

Anatomy of Motor Learning. II. Subcortical Structures and Learning by Trial and Error

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

Jueptner, M., C. D. Frith, D. J. Brooks, R.S.J. Frackowiak, and R. E. Passingham. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. *J. Neurophysiol.* 77: 1325–1337, 1997. We used positron emission tomography to study motor learning by trial and error. Subjects learned sequences of eight finger movements. Tones generated by a computer told the subjects whether any particular move was correct or incorrect. A control condition was used in which the subjects generated moves, but there was no feedback to indicate success or failure, and so no learning occurred. In this condition (free selection) the subjects were required to make a finger movement on each trial and to vary the movements randomly over trials. The subjects had a free choice of which finger to move on any one trial. On this task there was no systematic change in responses over trials and no change in the response times. Two other conditions were included. In one the subjects repetitively moved the same finger on all trials and in a baseline condition the subjects heard the pacing tones and auditory feedback but made no movements. Comparing new learning with the free selection task, there was a small activation in the right prefrontal cortex. This may reflect the fact that in new learning, but not free selection, the subjects rehearse past moves and adapt their responses accordingly. The caudate nucleus was strongly activated during new learning. It is suggested that this activity may be related either to mental rehearsal or to reinforcement of the movements as a consequence of the outcomes. The putamen was activated anteriorly on the free selection task and more posteriorly when the subjects repetitively made the same movement. It is suggested that the differences in the location of the peak activation in the striatum may represent the operation of different corticostriatal loops. The cerebellar nuclei (bilaterally) and vermis were more active in the new learning condition than during the performance of the free selection task. There was no difference in the activation of the cerebellum when the free selection task was compared with repetitive performance of the same movement. We tentatively suggest that the basal ganglia may be involved in the specification of movement on the basis of memory of either the movements or the outcomes, but that the cerebellum may be more directly involved in changes in the parameters of movement execution.

INTRODUCTION

In the companion paper (Jueptner et al. 1997) we compare the learning of a motor sequence with performance of a prelearned sequence. The sequence task differs from that used by other authors (Doyon et al. 1996; Grafton et al. 1994, 1995) in that the subjects learned the sequences by trial and error. On each trial the subjects were required to try one finger, and the computer told the subjects whether that move was or was not correct at that point in the se-

quence. Thus the subjects had to monitor and remember the outcomes of particular moves and use this information to learn the sequence.

The aim of the present experiment was to identify the brain areas that are involved in learning by trial and error. New learning of sequences was compared with a condition in which the subjects generated moves on each trial but in which no learning occurred. In the latter condition the subjects were required to generate a random sequence of finger movements. This “free selection” (FREE) task is like the new learning (NEW) task in that the subjects make new decisions on each trial as to what finger to move. Furthermore, to achieve a random series, subjects must keep track of previous movements and attend to what they are doing. The FREE task differs from the NEW task in that subjects do not have to monitor or remember the outcomes of past moves, and no learning occurs, and in that there is no systematic change in moves or the response times of moves over time.

In the present experiment the NEW condition was therefore compared with performance of the FREE task. The subjects were also tested in a condition in which they performed the same movement on all trials. Comparison of the FREE task with this repetitive (REP) condition identifies those areas that are involved in the selection of movements (Deiber et al. 1991; Playford et al. 1992).

The NEW task differs from sequence learning tasks such as the serial reaction time task (Doyon et al. 1997; Grafton et al. 1995) in that it involves a strong declarative component. Early in learning the subjects can say what some of the moves in the sequence are. Learning is also explicit, whereas with the serial reaction time task, effort is taken to ensure that it should be implicit (Grafton et al. 1995). The task also differs in that early in learning the subjects make errors and there is a decrease in errors over time. It is like the serial reaction time task in that there is a decrease in response time with learning (Jueptner et al. 1997), and when the task is overlearned the subjects may be unable to verbalize the moves (Jenkins et al. 1994).

The hypothesis was that there would be changes in subcortical structures, the basal ganglia, and cerebellum during learning by trial and error. Subcortical changes have been reported that are related to learning when subjects explicitly learn a visuomotor skill (Grafton et al. 1994) or implicitly learn a motor sequence (Doyon et al. 1996; Grafton et al.

1995). In the companion paper we show that there were differences in the basal ganglia and cerebellum between new learning of an explicit sequence by trial and error compared with overlearned performance. However, that study was not designed so as to allow us to dissociate generating responses from learning on the basis of feedback.

METHODS

Subjects

We studied 12 normal male volunteers with a mean age of 29.3 yr (range 20–51 yr). None of these subjects had a history of neurological or psychiatric disease, and none took any medication. All were strongly right-handed as measured by the Edinburgh Handedness Inventory (Oldfield 1971). Each subject gave written consent after the procedures had been fully explained. 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

The general experimental design was the same as in the previous study (Jueptner et al. 1997), and that paper gives further details. In each subject, 12 sequential measurements were made of regional cerebral blood flow (rCBF), with the use of $H_2^{15}O$ as a tracer to reflect neuronal synaptic activity (Jueptner and Weiller 1995). The subjects were scanned while learning new sequences (NEW), during a free selection condition (FREE), while performing repetitive movements of the right middle finger (REP), and during a baseline (BASE) condition.

In the NEW condition the subjects learned a new sequence of key presses eight moves long. The movements were paced by a tone once every 3 s. The subjects learned by trial and error. After each key press, a high or low tone was presented to tell the subjects whether the movement was correct (high) or incorrect (low).

Before scanning, the subjects learned a different sequence of finger movements. The sequence was identical to the prelearned sequence in the previous paper, and that paper gives the experimental details (Jueptner et al. 1997). The subjects practiced this sequence until they made no errors in three subsequent trials. This sequence was taught so as to give the subjects practice in learning; it was not tested during scanning.

In each NEW condition during scanning subjects were given new sequences. The sequences were the same as those used in the previous study (Jueptner et al. 1997). 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.

In the FREE condition, subjects were told to press any key randomly "as if you were tossing a coin each time." The movements were paced at a frequency of one every 3 s. Subjects were instructed not to repeat the same key twice. Before scanning, subjects practiced this task for 2 min.

In the REP condition the subjects were required to press the second of four keys with the middle finger on each trial. The four fingers rested on the keys as in the other conditions.

In the BASE condition the subjects made no movements, but the pacing tone and feedback tones was presented as in the other conditions.

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 head movements during the scans.

The pacing tone and feedback tones were produced by an Amiga computer. The computer also monitored performance of the tasks, that is, key presses, errors, number of omissions, 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. The sequences used in the NEW conditions were identical to those used in the first study. The tasks were performed in the following order: BASE, REP, FREE, NEW, BASE, REP, FREE, NEW, BASE, REP, FREE, NEW.

Data acquisition

The positron emission tomography (PET) scans were performed with the use of a CTI/Siemens 953B PET scanner (CTI, Knoxville, TN). Full details are given in the previous paper (Jueptner et al. 1997). The scanner collects data from an axial field of view of 10.65 cm. To examine the whole brain, we scanned six subjects "high" (including the vertex) and six subjects "low" (including the bottom of the cerebellum).

The complete data set extended from 52 mm below the inter-commissural 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. Radioactivity was administered as a bolus injection of $H_2^{15}O$. First a transmission scan was performed to correct the emission data for attenuation by the tissues of the head. The paradigm was started 30 s before data acquisition and continued for 2 min.

Data analysis

The randomness of key presses in the FREE task was assessed by comparing the subjects' data with a set of random numbers derived from the Cambridge Elementary Statistical tables (Lindley and Miller 1958). Redundancies were calculated for the occurrence of single key presses, couplets (e.g., 13, 23, etc.), triplets, or quadruplets. A redundancy of 2 indicates that the sequence was random. A redundancy of 0 implies that the next movement can be predicted with complete certainty from the previous movements. These calculations were performed on a MacIntosh computer with the use of the algorithm described by Attneave (1959).

All matrix operations 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 (MRC Cyclotron Unit, Hammersmith Hospital, London, UK; Frackowiak and Friston 1994) in the Matlab environment (Mathworks, Sherborn, MA). The scans were corrected for involuntary movement artefacts with the use of realignment to the first corrected image (Woods et al. 1992). All images were then transformed into the standard anatomic space (Talairach and Tournoux 1988) and reoriented to the intercommissural line (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 (Friston et al. 1990). Blood flow changes between the conditions were then 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 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 at the lower significance level of $P < 0.01$. 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.

The significant increases of rCBF were calculated with reference to the atlas of Talairach and Tournoux (1988). The foci of maximal change in rCBF were identified for each area. For further anatomic reference, the SPM{t} maps were superimposed onto a group MRI derived from six subjects as described previously (Jueptner et al. 1997). The results are shown in transverse sections with the left side of the image being the left side of the brain (left is left and right is right).

RESULTS

Task performance

During scanning, none of the subjects made omissions during any of the tasks; thus the number of key presses was identical for all subjects and all conditions. During new learning, four subjects learned one of the three sequences to criterion before the end of the scan. Three subjects learned two sequences, whereas another two subjects learned all three sequences before the end of the scan. Three subjects failed to learn any of the three sequences to criterion before the end of the scan. The mean errors during sequence learning were 9.3 on trial 1, 5.1 on trial 2, and 3.3 on trial 3.

The mean response times were 677 ± 250 (SD) ms for the NEW condition, 517 ± 138 ms for the FREE condition, and 430 ± 30 ms for the REP condition.

On average, subjects completed three trials of a new sequence during each scan. The mean response times were 776 ms on trial 1, 660 ms on trial 2, and 594 ms on trial 3. A significant decrease in response times occurred from trial 1 (776 ± 256 ms) to trial 3 [594 ± 215 ms; $F(2,96) = 4.8$, $P = 0.01$]. This decrease in response times was paralleled by a significant decrease in the number of errors per trial [$F(2,96) = 44.9$, $P = 0.000$] (Fig. 1).

In the FREE condition, on average the subjects completed five trials of eight movements each. No change of response times occurred from trial 1 to trial 5 [$F(4,160) = 0.4$, $P = 0.75$, analysis of variance (ANOVA)]. Subjects pressed all keys equally often (Fig. 1), and the movements were random, as indicated by a redundancy of 1.99 for single key presses.

To further assess the randomness of key presses, we compared the subjects' performance with a completely random data set derived from the Cambridge Elementary Statistical tables (Lindley and Miller 1958). We compared the mean redundancies of the free selection scans with 12 sets of random numbers. No differences in the redundancies for single key presses were found ($t = 1.86$, $df = 22$, $P = 0.08$). There were no differences in the redundancies between these two data sets for couplets ($t = 0.65$, $df = 22$, $P = 0.52$, unpaired t -test), triplets ($t = 0.3$, $df = 22$, $P = 0.70$, unpaired t -test), or quadruplets of key presses ($t = 0.47$, $df = 22$, $P = 0.65$, unpaired t -test).

The subjects did not develop a tendency toward any particular pattern of key presses (e.g., couplets, triplets, or quadruplets). This was assessed by examining changes in the redun-

dancies over the three free selection scans. There were no significant time effects for single key presses [$F(2,33) = 0.06$, $P = 0.94$, ANOVA], couplets [$F(2,33) = 0.31$, $P = 0.73$, ANOVA], triplets [$F(2,33) = 0.61$, $P = 0.55$, ANOVA], or quadruplets [$F(2,33) = 0.33$, $P = 0.72$, ANOVA] of key presses.

NEW versus FREE

Table 1 lists the areas in which there was more activation ($P < 0.001$) in new learning than in the FREE task. In this and all other tables the term "peak activation" refers to the activation that was statistically most robust. Significant relative increases of rCBF at this level were found in the following cortical areas: right prefrontal areas 46 and 9, right medial frontal cortex (area 32), right parietal cortex (areas 7, 40), and right insula. Significant activations were observed in the following subcortical areas: right caudate nucleus, right ventroanterior and dorsomedial thalamus, cerebellar vermis, and cerebellar nuclei bilaterally.

We also analyzed trends as indicated by increases of rCBF at a lower level of significance ($P < 0.01$). There were trends for activation at this level of significance in the right dorsolateral prefrontal area 10 (maximum z score 3.08), right cingulate cortex area 24 (maximum z score 2.81), right lateral premotor cortex area 6 (maximum z score 2.88), left premotor cortex area 6 (maximum z score 2.49), left insula (maximum z score 2.94), and left pulvinar nucleus of the thalamus (maximum z score 2.56).

Figure 2, *top rows* in *A* and *B*, shows the SPM{t} maps for the prefrontal cortex (*A*) and the anterior cingulate cortex (*B*). Figure 3, *top rows* in *A* and *B*, shows the SPM{t} maps for the basal ganglia (*A*) and cerebellum (*B*). Figure 5 shows the increases of normalized blood flow for selected brain areas.

NEW versus REP

Table 2 lists the areas in which there was activation ($P < 0.001$) comparing the NEW with the REP task. There were increases of rCBF at that level in the following cortical areas: dorsal prefrontal cortex (areas 9, 10, 46), cingulate cortex (areas 32, 24), premotor cortex (area 6), the supplementary motor area (SMA), parietal cortex (areas 7, 40), and the left insula. Significant activations were observed in the following subcortical areas: right caudate nucleus; bilateral putamen; left globus pallidus; right thalamus; and cerebellar vermis, nuclei, and hemispheres.

FREE versus REP

Table 3 lists the areas in which there was activation ($P < 0.001$) comparing the FREE with the REP task. There were increases of rCBF at that level in the following cortical areas: left prefrontal (area 10, 46, 9), right prefrontal (9, 10), cingulate (areas 24, 32), premotor, and parietal (areas 7, 40) cortex bilaterally. No significant changes of rCBF were detected in subcortical areas at the significance level of $P < 0.001$.

We also analyzed trends as indicated by increases of rCBF at a lower level of significance ($P < 0.01$). The maximum

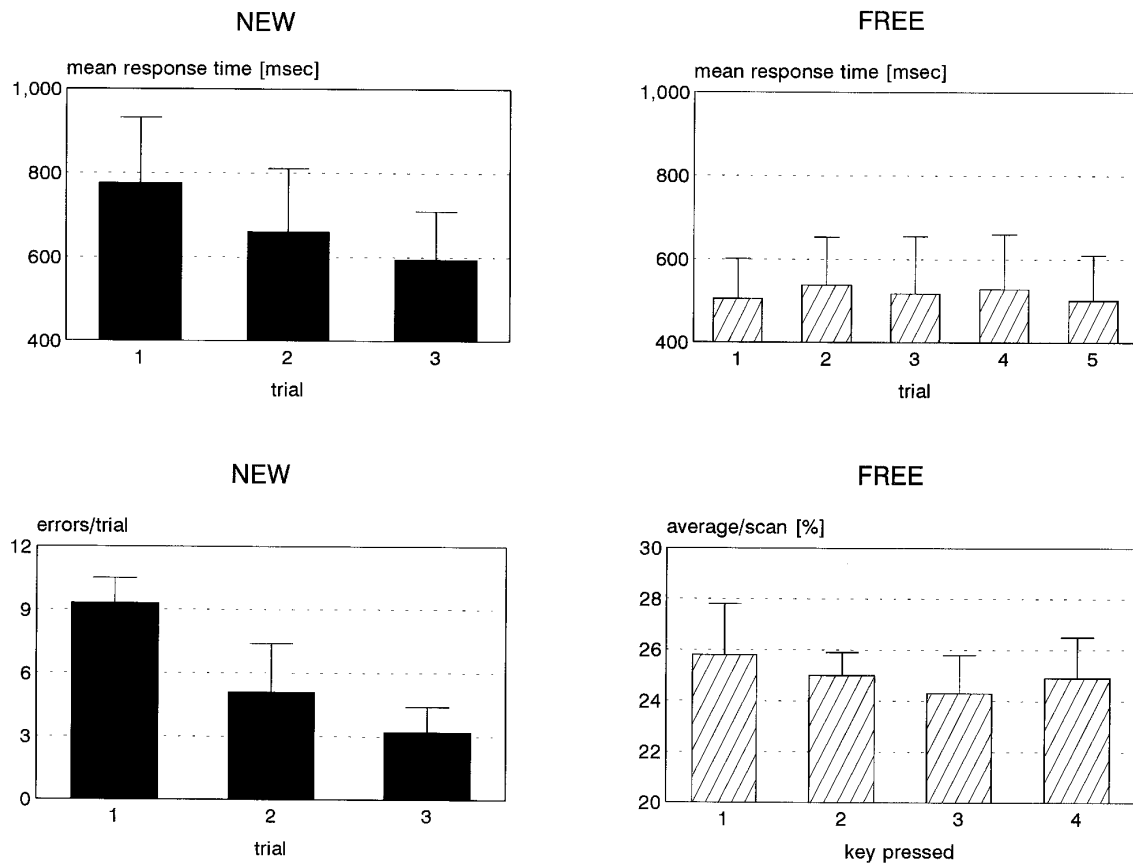


FIG. 1. Graphs illustrating task performance for the new learning (NEW) and free selection (FREE) tasks. Mean response times (reaction time plus movement time) and SD are given. In the NEW condition, subjects were required to learn a sequence of 8 finger movements. The 1st trial was finished when the subjects identified all 8 keys of the sequence for the 1st time. The subjects then returned to the 1st key in the same sequence to perform the next trial. In the NEW condition, the mean response times and the number of errors decreased. In the FREE task, no change in response times occurred; all keys (1 = index, 2 = middle, 3 = ring, 4 = little finger) were pressed equally often.

z scores for these activations are as follows: left insula, 2.90; left anterior putamen, 2.52.

Figure 2, *bottom rows* in *A* and *B*, shows the SPM $\{t\}$ maps for the prefrontal and anterior cingulate cortex (*A*)

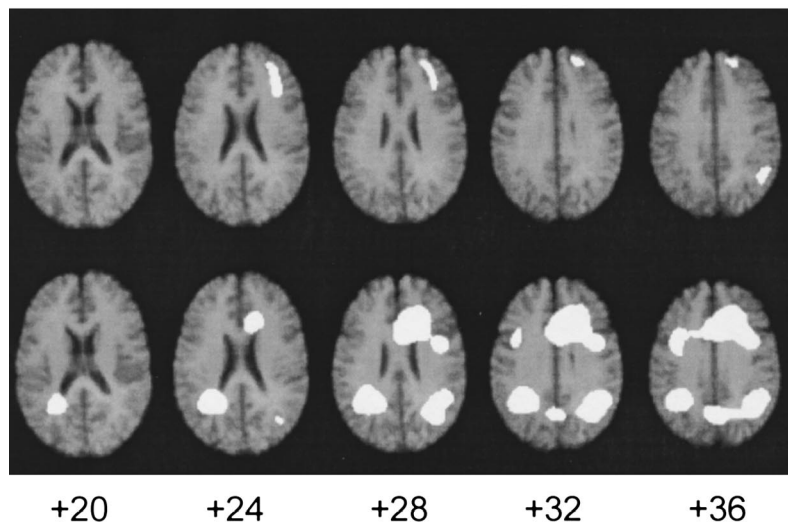
and the premotor and parietal cortex (*B*). Figure 3, *bottom rows* in *A* and *B*, shows the maps for the basal ganglia (*A*) and cerebellum (*B*). Figure 5 shows the increases of normalized blood flow for selected brain areas.

TABLE 1. Comparison of NEW vs. FREE: 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 46, 9 (R)	+16 to +36	26, 36, 24	3.65	3.05
Cingulate cortex				
Area 32 (R)	+40	4, 16, 40	3.89	2.06
Parietal cortex				
Areas 7, 40 (R)	+40 to +44	44, -52, 40	3.72	4.60
Insula (R)	-8 to +8	26, 12, -8	4.45	3.00
Basal ganglia				
Caudate nucleus (R)	-4 to +16	16, 20, 4	3.84	2.73
Thalamus				
Ventral (R)	-4 to 0	2, -12, 0	4.25	2.56
Cerebellum				
Vermis	-32 to -16	8, -44, -28	5.26	4.06
Nuclei (L)	-24	-4, -66, -24	4.95	3.07
Nuclei (R)	-24 to -20	10, -50, -24	4.63	3.24

NEW, new learning; FREE, free selection; rCBF, regional cerebral blood flow; AC-PC, intercommissural; R, right; L, left.

A



B

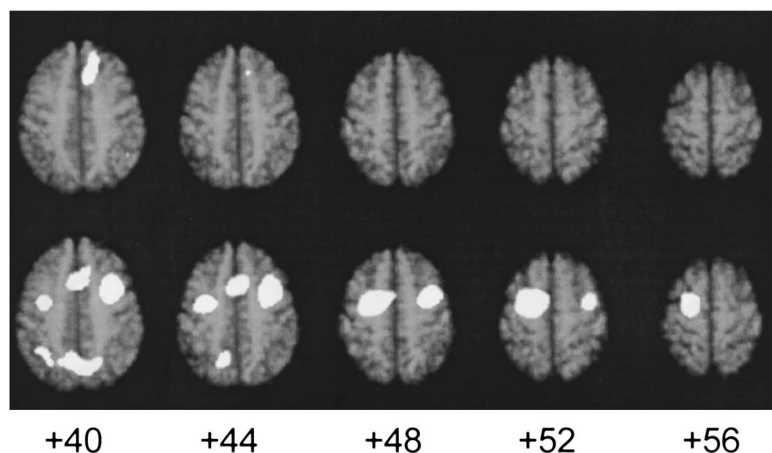


FIG. 2. *Top rows in A and B:* statistical parametric (SPM{t}) maps of significant increases of regional cerebral blood flow (rCBF) in the NEW condition compared with free selection (FREE). *Bottom rows in A and B:* SPM{t} maps of significant increases of rCBF in the FREE condition compared with the repetitive (REP) task. *A:* prefrontal cortex. There was a small difference in activation of the right prefrontal cortex comparing new learning with free selection. *B:* in this comparison, premotor cortex was not significantly activated in NEW vs. FREE at a significance level of $P < 0.001$, but there was a trend at the lower significance level ($P < 0.01$). In Figs. 2–4 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 give a significant peak within that area. The coordinates of these peaks are given in the tables.

NEW versus BASE

Table 4 lists the areas in which there was activation ($P < 0.001$) comparing the NEW task with the BASE condition. There were increases of rCBF at that level in the following cortical areas: prefrontal cortex (areas 9, 10, 46), cingulate cortex (areas 32, 24), premotor cortex (area 6), SMA, motor cortex (area 4), parietal cortex (areas 7, 40), and right insula. Significant activations were observed in the following subcortical areas: right caudate; putamen bilaterally; globus pallidus; thalamus; and cerebellar vermis, nuclei, and hemispheres.

FREE versus BASE

Table 5 lists the areas in which there was activation ($P < 0.001$) comparing the FREE with the BASE condition. There were increases of rCBF at that level in the following cortical areas: right prefrontal cortex (areas 10, 46, and 9), anterior cingulate cortex (areas 32 and 24) bilaterally, premotor cortex bilaterally, left primary motor cortex, parietal

cortex bilaterally, and left insula. Significant increases of rCBF were found in the following subcortical areas: left anterior putamen, cerebellar vermis, and right cerebellar nuclei and hemisphere.

The following trends were found, that is, increases of rCBF at a lower significance level ($P < 0.01$): left prefrontal cortex area 46 (maximum z score 2.45), left prefrontal cortex area 9 (maximum z score 2.37), left cingulate cortex area 23 (maximum z score 3.04), right insula (maximum z score 2.57), right anterior putamen (maximum z score 2.73), left dorsomedial thalamus (maximum z score 3.01), and right ventrolateral thalamus (maximum z score 2.91).

Figure 4 shows the SPM{t} maps for the basal ganglia.

REP versus BASE

Table 6 lists the areas in which there was activation ($P < 0.001$) comparing the REP task with the BASE condition. There were increases of rCBF at that level in the following cortical areas: left cingulate cortex (areas 23 and

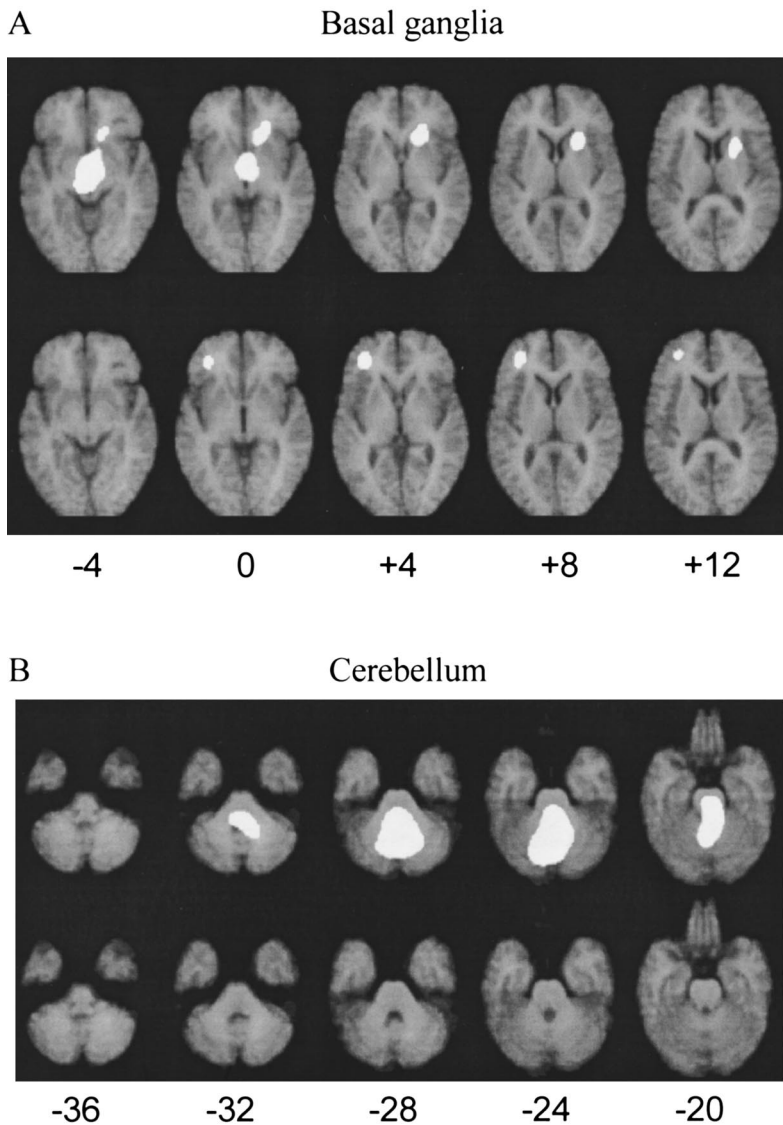


FIG. 3. *Top rows in A and B:* SPM{t} maps of significant increases of rCBF in the NEW condition compared with free selection (FREE). *Bottom rows in A and B:* SPM{t} maps of significant increases of rCBF in the FREE condition compared with the REP task. *A, top row:* significant increase of rCBF in the caudate nucleus and ventral thalamus when subjects learn new sequences (NEW vs. FREE). *B, top row:* significant activations in the cerebellar nuclei for NEW vs. FREE. *B, bottom row:* absence of significant increases of rCBF in the cerebellum when subjects select movements (FREE vs. REP).

24), left motor cortex, left putamen, right cerebellar hemisphere and nuclei, and cerebellar vermis.

The following trends were found, that is, increases of rCBF at a lower significance level ($P < 0.01$): left inferior parietal cortex, area 40 (maximum z score 2.54), left insula (maximum z score 2.66), and right insula (maximum z score 2.87).

Figure 4 shows the SPM{t} maps for the basal ganglia.

DISCUSSION

Task performance

During the NEW condition, the key presses, number of errors, and response times were continuously monitored by the computer. All three parameters reflect the learning process. Of 12 subjects, 9 completed one or more sequences before the end of the scan. Even when subjects did not identify all the moves in a sequence before the end of the scan, there was a significant decrease in the number of errors and the response times. Consequently, we were able to dem-

onstrate changes in performance in terms of key presses, numbers of errors, and response times.

In the FREE condition, subjects were told to press any key ("as if they were tossing a coin each time"). Subjects were instructed not to repeat the same key twice. The analysis of task performance revealed that all subjects obeyed these instructions, as reflected by a redundancy of 1.99. A redundancy of 2 indicates complete randomness, whereas a redundancy of 0 reflects completely stereotyped movements.

Prefrontal cortex

We found activation of the dorsal prefrontal cortex bilaterally during performance of the FREE task (FREE vs. REP) but not during performance of the REP task (REP vs. BASE). The activation on the right in FREE versus REP lies at a laterality that makes the assignment of the activated region uncertain, but it probably represents a sulcal activation of the dorsal prefrontal cortex. There was only a trend ($P < 0.01$) for activation of the left dorsal prefrontal cortex in FREE versus BASE. The accompanying paper (Jueptner

TABLE 2. Comparison of NEW vs. REP: 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 +20	-30, 28, 24	5.00	3.58
Areas 10, 46, 9 (R)	-8 to +36	24, 22, 32	5.79	5.18
Cingulate cortex				
Areas 24, 32 (R)	+24 to +44	4, 16, 36	7.27	4.67
Premotor cortex				
Area 6 (L)	+28 to +60	-36, 2, 36	5.10	3.49
Area 6 (R)	+28 to +60	32, 2, 8	6.22	5.59
SMA				
Area 6 (R)	+48 to +56	4, 14, 48	5.78	5.49
Parietal cortex				
Areas 7, 40 (L)	+28 to +48	-30, -54, 28	5.38	4.13
Areas 7, 40 (R)	+20 to +48	44, -56, 36	6.56	8.42
Insula (L)	+12 to +20	-32, 16, 20	4.07	2.98
Basal ganglia				
Caudate nucl. (R)	+4 to +16	16, 14, 16	3.38	2.96
Putamen (L)	0 to +4	-18, 2, 4	3.82	2.41
Putamen (R)	-4 to +4	18, 2, 4	3.64	2.71
GP (L)	-4	-24, -8, -4	3.55	2.21
Thalamus				
dm,va (R)	0 to +12	4, -14, 0	5.79	3.18
Cerebellum				
Vermis	-36 to -20	-6, -66, -24	5.11	3.18
Nuclei (R)	-28 to -24	14, -54, -28	5.07	3.52
Hemisphere (L)	-32 to -24	-22, -56, -28	3.36	2.39
Hemisphere (R)	-36 to -24	22, -50, -32	3.43	3.25

REP, repetitive movement; SMA, supplementary motor area; GP, globus pallidus; for other abbreviations see Table 1.

et al. 1997) discusses how comparisons with a resting condition may be less sensitive because there is no control over the subjects' attention and the direction of their thoughts.

During both the NEW and the FREE tasks the subjects must generate finger movements and remember the fingers they have moved on previous trials. The remaining activation in the comparison of NEW versus FREE may reflect in part the fact that in new learning the subjects have to remember the outcomes of past moves and adapt their responses accordingly. It is known that the dorsal prefrontal cortex is activated when subjects must hold past responses in memory

and regulate their responses on this basis (Petrides et al. 1993).

The activation for NEW versus FREE was in the right dorsal prefrontal cortex, although the subjects responded with their right hands. Fletcher et al. (1995) have reported right prefrontal activation in retrieval of a verb paired associate task. Fletcher et al. tentatively propose that the right prefrontal cortex may be especially involved in internal verification or monitoring.

The anterior cingulate area 32 was also activated in new learning (NEW vs. FREE). As discussed in the previous

TABLE 3. Comparison of FREE vs. REP: foci of significant ($P < 0.001$) increases of rCBF in FREE

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)	0 to +36	-28, 42, 16	3.56	2.38
Areas 9, 10 (R)	+24 to +36	22, 26, 24	3.30	2.93
Cingulate cortex				
Area 32 (L)	+44 to +52	-2, 4, 48	3.90	3.17
Area 24, 32 (R)	+24 to +40	6, 16, 32	5.92	3.87
Premotor cortex				
Area 6 (L)	+32 to +60	-20, -10, 56	5.18	5.43
Area 6 (R)	+28 to +56	28, 4, 48	4.39	3.73
Parietal cortex				
Areas 7, 40 (L)	+24 to +52	-34, -52, 36	4.27	4.11
Areas 7, 40 (R)	+28 to +44	34, -58, 32	4.02	4.04

For abbreviations see Tables 1 and 2.

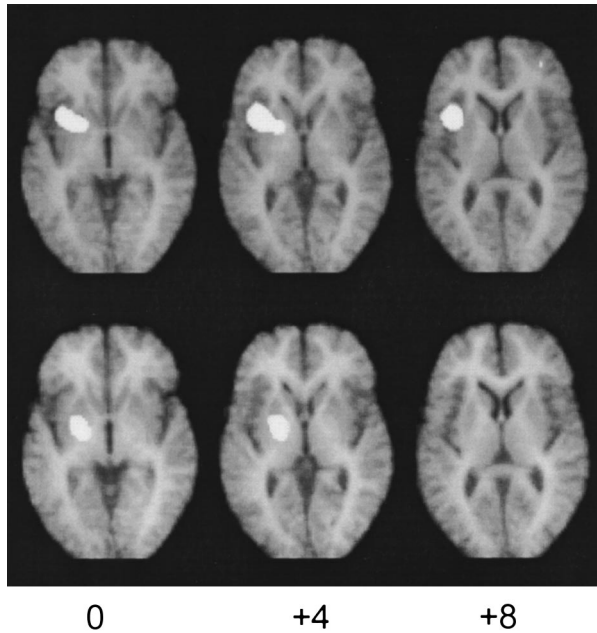


FIG. 4. SPM{t} maps for significant increases of rCBF in the basal ganglia for free selection [FREE vs. baseline condition (BASE)] (top row) and performance of the REP task (REP vs. BASE) (bottom row).

paper (Jueptner et al. 1997), the present experiments do not distinguish between the contributions of the dorsal prefrontal cortex and the anterior cingulate area 32.

Premotor areas

Comparing new learning with free selection, there was a bilateral activation of the lateral premotor cortex (NEW vs. FREE) ($P < 0.01$). In the previous paper we also showed that the lateral premotor cortex was more active during new learning than in performance of prelearned sequences (PRE) (Fig. 1B in Jueptner et al. 1997).

It has been reported in monkeys that there are cells in the lateral premotor cortex that change their activity as the animal learns a visual conditional task (Mitz et al. 1991). The animals had to move a joystick left, right, or down or to withhold a response as instructed by visual cues. The animals were so well trained that they were able to learn new associations within a few trials. Sixty-three percent of the cells in the lateral premotor cortex were activated when these monkeys learned to select movements according to the visual cues.

Mitz et al. (1993) have also scanned human subjects with PET while the subjects learned a visual conditional task. As in the study with monkeys, visual patterns were associated with movement of a joystick in particular directions. Mitz et al. found that there was a negative correlation between

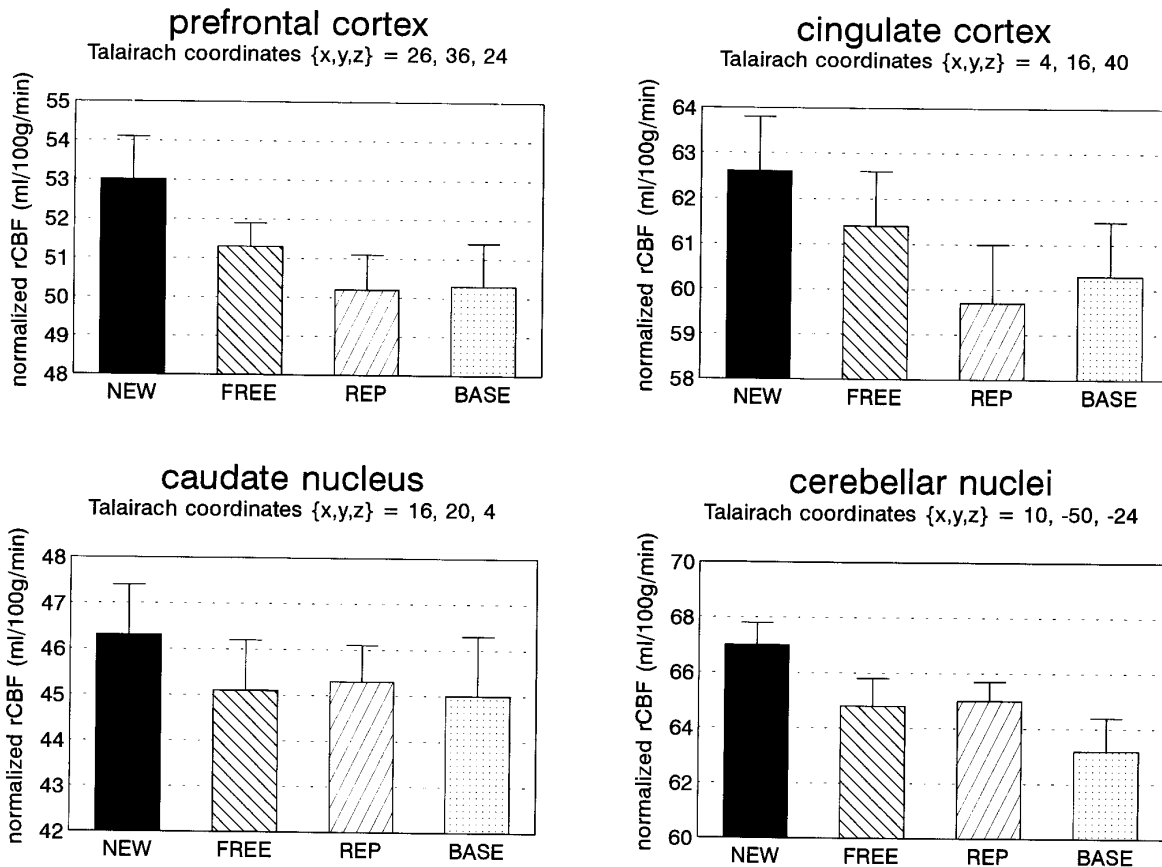


FIG. 5. Graphs illustrating changes of rCBF across the 4 conditions: 1) NEW condition; 2) FREE condition; 3) REP task; 4) BASE condition. The mean normalized rCBF values and SE are given for the peak activation (specified in terms of Talairach coordinates).

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)	+4 to +28	-32, 42, 12	3.89	4.02
Areas 10, 46, 9 (R)	-4 to +36	32, 32, 28	6.34	6.03
Cingulate cortex				
Areas 24, 32 (L)	+24 to +36	-8, 8, 36	3.66	1.89
Areas 24, 32 (R)	-4 to +36	8, 12, 32	4.68	2.65
Premotor cortex				
Area 6 (L)	+44 to +64	-32, -16, 60	5.67	6.85
Area 6 (R)	+36 to +68	16, -8, 60	7.48	6.46
SMA				
Area 6 (L)	+56 to +68	-4, -8, 56	5.62	4.75
Area 6 (R)	+56 to +64	2, -6, 60	6.06	5.22
Motor cortex				
Area 4 (L)	+32 to +60	-36, -24, 48	7.96	8.25
Parietal cortex				
Areas 7, 40 (L)	+36 to +52	-30, -32, 52	5.23	6.03
Areas 7, 40 (R)	+32 to +56	30, -48, 44	5.81	4.82
Insula (R)	+4 to +20	32, 18, 8	5.46	4.44
Basal ganglia				
Caudate nucl. (R)	+12 to +16	12, 12, 12	3.86	3.66
Putamen (L)	0 to +8	-22, 10, 4	3.84	2.08
Putamen (R)	-4 to +4	24, 8, 4	4.78	2.83
GP (L)	0 to +8	-14, -8, 4	3.67	1.83
GP (R)	0 to +4	16, -6, 0	3.48	3.14
Thalamus				
dm,va (L)	+4 to +12	-10, -22, 4	5.38	4.39
dm,va (R)	0 to +12	8, -24, 12	4.84	5.30
Cerebellum				
Vermis	-40 to -12	4, -50, -40	5.13	4.27
Nuclei (L)	-28 to -24	10, -60, -28	5.86	3.06
Hemisphere (L)	-36 to -24	-32, -62, -32	4.76	2.48
Hemisphere (R)	-40 to -24	34, -58, -32	5.51	3.09

BASE, baseline; for other abbreviations see Tables 1 and 2.

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

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 (R)	+4 to +24	22, 26, 24	3.59	3.32
Cingulate cortex				
Areas 24, 32 (L)	+24 to +40	-12, 6, 32	5.59	5.89
Areas 24, 32 (R)	+20 to +36	14, 4, 28	4.44	3.09
Premotor cortex				
Area 6 (L)	+36 to +48	-14, 4, 36	5.85	5.47
Area 6 (R)	+40 to +56	26, -6, 52	4.16	4.67
Motor cortex				
Area 4 (L)	+32 to +64	-18, -10, 56	5.37	5.96
Parietal cortex				
Areas 7, 40 (L)	+28 to +56	-28, -52, 28	3.97	2.97
Areas 7, 40 (R)	+28 to +48	34, -40, 28	3.43	3.18
Insula (L)	0 to +12	-40, 4, 4	4.30	2.68
Basal ganglia				
Putamen (L)	0 to +4	-26, 4, 0	3.52	1.93
Cerebellum				
Vermis	-20 to -16	12, -48, -16	3.70	1.85
Nuclei (R)	-24 to -20	20, -50, -24	5.10	3.34
Hemisphere (R)	-32 to -20	32, -52, -28	4.41	3.19

For abbreviations see Tables 1 and 4.

activity in the lateral premotor cortex and the level of performance. The more practiced the task, the less the activation. This effect has also been reported by Chen and Wise (1995), who taught monkeys visual conditional oculomotor associations and found that many cells in the supplementary eye field showed decreases in activity when the task had been well practiced.

Basal ganglia

Comparing new learning with the FREE task, we found that there was activation of the right caudate nucleus (NEW vs. FREE), and it extended into the more ventral part of the striatum. In the previous paper (Jueptner et al. 1997) we found that, along with the dorsal prefrontal cortex, the caudate nucleus was activated during new learning (NEW vs. PRE task) but not when the sequences had been overlearned (PRE task vs. BASE).

The putamen was activated on the FREE task (FREE vs. BASE) and in new learning compared with performance of the PRE task (Jueptner et al. 1997). However, the putamen was no more activated during new learning than during performance of the FREE task (NEW vs. FREE). Although Grafton et al. (1995) found activation in the putamen that was related to motor learning, in the present study the anterior part of the putamen was also activated in the free selection of movement (FREE vs. BASE) (Fig. 4).

There are several possible interpretations of the results.

1) The first possibility is that the activation of the right caudate in new learning (NEW vs. FREE) reflects the process of permanent storage. This is unlikely because the caudate was not active during overlearned performance (PRE task vs. BASE).

2) The second possibility is that the right caudate activation reflects the mental rehearsal of the sequence or preparation for the next move in the sequence. Grafton et al. (1995) reported decreasing activation of the caudate with learning when subjects performed the serial reaction time task under conditions in which subjects could become aware that the sequence repeated. However, Logan and Grafton (1994) also reported activation of the caudate nucleus during eye blink conditioning, although the activation did not change with learning. In this task learning is explicit but although it involves preparation of responses, there is no mental rehearsal.

The dorsal prefrontal cortex sends a heavy projection to the caudate (Selemon and Goldman-Rakic 1985), and it is known that the prefrontal cortex is activated when subjects remember lists of items (Petrides et al. 1993). Furthermore, in the previous experiment (Jueptner et al. 1997) there was a trend for activation of the caudate ($P < 0.01$) when subjects prepared for the next movement.

3) A third possibility is that the activity in the right caudate is related to the process of reinforcement. The activation extended into the more ventral part of the striatum. Doyon et al. (1996) have reported activation of the ventral striatum on a serial reaction time task, but the activation was demonstrated when the task was highly practiced, not during new learning. Similarly, Grafton et al. (1995) reported an increase in the activation of the ventral striatum with learning as subjects practiced the serial reaction time task.

Electrophysiological studies have shown that there are cells in the striatum that change their firing during learning (Aosaki et al. 1994b; Tremblay et al. 1994). Aosaki et al. (1994a) have also shown that these changes fail to occur if dopamine is depleted in the striatum. Schultz et al. (1992) have also reported that many cells in the ventral part of the striatum are sensitive to reward and signals for reward, and that dopamine cells in the substantia nigra change their sensitivity to reward during learning (Llunberg et al. 1992). It is possible that the reward mechanisms that reinforce learning in animals also operate in human experiments in which the outcomes tell the subject whether the responses are correct or incorrect.

Corticobasal ganglia loops

There is an indication that the primary locus of activation in the basal ganglia changes during learning. This is evidenced when the results of the present experiment are combined with those of the previous one (Jueptner et al. 1997). First, as mentioned above, the caudate is activated during new learning (NEW vs. PRE, NEW vs. FREE), but not when the task has been overlearned (PRE vs. BASE). Second, in new learning (NEW vs. BASE) the peak activation in the putamen lies in front of the VCA line ($y = 14$ on left, $y = 12$ on right), whereas for performance of the PRE task it lies behind the VCA line ($y = -14$) (Jueptner et al. 1997). The REP task is also a simple automatic task, and

TABLE 6. Comparison of REP vs. BASE: foci of significant ($P < 0.001$) increases of rCBF REP

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)	+32 to +44	-14, 4, 36	3.59	2.84%
Motor cortex				
Area 4 (L)	+36 to +48	-48, -24, 44	3.26	3.83%
Basal ganglia				
Putamen (L)	0 to +4	-26, -8, 0	3.63	2.13%
Cerebellum				
Vermis	-20 to -16	12, -48, -16	3.89	2.06%
Nuclei (R)	-24 to -20	16, -48, -20	4.66	2.62%
Hemisphere (R)	-24 to -16	18, -50, -24	4.38	2.99%

For abbreviations see Tables 1, 2, and 4.

again the peak activation lies behind the VCA line ($y = -8$) (Fig. 4). The activation appears, however, to be more extensive for performance of a prelearned sequence (PRE vs. BASE) (Jueptner et al. 1997) than for repetitive movements of the same finger (REP vs. BASE).

It is possible that these differences reflect the operation of different corticobasal ganglia loops. Each frontal cortical area sends projections to a different region of the striatum, and Alexander et al. (1991) have pointed out that the basal ganglia send projections via the thalamus to each of these frontal regions.

In monkeys the prefrontal cortex projects heavily to the caudate nucleus, and the premotor areas to the lateral putamen including the head of the putamen (Kunzle 1975; Selemon and Goldman-Rakic 1985). The heaviest projection from the motor cortex is to the lateral part of the putamen (Kunzle 1975; Percheron et al. 1984). These projections follow the principle that the cortical areas project to the nearest part of the striatum. So prefrontal cortex lies more anterior than the premotor and motor cortex and it projects heavily to the medial striatum (caudate), as well as to the medial putamen. The premotor areas lie in front of the motor cortex and their heaviest projections are to more anterior parts of the putamen, although they also project more posteriorly (Selemon and Goldman-Rakic 1985).

The changes in rCBF in the basal ganglia observed in the present study may be related to changes observed in the cortex. During new learning and free selection, anterior cortical areas are activated (prefrontal cortex, anterior cingulate area 32), whereas these areas are not activated in performance of the PRE task or of a simple task that does not require practice (REP). Similarly, during new learning there was activation anterior to the VCA line (NEW vs. BASE), but during performance of the overlearned sequence the activation lay on the borders between the posterior part of the premotor cortex and the motor cortex (PRE task vs. BASE) (Jueptner et al. 1997).

There appears to be a similar pattern in the basal ganglia. The caudate is activated in new learning, of premotor cortex and the anterior part of the putamen in new learning and in free selection (Fig. 4). These areas are not activated in the PRE or REP tasks.

It is impressive that when the subjects performed the simple REP task the activation was restricted to those motor structures that are linked most directly with the motor cortex, the posterior part of the putamen, and the cerebellum (REP vs. BASE). During performance of the PRE task there was also activation of the posterior SMA (PRE vs. BASE) (Jueptner et al. 1997).

Our findings suggest that more anterior cortical areas are engaged only when the demands of the task are greater, for example when the subjects must attend to what they are doing, must prepare for future responses, or must make new decisions. In such circumstances cortical areas are activated that are less directly linked with the motor cortex. This means that the circuitry is longer, and this has penalties in terms of response time. During new learning the response times are long and variable, whereas when the task is overlearned they are shorter and less variable (Jueptner et al. 1997). Once a task has become automatic, only the posterior executive strips of the motor system are involved in its performance and the anterior strips of the motor system are free to be engaged in a new task.

Cerebellum

Comparing new learning with free selection, we found activation in the cerebellum (NEW vs. FREE). However, there was not even a trend for a difference in activation of the cerebellum when subjects chose between different movements compared with repeating the same movement (FREE vs. REP). Furthermore, in the previous experiment (Jueptner et al. 1997) the cerebellum was not activated when subjects attended to or prepared their actions.

For new learning versus free selection (NEW vs. FREE), the activation was in the vermis and the cerebellar nuclei. Changes in blood flow are thought to be related to synaptic activity (Jueptner and Weiller 1995; Raichle 1987). The activation of the cerebellar nuclei may therefore reflect the activity of the neurons that project to these nuclei, and these include the Purkinje cells of the cerebellar cortex.

The activation in the cerebellum during learning was bilateral whether new learning was compared with free selection (NEW vs. FREE) or prelearned performance (NEW vs. PRE, NEW vs. BASE) (Jueptner et al. 1997). Yet, when subjects moved the right hand without learning (FREE vs. BASE, REP vs. BASE), the activation was in the right cerebellum alone. These results suggest that although the right cerebellum controls movements of the right hand, the whole cerebellum is engaged when subjects learn.

Doyon et al. (1996) have also compared a motor learning condition with a condition in which no learning occurs. Comparing overlearned performance of the sequence with the random condition, there was also more activation in the cerebellar nuclei. Doyon et al. also found more cerebellar activation when they compared new learning of the sequence with their perceptual control condition. However, using a similar task, Grafton et al. (1995) did not report cerebellar activity to be related to learning. Yet Grafton et al. (1994) reported that on a visual tracking task the changes in cerebellar activity were related to learning, and Logan and Grafton (1994) found the same for eye blink conditioning. It is not clear how the discrepancy between the studies is to be explained.

The results of the present paper and the previous one (Jueptner et al. 1997) show that the cerebellum is involved in motor learning. Nonetheless, it is difficult to carry out an experiment that shows conclusively that the activation in the cerebellum represents learning. There may be other changes that accompany learning, for example in coordination (Bloedel 1992; Llinas and Welsh 1993). However, the results of the present experiments are unlikely to be explained in terms of coordination. The movements were spaced at one every 3 s; the task was not like the learning of a rapid scale on the piano. Nonetheless, there are several differences between NEW and FREE, but the design of the present experiment does not identify which of these is correct.

There has been a similar debate in the literature on the effect of cerebellar lesions on motor learning. Circumscribed lesions in the cerebellar cortex (lobule HVI) and cerebellar nuclei abolish the acquisition of the conditioned response (Yeo and Hardiman 1992). There has been controversy as to whether cerebellar lesions affect the unconditioned response (Welsh and Harvey 1989; Yeo 1991). However, Thach et al. (1992) have reported that, despite otherwise normal per-

formance, patients with cerebellar and inferior olive disease are unable to recalibrate the trajectory of an arm throw while wearing wedge prism spectacles.

Other studies indicate that interference with the normal functioning of the cerebellum can affect motor learning but not motor performance. Nagao and Ito (1991) applied hemoglobin subdurally to the flocculus so as to interfere with long-term depression in the parallel fiber synapses (Ito 1989, 1993). Nagao and Ito were able to block the adaptation of the vestibuloocular reflex without affecting the dynamics of the reflex itself. Yanagihara and Udo (1994) have trained decerebrate cats to walk with each paw on a separate treadmill; normal cats can adjust to a change in speed of one of these treadmills. If hemoglobin is applied subdurally, the cats can still walk on the treadmills, but they are poor at adapting to a change in speed (Yanagihara and Udo 1994).

In the previous paper we show that the cerebellum is more active during learning than overlearned performance (NEW vs. PRE) (Jueptner et al. 1997). Ojakangas and Ebner (1992) have recorded from single cells in cerebellar cortex while monkeys adapted to changes in gain in the handle the monkeys moved. Ojakangas and Ebner report that there are changes in simple and complex spikes during the period when the animals make errors. They also report that for many cells there is an increase in activity during initial learning followed by a decrease when the monkey has become proficient.

Basal ganglia and cerebellum

It is one thing to say that the basal ganglia and cerebellum are involved in motor learning or motor memory, but another to identify the roles they play in learning. In the present study we do not distinguish between the contributions made by the basal ganglia and cerebellum to motor learning. During motor learning there were changes in the probability of moving a finger at a particular point in the sequence, and there were also changes in the mean response times and the variability of the response times.

There are indications that the basal ganglia may play a role in the specification of the movement, whether in selection, preparation, or retention of the movement to be performed. Comparing the FREE task with the REP task (FREE vs. REP), there is activation in the basal ganglia ($P < 0.01$) but not the cerebellum. In the FREE task the subjects select which movement to make, whereas on the REP task subjects simply repeat the movement they have been instructed to make. Furthermore, in the previous paper we found that there was activation of the caudate when subjects attended to the next movement on a prelearned sequence: the activation only just failed to reach significance at the level of $P < 0.001$ ($z = 3.08$).

On the other hand, there are indications that the cerebellum is more directly involved with the parameters of movement execution than are the basal ganglia. PET studies have shown that there is a relation between the degree of activation of the cerebellum and the rate of movement (Jenkins et al. 1994) and force of movement (Dettmers et al. 1995). The same studies found no relation between the activation of the basal ganglia and these parameters. These results suggest that cerebellar activity is more closely tied to the execu-

tion of movement than is the activity of the basal ganglia. This suggestion is supported by the finding that microstimulation evokes movements if applied to the cerebellar territory of the thalamus, but not if applied to the basal ganglia territory (Buford et al. 1996; Miall et al. 1993). It would therefore be worth investigating whether the changes in cerebellar activity during motor learning can be related to changes in the parameters such as the timing of movement.

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