subjects improve their response times as the sequence repeats. The authors found activity in the putamen that was related to learning. This was true even though the subjects were unaware that the sequence repeated because they were required to perform a secondary task at the same time. As in the present study, the number of movements was the same in all scans.

Attention to action

The changes of rCBF in the ATT condition were compared with the automatic performance of the same prelearned sequence (ATT vs. PRE). The most robust activations in this comparison were found in the left prefrontal cortex and in the right anterior cingulate cortex (areas 32 and 24). There was a trend for activation in the caudate nucleus that was almost significant at the level of omnibus $P < 0.001$. There were trends for other areas, but the cortical changes were the more robust.

The dorsal prefrontal cortex was significantly activated in the ATT versus PRE comparison but not in the ATT versus BASE comparison. It will be seen from Fig. 4 that there was a tendency for the rCBF to be higher in the BASE condition than during the PRE task. It is not clear why this was so. One possibility is that there is a depression in prefrontal activity when subjects perform a task automatically. Another is that during a BASE condition subjects are alert and engaged in thought. A more appropriate control condition would have been to require the subjects to repeat the same movement on each trial.

The peak coordinate for the anterior cingulate cortex for the ATT versus PRE comparison lies more dorsally than for the ATT versus BASE comparison. This suggests that, although the ventral part of anterior cingulate cortex is not activated during the PRE task (PRE vs. BASE), there may be slight, although nonsignificant, activation of this ventral area in that condition. Paus et al. (1996) reviewed studies showing activation of the anterior cingulate cortex, and the review shows peaks both dorsally and ventrally within this area. However, the comparison of the different tasks does not immediately suggest the nature of the functional subdivisions within this area.

The term ''attention to action'' is not precise. To say that subjects must attend to a task is to say that they would be unable to do another task at the same time without interference. Passingham (1996) has shown that when the sequence task is routine and overlearned, the subjects can perform another task, verb generation, at the same time with little interference; but there is considerable interference between verb generation and new learning of a sequence. Evidence that the subjects were performing the task less automatically in the ATT condition comes from the response times. These were slightly longer in ATT than in PRE.

However, to say that the subjects must attend is not to specify which of several mental operations they must perform. The instructions to the subjects were to ''think of the next movement.'' However, although the subjects no longer needed to monitor or remember the outcomes, there is no guarantee that they did not do so. Nonetheless, there is independent evidence that the prefrontal cortex can be activated when subjects attend to movement preparation. In a recent experiment (Krams, Rushworth, and Passingham, unpublished data) we found activation of the left dorsal prefrontal cortex (−46, 28, 28) when subjects were required to prepare for 3 s to move a finger, attending to the finger all the time. In one condition (''execution'') the subjects responded as soon as a finger was marked on a photograph of a hand on a screen, and in another condition (''preparation'') the subjects had to wait 3 s before responding. However, the prefrontal cortex was not activated in a related study (Deiber et al. 1996). An important difference between the studies is that in the study by Krams et al., subjects were specifically instructed to attend to the finger during the delay.

The activation in the present study was in the left dorsal prefrontal cortex. This was true also in the study by Krams et al., even though in that study the subjects moved the fingers of the left hand. Kimura (1993) has proposed that the left hemisphere is specialized for the higher direction of hand movements, and these results are supportive of that view. The activation of the anterior cingulate cortex was on the right for the ATT versus PRE comparison. However, it would be unwise to place too much emphasis on this, because this area was activated bilaterally for the ATT versus BASE comparison.

Others have compared implicit and explicit learning, and have shown that the prefrontal cortex is activated when subjects are aware that there is a task to be solved. Doyon et al. (1996) used the serial reaction time task, and they reported that the prefrontal cortex was activated when subjects were asked to anticipate the next move in the sequence. Grafton et al. (1995) used the same task, and they found that the dorsal prefrontal cortex and anterior cingulate areas 32 and 24 were more activated in subjects who became aware of the sequence than in subjects that did not.

There is also an indication in the present experiment that the subjects were attending to the fingers. There was an increase in activation of the primary sensory cortex when subjects attended to the prelearned sequence versus they did not (ATT vs. PRE) ($P < 0.01$). This may reflect an increase in attention to the feel of the keys and finger movements. Meyer et al. (1991) showed that there was an enhancement

in the activity of the somatosensory cortex when subjects attended to the feel of a vibrator on the finger, and Pardo et al. (1991) also found activation of the parietal somatosensory and association cortex when subjects attended to external stimulation of a toe.

Further experiments are required to clarify the differential contributions of the prefrontal cortex and cingulate areas 32 and 24. Others have proposed in the past that the prefrontal and anterior cingulate cortex might be involved in attention to action (Knight 1994; Mesulam 1990, 1994; Shallice 1988; Vogt et al. 1992). The present study provides evidence that these areas are activated when subjects attend to the actions they are about to perform. Posner and Petersen (1990) have reviewed other evidence from PET that the anterior cingulate cortex plays an important role in attention to action. One clue is provided by the finding that the anterior cingulate but not the dorsal prefrontal cortex is activated during performance of the ''Stroop'' task (Pardo et al. 1990). On this task subjects must attend to a stimulus dimension and inhibit responses (Taylor et al. 1994), but there is no requirement that the subjects prepare responses or manipulate responses in memory.

The parietal association cortex was also activated in the ATT condition (ATT vs. BASE). However, these areas were not differentially activated in the comparison of ATT versus PRE. Parietal area 40 is activated during response preparation, whether subjects are explicitly instructed to attend to their responses (Krams et al., unpublished data) or not (Deiber et al. 1996). The ATT versus BASE comparison therefore reveals the contribution of this area to response preparation. However, the fact that there was no difference for ATT versus PRE suggests that this area is not specifically involved in attention to responses. Corbetta et al. (1993) have shown with the use of PET that the parietal association cortex is activated when subjects attend to the left or right visual space. The subjects fixated a central spot, but in the attention condition they covertly attended to one side of visual space because all the targets they had to identify appeared on the same side in any particular run. In the present study the subjects attended to their actions, not to a point in visual space.

The present results suggest that there is a functional dissociation between anterior and posterior areas involved in attention. The anterior system (prefrontal and cingulate cortex) seems to be more engaged when subjects pay attention to action, whereas the posterior system is more engaged when subjects direct attention toward extrapersonal space or sensory events. The results are consistent with proposals made in the past concerning differences between the anterior and posterior attentional systems (Mesulam 1990; Posner and Raichle 1994; Shallice 1988).

New learning and attention

New learning involves several processes, of which attention to action is only one. There was more activity in the prefrontal cortex and anterior cingulate cortex (areas 32, 24) when subjects learned new sequences compared with attending to a prelearned sequence (NEW vs. ATT).

The activation could reflect greater attention to response preparation than in the ATT condition. However, in new learning there are also operations that need not be performed if subjects are simply required to ''think of the next response'' as in the ATT condition. For example, the subjects must generate new moves, monitor the outcomes, and remember the moves that proved correct. These are also operations that demand attention. This is true in the operational sense that there is interference if subjects are required to learn a new sequence at the same time they are generating verbs (Passingham 1996). New sequence learning is a nonroutine task. In this sense, the activation of the dorsal prefrontal cortex for NEW versus ATT may reflect the greater attentional demands. However, to further the analysis it is necessary to specify what operations must be performed that are nonroutine.

The prefrontal cortex and anterior cingulate area 32 are activated when subjects generate new moves, deciding what to do (Deiber et al. 1991; Frith et al. 1991; Jueptner et al. 1997; Playford et al. 1992) or when to do it (Jahanshani et al. 1995). When subjects learn new sequences, they also monitor and mentally rehearse the sequence. Stephan et al. (1995) have reported more activity in the dorsal prefrontal cortex when subjects imagine moving a joystick compared with when they actually execute the movement. The subjects decided between directions each time they heard a pacing tone, but in the imagination condition the subjects carried out the movement in their head. Petrides et al. (1993) have also shown that the dorsal prefrontal cortex is activated when subjects rehearse a list of items in their head; this task also required the subjects to monitor their own performance and manipulate items in memory (Owen et al. 1996). Thus it is likely that the rehearsal of a series of movements contributes to the activation of the prefrontal cortex during new learning (NEW vs. PRE).

The present experiment does not distinguish the contributions of each of these operations to the activation of the dorsal prefrontal cortex. In the companion paper (Jueptner et al. 1997) we start this analysis by comparing trial and error learning with the generation of new moves on each trial.

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