

Functional Mapping of Sequence Learning in Normal Humans

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Abstract

■ The brain localization of motor sequence learning was studied in normal subjects with positron emission tomography. Subjects performed a serial reaction time (SRT) task by responding to a series of stimuli that occurred at four different spatial positions. The stimulus locations were either determined randomly or according to a 6-element sequence that cycled continuously. The SRT task was performed under two conditions. With attentional interference from a secondary counting task there was no development of awareness of the sequence. Learning-related increases of cerebral blood flow were located in contralateral motor effector areas including motor cortex, supplementary motor area, and putamen, consistent with the hypothesis that nondeclarative motor learning occurs in cerebral areas that control limb movements. Additional cortical sites included the rostral prefrontal cortex and

parietal cortex. The SRT learning task was then repeated with a new sequence and no attentional interference. In this condition, 7 of 12 subjects developed awareness of the sequence. Learning-related blood flow increases were present in right dorsolateral prefrontal cortex, right premotor cortex, right ventral putamen, and biparieto-occipital cortex. The right dorsolateral prefrontal and parietal areas have been previously implicated in spatial working memory and right prefrontal cortex is also implicated in retrieval tasks of verbal episodic memory. Awareness of the sequence at the end of learning was associated with greater activity in bilateral parietal, superior temporal, and right premotor cortex. Motor learning can take place in different cerebral areas, contingent on the attentional demands of the task. ■

INTRODUCTION

Skills that involve complex sequences of movements are a central feature of human behavior. While the performance of an expert typist may appear effortless, the acquisition of such a skill is demanding and requires extensive practice. Sequence acquisition can occur in a variety of behavioral contexts that may affect the specific learning strategy that will be employed. For example, subjects may be completely unaware of a complex sequence hidden in a long movement cycle, yet show performance gains with practice (Pew, 1974). With additional practice, subjects may develop explicit awareness of the sequence with further gains in performance (Cleeremans, 1993). Conversely, in certain situations, subjects may use declarative strategies at the onset of a motor learning task (Fitts, 1964; Posner & Keele, 1968). Thus, the sequence acquisition can occur as either a nondeclarative process, a declarative process, or both over the course of a learning experience.

Behavioral paradigms have been developed to study the relationship of sequence acquisition, awareness, and

attention. Nissen and Bullemer (1987) introduced the serial reaction time (SRT) task. In this task, stimuli are presented in succession at one of four locations. Subjects are instructed to press keys corresponding to each location. As soon as one response is made, the next stimulus location is illuminated. Thus, the task involves sequential responding to externally cued locations. For separate groups of subjects, the locations of the stimuli were determined either randomly or according to a sequence. For the latter group, Nissen and Bullemer used a 10-element sequence that cycled continuously 10 times. Subjects who received the sequence were considerably faster in responding, thus indicating learning. The role of awareness was not formally tested with this experimental design. Nevertheless, amnesic patients were found to show comparable levels of learning on the reaction time (RT) measure while failing to demonstrate any explicit knowledge of the sequence (Nissen, Willingham, & Hartman, 1989). Thus, it appears that awareness is not a prerequisite for sequence learning of this type.

Nissen and Bullemer (1987) draw a distinction between the contributions of awareness and attention on

sequence learning. In a second experiment, they added a distracter task in which subjects were required to monitor a stream of tones presented concurrently with the SRT task. Under these conditions, no evidence of sequence learning was obtained, either in the subjects' self-reports or from the RT measure of learning. These results suggest that while awareness is not necessary for sequence learning, attention is necessary.

This conclusion was qualified in subsequent research with the SRT. Cohen, Ivry, and Keele (1990) examined the interaction of sequence complexity and attention. They compared two types of sequences. Hybrid sequences were defined as those containing at least one unique pairwise association. For example, in a 6-element sequence, the order might be 1-3-2-4-2-3, where the numbers indicate positions going from left to right. In this sequence, positions 2 and 3 are ambiguous based on pairwise associations: these locations do not consistently predict the next stimulus. Positions 1 and 4 are always followed by the same location. In Hierarchic sequences, there are no unique pairwise associations. In the sequence 1-3-2-1-2-3, each position is followed by different positions at different points in the sequence. Note that the only difference between these two sequences is that a 4 is substituted for a 1 in the Hybrid condition.

This change in sequence structure had dramatic effects on learning. Under single task conditions, the two groups showed similar learning, both on the RT measure and in terms of their explicit knowledge of the sequences. In contrast, when the SRT task was performed with the secondary tone counting task, only those subjects who responded to Hybrid sequences showed evidence of sequence learning. In spite of this clear evidence of learning in terms of a performance measure, these subjects did not report explicit knowledge of the sequences. Cohen et al. concluded that while attention is necessary for awareness, it is not necessary for learning sequences with unique pairwise associations.

The relationship between implicit and explicit memory systems has been discussed extensively (see Squire, 1986). In terms of motor sequence acquisition, it has been proposed that explicit and implicit learning systems may be independent of one another. Willingham, Nissen, and Bullemer (1989) tested subjects with a 10-element Hierarchic sequence. All of the subjects showed substantial learning, but a subgroup demonstrated no explicit knowledge of the sequence. When transferred to a new sequence, these subjects showed no savings in learning when compared to inexperienced subjects. In contrast, positive transfer was observed for those subjects who were aware of the initial sequence. These results suggest that implicit learning is specific to particular sequences, while explicit learning involves a more general capability. It might be concluded that implicit and explicit learning are hierarchically arranged where implicit learning precedes explicit learning. However, in a second study, Willingham et al. (1989) report

low correlations between measures of implicit and explicit learning. For example, implicit learning measures such as the decrease in reaction time on sequence blocks in comparison to random blocks did not predict whether or not subjects developed awareness of the sequence.

Working with the dual task paradigm, Curran and Keele (1993) found additional evidence for the independence of the two systems. First they trained two groups of subjects under single task conditions on a Hybrid sequence. The intentional group of subjects was told that the stimuli would occur in sequence and that they should attempt to learn it; the incidental group was told nothing about the presence of sequence. After the single-task training phase, subjects were asked to report as much of the sequence as they could, and, based on their responses, the incidental group was further divided into a less aware and more aware group. All three groups showed substantial improvement in RT during the sequence blocks, although the less aware groups showed less improvement than the others. However, when the subjects were then asked to perform under dual-task conditions, the three groups exhibited near-identical improvement in the sequence blocks compared to random blocks. Similar results were obtained in a between-subject design in which one group of subjects learned in single-task conditions and a second group with dual-task. Performance differed dramatically during training. But, when the subjects were tested under dual-task conditions, the degree of sequence learning (using an implicit measure) was equivalent for the two groups. Curran and Keele interpreted the differences in the single-task blocks as emerging from the explicit system. However, when the distracter task blocks this system from expressing its knowledge of the sequence, only the implicit system is active and this system had achieved comparable levels of learning during the single-task phase. Furthermore, initial training with Hierarchic sequences without distracter will not produce any transfer when a distracter task is added. This finding is consistent with the conclusion of Cohen et al. that implicit learning does not occur with Hierarchic sequences.

The brain areas where learning-related changes might occur during different types of sequence acquisition are unknown. To further clarify the localization of sequence learning and to investigate the hypothesis that sequence learning can occur in more than one cerebral system, we used positron emission tomography (PET) to identify foci of changing local synaptic activity during the acquisition of movement sequences under two attentional load conditions. The SRT task was first performed under dual-task conditions to isolate the implicit learning system. Following the completion of this phase, the same subjects were tested with a new sequence, without the distracter task. This phase was designed to identify regions involved in the explicit learning of motor sequences. In both phases, the behavioral index of learning

was a decrease in reaction time across blocks. A fixed interstimulus interval was used so that a constant number of movements was made across all blocks of trials. PET scans were acquired every third trial, beginning with the second block of each condition as shown in Figure 1. The PET analysis focused on longitudinal changes of cerebral blood flow as a measure of learning that occurred while there was a change of the performance measure.

RESULTS

Performance

Median reaction times for correct responses became progressively faster over the blocks of trials where a sequence was used. In the dual task condition, the median RT dropped from 386 msec in Block 8 to 353 msec in Block 15 [$t(11) = 2.97, p < 0.02$]. In the single task condition, the median RT on Block 25 was 337 msec, in comparison to 185 msec on Block 32 [$t(11) = 3.55, p < 0.005$]. While both of these decreases were significant, this measure of sequence learning is problematic, especially for the dual task condition. During the dual task phase of the experiment, RTs also decreased over the initial random Blocks (#1-7) [$t(11) = 2.16, p < 0.06$]. This improvement of performance presumably reflects general features of the learning such as the mapping between the stimulus and response locations and a strategy for counting the tones. Note that a similar improvement was not present in the random Blocks (#18-24) of the single task [$t(11) = -2.02, p < 0.07$]. At this point, subjects were well practiced with the general features of the task.

A stronger measure of sequence related learning is obtained by assessing the changes in median RT when the sequence is removed. In the dual task condition, this critical transition occurs between Blocks 15 and 16; in

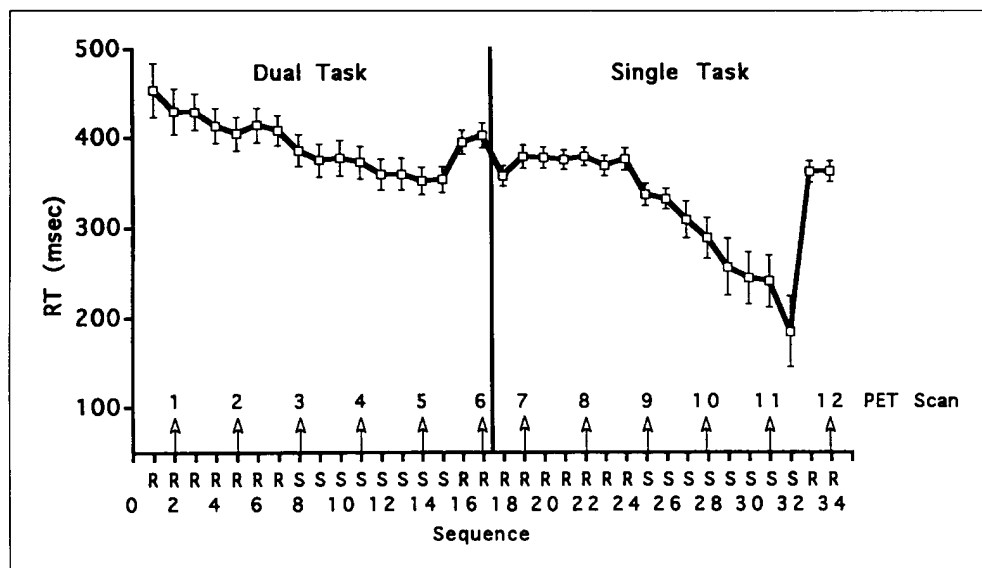
the single task the corresponding transition is between Blocks 32 and 33. For comparison, transition scores were obtained by assessing changes in median RT when the sequence is removed. Transition scores were computed between the median RT on Blocks n and $n - 1$, where $n = \{10...17, 27...34\}$. A Tukey test performed on the resulting scores revealed a significant disruption to performance when subjects switched from a sequence block to a random one. The sequence-random transition was significant whereas no other n versus $n - 1$ differences were significant ($p < 0.01$ for all comparisons in single task; $p < 0.01$ for all comparisons in dual task except for the comparison of sequence to random where $p < 0.02$). Figure 1 demonstrates an increase in median RT with the switch from sequence to random blocks for both the dual and single tasks. This result indicates that the improvement was not simply a general practice effect, but was dependent on the sequential nature of the stimuli and responses. Not surprisingly, improvement was greater in the single task when attention was unrestricted. Responses after learning were completely anticipatory for some subjects in this condition, occurring with a mean latency of under 50 msec.

The mean frequency of mistakes in the dual task was 3.4 and 2.4% for the single task. The mean frequency of mistakes remained below 10% for every block and there was no systematic increase or decrease of mistakes across random or sequence blocks. Tone counting errors were less than 10% for all subjects in the dual task and there were no systematic changes in the frequency of errors over the course of the experiment.

Imaging—Dual Task

Cerebral sites were identified in which rCBF significantly increased or decreased monotonically across the three scans obtained during presentation of sequence blocks

Figure 1. Changes of performance during SRT learning under two attentional loads. Subjects performed the SRT task in the dual-task condition (with attentional interference) followed by the single-task condition (without attentional interference). Seventeen blocks of trials were obtained in each condition using either random stimuli (R) or a hybrid structured sequence (S). Six PET scans were obtained for each condition to identify learning-related changes of rCBF. Learning-related improvements of reaction times are present in both the single- and dual-task conditions.



(PET scans 3, 4, and 5). In the dual-task condition, learning-related increases of rCBF were observed primarily in motor related areas of the left hemisphere, as shown in Figure 2.

The location of these sites in Talairach coordinates and relative statistical significance are summarized in Table 1. Representative sites with increasing activity include the left primary sensorimotor cortex, the supplementary motor area, left prefrontal cortex, left parietal cortex, and bilateral putamen. Some of these sites with learning-related augmentations of activity also demonstrate increased rCBF during execution of a variety of other motor behaviors when compared to scans taken without movement (Roland, Skinhøj, Lassen, & Larsen, 1980; Deiber, Passingham, Colebatch, Friston, Nixon, & Frackowiak, 1991; Grafton, Mazziotta, Woods, & Phelps, 1992;

Grafton, Woods, & Mazziotta, 1993). Together, we refer to these sites as motor effector areas.

The metabolic changes in the motor effector areas and prefrontal cortex during this nondeclarative SRT learning cannot be attributed to changes in the total number of responses since the number of movements was identical across all blocks. Moreover, the change of rCBF in motor effector areas was present only during presentation of structured sequences and not during the initial presentation of random blocks. To confirm this, PET scans 1 and 2 (during presentation of random blocks) were compared with a *t* test and there was no change in any of the sites in Table 1. Only when there was structure in the sequence was there a change of rCBF present in motor effector areas in the dual task condition. Similarly, none of these sites showed simple time-

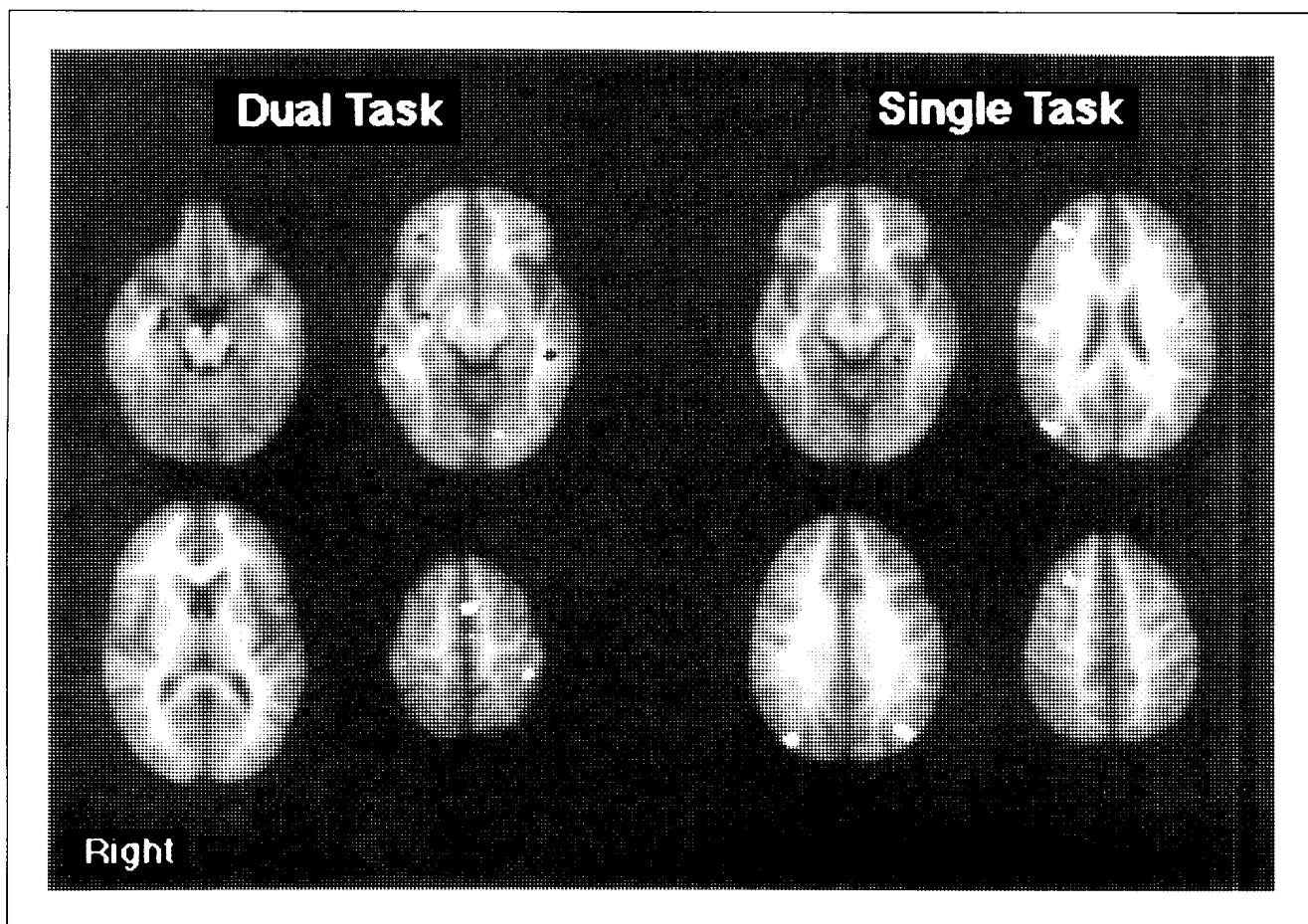


Figure 2. Areas of longitudinally increasing rCBF during learning are displayed in white, decreases are shown in black, superimposed on an MRI reference atlas centered in Talairach coordinate space. Subjects' left is on image right. (Dual Task) Changes of regional cerebral blood flow during motor sequence learning with attentional interference are shown on the left half of the figure. Significance was determined with a repeated measures ANOVA between PET scans 3, 4, and 5. Increasing responses are present in left primary motor cortex (lower right image), supplementary motor cortex (lower right image), and anterior prefrontal cortex (lower left image). Decreases are present in right hippocampus (upper left image) and bilateral temporal cortex (upper right image). Dual-task axial images are at -6, -15, 12, and 57 mm relative to the anterior-posterior commissural axis, starting from top left. (Single Task) Changes of rCBF during motor sequence learning when there is no attentional interference are shown on the right half of the figure. Significance was determined with repeated measures ANOVA between PET scans 9, 10, and 11. In this condition, changes are located primarily in right dorsolateral prefrontal (upper right image), right premotor (lower right image), inferior basal ganglia (upper left image), and bilateral parietal cortex (lower left image). Single task axial images are at -8, 26, 35, and 50 mm relative to the anterior-posterior commissural axis, starting from top left.

Table 1. Motor Sequence Learning with Distraction of Attention^a

Region	Talairach Coordinates (mm)				F omnibus	p value
	x axis	y axis	z axis			
Increasing rCBF						
Left anterior frontal (10)	-12	55	9	29.53	***	
Left sensorimotor cortex	-36	-18	55	20.20	**	
Right putamen	25	-15	9	16.94	**	
Left parietal (40/7)	-36	-37	57	13.16	*	
Left putamen	-27	-15	12	12.44	*	
Supplementary motor area (6)	-1	1	57	9.11	*	
Left lingual gyrus (18)	-12	-79	1	9.11	*	
Decreasing rCBF						
Right hippocampus	27	-12	-15	20.65	***	
Right middle temporal (21)	57	-34	-4	16.24	**	
Left posterior cingulate (31)	-7	-43	40	15.87	**	
Left middle temporal (21)	-49	-36	-10	15.64	**	

^aThe location and significance of all learning-related changes of rCBF are summarized for the dual-task condition, when subjects learned the serial reaction time task with attentional interference from a secondary task. Significance was determined with a repeated measures ANOVA between PET Scans 3, 4, and 5. Approximate Brodmann's areas are in parentheses.

* $p < 0.005$.

** $p < 0.001$.

*** $p < 0.0005$.

related increases of activity when comparing PET scans 1, 2, and 6 with an *f*-omnibus test.

We also tested for longitudinal decrements of rCBF during learning. As summarized in Table 1, decreasing activity was observed in the right hippocampus, bilateral middle temporal cortex, and left posterior cingulate cortex (Fig. 2).

As an additional control, we identified areas that were activated in association with the secondary auditory tone counting task. These were identified by comparing PET scans #2 and 8 (random blocks, dual versus single task). Responses were primarily located in temporal auditory association cortex and inferior occipital cortex, as shown in Table 2. Increasing rCBF changes during dual task sequence learning were not located at sites involved in the tone counting task. In contrast, the decreasing rCBF in bilateral middle temporal cortex during sequence acquisition may be related to time effects of the tone counting task.

Imaging—Single Task

Strikingly, when attention was not diverted by tone counting in the single task condition, metabolic changes occurred in a different set of cerebral areas. Learning-related increases of rCBF between PET scans 9, 10, and 11 were observed in the right dorsolateral prefrontal cortex, right premotor cortex, and bilateral inferior parietal

cortex. Subcortical increase of rCBF was limited to the right inferior putamen/nucleus accumbens (see Fig. 3 and Table 3). Decreasing rCBF during learning was present in the left parietal operculum, left caudate, left superior temporal gyrus in the region of the auditory cortex, and left ventral premotor cortex (Table 3).

No significant increase of rCBF during learning was present in the contralateral motor effector regions in the single task condition. This lack of learning-related changes in motor effector regions in the single task condition may seem surprising. It is unlikely that this null result reflects an order effect (the dual task always preceded the single task) since different sequences were used for each task. There are at least two alternative hypothesis. One, motor effector regions involved in motor sequence acquisition are not activated at all when the task is performed explicitly. This is not likely, however, as shown in Figure 3. Responses in left motor cortex remained elevated at the start of the sequence blocks of the single task. As activity increased in right dorsal prefrontal cortex during learning in the single task there was a concurrent gradual decline in activity in left motor cortex. A more plausible explanation is that increased activity in motor cortex during implicit motor learning is conditional and attenuates when other systems including prefrontal and biparietal cortex are recruited to learn the task with explicit strategies. This is compatible with the findings of Pascual-Leone and co-

Table 2. Secondary Task Effects (Tone Counting)^a

Region	Talairach Coordinates (mm)			% Change of RCBF	<i>t</i> statistic	<i>p</i> value
	<i>x</i> axis	<i>y</i> axis	<i>z</i> axis			
Left cerebellum	-36	-57	-21	3	7.34	***
Right occipital - fusiform (18)	27	-73	-9	2	4.31	*
Left occipital - fusiform (19)	-19	-60	-7	9	4.91	***
Right middle temporal (21)	58	-19	-7	8	7.01	***
Left middle temporal (21)	-60	-16	-9	12	3.66	*
Left inferior occipital (18)	-28	-93	-3	2	4.46	**
Left posterior temporal (39)	-49	-55	16	5	5.23	***

^aLocalization of areas associated with secondary auditory tone counting task. Areas were identified by comparing PET scans 2 and 8 (random blocks, dual task > single task). Significance determined by paired *t* test.

**p* < 0.005.

***p* < 0.001.

****p* < 0.0005.

workers who observed that the increased amplitude and size of responses in motor cortex disappeared as subjects became aware of the sequence (Pascual-Leone, Grafman, & Hallett, 1994). As with the dual task, the changes of rCBF during presentation of the sequence were not present during presentation of the random blocks (PET scans 7, 8) and could not be due to a simple time effect (PET scans 7, 8, and 12).

Awareness of a Sequence

At the end of the experiment, 7 of the 12 subjects reported becoming aware of the sequence during the single task condition with 100% accuracy. The remaining

5 subjects had no knowledge that a sequence was present. When the PET data analysis was restricted to just those subjects with awareness, learning-related changes were again located in the same sites as summarized in Figure 3 and Table 3. In contrast, these areas did not show significant changes in activation when the analysis was restricted to the five subjects who did not become aware of the sequence. By comparing those who were aware with those who were unaware at the end of learning it is possible to identify brain systems involved in explicit representation of the sequence. To do this, PET scan #11 was compared between the 7 aware subjects and 5 unaware subjects with an unpaired *t* test. As summarized in Table 4 and shown in Figure 4, awareness

Figure 3. Changes of rCBF in right dorsal prefrontal and left motor cortex during presentation of sequence blocks in the single- and dual-task paradigms. Motor cortex activity progressively increased during implicit learning in the dual-task paradigm. This level of activity persisted until new sequences were presented in the single task and subjects developed awareness of the sequence structure. Then, motor cortex activity gradually declined. In contrast, prefrontal activity remained constant until sequence blocks were presented without attentional interference, at which point learning-related changes of activity were observed.

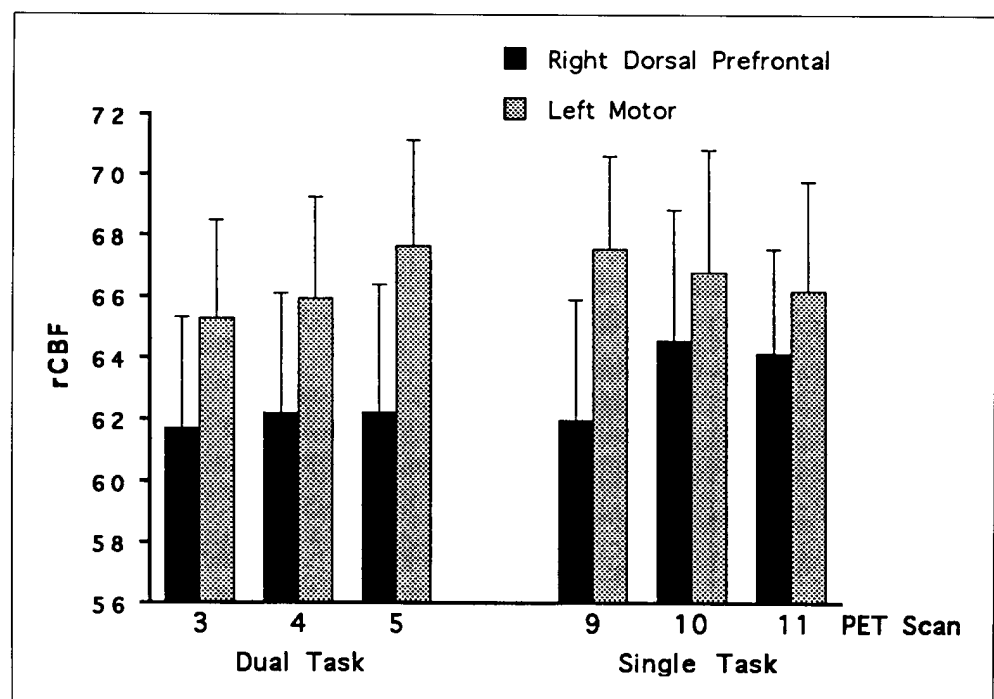


Table 3. Motor Sequence Learning without Distraction of Attention^a

Region	Talairach Coordinates (mm)			F-omnibus	p value
	x axis	y axis	z axis		
Increasing rCBF					
Left parietal/occipital (19/39)	-36	-73	36	30.49	***
Right dorsolateral frontal (46)	31	39	22	23.69	***
Right middle temporal (21)	55	-43	0	22.24	***
Right premotor (6)	37	1	54	16.81	**
Right superior frontal (6/8)	24	15	49	15.65	**
Right N accumbens/putamen	15	15	-7	15.07	**
Right parietal/occipital (19/39)	36	-81	30	13.84	*
Right middle frontal (10)	28	51	13	8.87	*
Decreasing rCBF					
Left parietal operculum (43)	-51	-6	16	29.92	***
Left caudate	-9	15	12	20.57	***
Right hippocampus	21	-16	-12	14.32	*
Left superior temporal (42)	-45	-22	10	13.57	*
Left inferior premotor (6)	-37	-12	30	12.69	*
Right fusiform (37)	28	-58	-13	11.67	*
Left precuneate (7)	-12	-30	54	11.35	*

^aThe location and significance of all learning-related changes of rCBF are summarized for the single-task condition, when subjects performed the serial reaction time task alone. Significance was measured by repeated measures ANOVA between PET scans 9, 10, and 11. Approximate Brodmann's areas are in parentheses.

* $p < 0.005$.

** $p < 0.001$.

*** $p < 0.0005$.

of a sequence recruited bilateral inferior parietal cortex, right premotor cortex, anterior cingulate cortex, and bilateral temporal cortex. In contrast, areas with relatively greater activity in unaware subjects were limited to bilateral superior temporal cortex and insular cortex.

DISCUSSION

The findings of this experiment suggest that sequence learning can occur in different cerebral systems, dependent on the context and attentional demands of the learning task. When attention is diverted by a counting task, learning occurs implicitly. In contrast, learning with unrestricted attention allows for the development of an explicit representation of the sequence.

Implicit Motor Learning

We observed marked increases of rCBF changes in motor cortex during sequence acquisition. The changes are very similar to functional imaging results obtained in procedural learning tasks requiring extensive motor practice (Lang et al., 1988; Grafton, Mazziotta, Presty,

Friston, Frackowiak, & Phelps, 1992; Grafton, Woods, & Tyszka, 1994; Schlaug, Knorr, & Seitz, 1994). More recently, modulation of motor cortex activity during sequence learning has been studied with transcortical magnetic stimulation. Using a more complex version of the single task SRT paradigm, Pascual-Leone et al. observed an increase in size and amplitude in the motor cortex field during the early implicit stage of motor learning (Pascual-Leone, Grafman, & Hallett, 1994). Furthermore, Asanuma and co-workers have shown that the projections from sensory to motor cortex are critical for motor skill acquisition (Iriki, Pavlides, Keller, & Asanuma, 1989). Together, these different mapping methods implicate the motor cortex as being necessary for procedural learning of movement. The change of activity in motor cortex occurs rapidly, suggesting an unmasking of previously existing synaptic connections. Unmasking has been observed in other types of learning and motor cortical plasticity and may be mediated by either long-term potentiation or disinhibition of intracortical connections (Sakamoto, Porter & Asanuma, 1987; Jacobs & Donoghue, 1991; Pavlides, Miyashita, & Asanuma, 1993).

Our PET results show augmentation of activity in

Table 4. Awareness of Sequence^a

Region	Talairach Coordinates (mm)			% Change of RCBF	<i>t</i> statistic	<i>p</i> value
	<i>x</i> axis	<i>y</i> axis	<i>z</i> axis			
Aware > unaware						
Right temporal (21)	48	-28	-18	17	5.43	***
Left temporal (21)	52	-33	-12	14	4.81	**
Right anterior cingulate (24)	12	30	-3	17	4.01	*
Right middle frontal (46)	34	34	28	9	3.89	*
Right superior occipital (19)	31	-72	28	13	4.04	*
Right frontal (9)	36	25	34	8	5.10	***
Right anterior cingulate (32)	-1	22	37	7	3.97	*
Left inferior parietal (40)	-42	-48	39	16	3.94	*
Right inferior parietal (40)	36	-52	39	17	6.31	***
Right premotor	40	-6	40	10	5.33	**
Unaware > aware						
Right superior temporal (22)	36	-48	18	-13	-4.98	*
Left superior temporal (22)	-33	-43	21	-16	-5.48	***
Right insula	24	-27	18	-9	-4.58	*

^aLocalization of areas associated with explicit awareness of sequence pattern, based on a comparison of subjects with awareness ($n=7$) and those without ($n=5$) at the end of sequence acquisition (scan 11) in the single-task condition. Significance determined by unpaired *t* test.

* $p < 0.005$.

** $p < 0.001$.

*** $p < 0.0005$.

additional areas besides motor cortex, including left anterior frontal cortex, inferior parietal cortex, rostral supplementary motor cortex, and putamen. The supplementary motor area has been implicated in learning of sequential and visually guided movements using measures of rCBF and movement evoked potentials in humans and nonhuman primates (Deecke, Komhuber, Lang, Lang, & Schreiber, 1985; Lang et al., 1988; Grafton et al., 1992; Aizawa, Inase, Mushiake, Shima, & Tanji, 1993; Schlaug et al., 1994; Tanji, 1994; Tanji & Shima, 1994).

The putamen receives direct projections from supplementary motor area and motor cortex. Other researchers have focused on the role of the basal ganglia in sequence learning using patients with focal abnormalities and nonhuman primates. For example, a well-ordered sequence in grooming behavior is disturbed following striatal lesions, despite the animal's ability to produce the isolated components (Mishkin, Malamut, & Bachevalier, 1984; Berridge & Whishaw, 1992). The learning-related change in putamen is concordant with clinical studies of implicit learning that have suggested the basal ganglia are necessary for procedural motor learning (Heindel, Butters, & Salmon, 1988; Saint-Cyr, Taylor, & Lang, 1988; Willingham et al., 1989; Knopman & Nissen, 1991; Jahanshahi, Brown, & Marsden, 1992; Pascual-Leone et al., 1993). For example, Knopman and Nissen (1991) reported that patients

with Huntington's disease were impaired on both implicit and explicit measures of sequence learning using the SRT task. This result is in accord with the hypothesized role of the striatum in this form of learning. We were able to identify modest increases of activity in bilateral putamen during sequence learning in the dual task condition. In the single task condition the change was limited to the inferior putamen on the right side, ipsilateral to the moving limb.

It is noteworthy that sensorimotor cortex, SMA, and putamen are principal components of a cortical-subcortical motor loop involved in regulating voluntary movement (Alexander, Crutcher, & DeLong, 1990). The results of the present study show that localization of learning is not exclusive to the putamen. More likely, motor sequences may ultimately be represented in a distributed way, throughout both cortical and subcortical sites that constitute the cortical basal ganglionic motor loop.

The cerebellum has also been implicated in the expression of well-learned motor skills, leading some researchers to hypothesize a cortical to cerebellar shift in control as a task becomes automated (Stein, 1986; Sanes, Dimitrov, & Hallett, 1990). Pascual-Leone et al. reported a deficit in both explicit and implicit sequence learning in patients with bilateral atrophy of the cerebellar hemispheres (Pascual-Leone et al., 1993). We were surprised

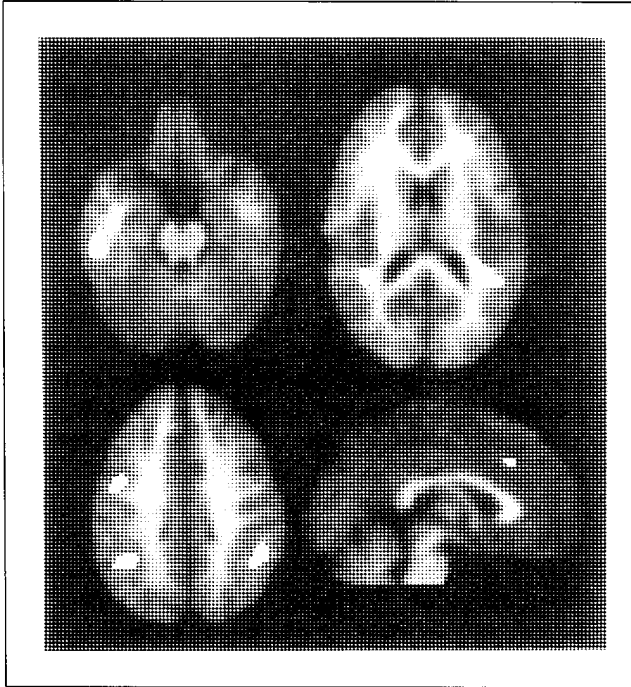


Figure 4. The effect of awareness on brain activity. The difference between 7 aware and 5 unaware subjects after learning (PET scan 11) was compared with an unpaired *t* test. Sites where rCBF of aware subjects is greater than unaware subjects are shown in white (threshold of $p < 0.005$). Awareness recruits middle right temporal (top left), bilateral superior temporal (top right), bilateral inferior parietal and right premotor (bottom left), and anterior cingulate cortex (bottom right). Axial images from top left are at -18, +18, and +51 mm relative to the AC-PC line. The sagittal image is at the midline. Subject's right is on image left.

then to observe no longitudinal change of cerebellar activity in either version of the SRT task. Negative effects are difficult to interpret with PET imaging, as the test statistics typically have weak power. Thus, with our stringent statistical thresholds we may be missing small but significant modulation in cerebellum.

Several sites displayed decreasing activity during implicit sequence learning, including bilateral middle temporal cortex and the right hippocampus. The longitudinal decrements of bilateral temporal lobe activity during the dual task may be simply due to time effects involving the secondary tone counting task. The right hippocampus has previously been implicated in verbal memory in tasks requiring completion of 3-letter word stems (Squire, Ojemann, Miezen, Petersen, Videen, & Raichle, 1992). We also observed a decrease of right hippocampal activity during the single task paradigm, suggesting the effect is general. It is not clear from our data what role the hippocampus has in the acquisition of movement sequences.

Learning without Attentional Interference

The results for the single task learning condition revealed involvement of entirely different brain areas. Be-

haviorally, this version of the task is associated with a greater improvement in performance characterized by large decrements of movement reaction time. In addition, the task became an explicit learning task in 7 of the subjects. Of note, the location of increasing activity in right dorsolateral prefrontal cortex with learning corresponded to areas previously shown to be involved in spatial working memory (Jonides, Smith, Koeppe, Awh, Minoshima, & Mintun, 1993). With the present task, spatial working memory may be important for representing the sequence of stimulus and/or response locations. This hypothesis leads to the intriguing prediction that non-spatial, symbol-based motor sequence learning may show a reverse pattern of hemispheric asymmetry or possibly a shift to more inferior right prefrontal cortex (Petrides, Alivisatos, Evans, & Meyer, 1993; Wilson, Scaldie, & Goldman-Rakic, 1993). We postulate that in sequence learning, there is marked recruitment of spatial working memory (dorsolateral prefrontal cortex) as well as parietal areas involved in perceptual attention. Further support for parietal involvement emerges from the comparison of aware and unaware subjects after single task learning. Awareness of a sequence was associated with activation of bilateral inferior parietal cortex. The parietal and prefrontal cortical areas are linked by cortico-cortical connections and constitute putative components of an attentional/cognitive network (Mesulam, 1981; Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990).

An alternative explanation of our right sided prefrontal learning effect is that learned sequences can be represented with verbal episodic memory. Tulving has proposed that retrieval of episodic memory recruits right prefrontal cortex to a greater degree than left prefrontal cortex, which may be more active during memory encoding (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Additional experiments are required to address this possibility as our experimental design cannot clearly distinguish an encoding phase of learning from a retrieval phase.

Various types of explicit memory including episodic memory have been linked to temporal cortex and limbic areas (Squire, Cohen, & Zouounis, 1984; Nissen et al., 1989; Squire et al., 1992; Stadler, 1994). The present results suggest that the prefrontal cortex and not temporal-limbic areas is critical for representing explicit sequence grammars linked to finger movements. It is useful to compare our results with another experiment that examined practice effects in a verb generation task (Raichle et al., 1994). In the verb generation task, perisylvian and insular cortex were implicated as a second system that was accessed after practice. Although the specific localizations of practice effects are different in our sequence learning and verb generation, they share a common general feature. In both experiments, it appears that different cerebral systems can be activated during the performance of a cognitive or motoric task depending on the level of practice and attentional demands.

Additional experiments are required to establish if explicit and implicit systems operate independently, hierarchically, or in concert. Our results suggest that implicit and explicit motor learning systems operate in an either/or manner, with explicit learning dominating provided attention is not diverted.

Interpretation of the present results requires modest caution because of several methodological limitations. The PET method employed used intersubject averaging. Although our method for between subject coregistration is "state-of-the-art," the approach still limits the localization to only those sites that are common across a population. Learning changes peculiar to each individual are missed, and anatomic areas that are not adequately aligned across subjects may fail to reveal significant changes as demonstrated previously (Schlaug et al., 1994). Nevertheless, these drawbacks are conservative in that false-positive changes of activity are less likely to be identified. A second drawback is that the number of scans per subject is limited so that detailed correlation of performance with rCBF magnitude is of questionable accuracy. MRI based functional imaging with many repeat scans will be necessary to relate performance and local activity with any degree of reliability. A third limitation of the study is the order effect inherent in the experimental design. All subjects performed the dual task prior to the single task. This was done to ensure that subjects would remain unaware of the presence of sequence structure at the start of both tasks. As argued in the results section, the learning-related changes in these two tasks are not likely to be due to order effects. In recent pilot experiments we have studied four additional subjects who performed the single task prior to the dual task. In these four we do not see a learning effect in the motor effector areas when the single task is presented first, suggesting that changes in these areas are because the task is being learned implicitly and not because it was learned in an implicit condition first. A fourth potential methodological confound is the use of spatial locations to represent the sequence. This might evoke learning of eye movements as well as finger movements. Finally, there may be a priming effect related to the position of targets (Tulving & Schacter, 1990).

Despite these potential limitations, our results are consistent with many other functional imaging experiments of sequence based motor learning. Our findings may explain some of the discrepancies of localization associated with sequence learning observed in prior functional imaging studies. A key feature to consider in the experimental design is the degree to which a task sequence is represented explicitly or implicitly. A second important issue is whether subjects are tested during acquisition of a task or during retrieval of a previously learned memory. For example, in the studies by Friston, Seitz, and Schlaug, an explicit strategy was used as subjects retrieved previously learned sequence patterns. Using a very simple sequence pattern, Friston observed progressive decre-

ments of activity in cerebellar vermis and lateral hemisphere (Friston, Frith, Passingham, Liddle, & Frackowiak, 1992). The rate of movements was held constant. Seitz observed progressive decreases in motor effector areas including sensorimotor cortex *ipsilateral* to the moving limb (Seitz, Roland, Bohm, Greitz, & Stone-Elanders, 1990). Schlaug repeated this experiment and observed progressive increases of activity in *contralateral* primary sensory motor cortex, SMA, and bilateral putamen (Schlaug et al., 1994). These latter findings are more consistent with the results in our dual task, the findings of Pascual-Leone, and other forms of implicit learning (Lang et al., 1988; Grafton et al., 1992; Pascual-Leone et al., 1994). Unfortunately, the number of movements in the experiments by Seitz and Schlaug increased during learning, so the changes of activity in motor related areas are very difficult to interpret. A more recent study by Jenkins helps to clarify these results (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994). A paced explicit task was used throughout. In one case, subjects performed a previously learned sequence and in another case they were scanned while determining a correct sequence pattern by trial and error. Thus, the paradigm examined explicit sequence retrieval versus sequence encoding. The retrieval task was clearly automated as the subjects could also perform a secondary task without disruption of performance. Sequence retrieval was associated with relatively greater activity in supplementary motor area whereas sequence encoding recruited multiple areas, including prefrontal and premotor cortex. They also noted that parietal and cerebellar responses tended to be more active in new sequence acquisition although they were clearly present in both types of motor behavior. Correlating these findings with the current data, we see that increasing supplementary motor area activity occurs during implicit learning and in highly practiced sequences that are learned explicitly. We would predict that SMA activity would also increase in our single task condition after overlearning the sequence with additional practice. The studies also show that prefrontal and parietal systems are recruited when explicit searching is used to identify a sequence and are also recruited in subjects who are not using a search strategy provided that attention is not diverted. Our comparison of subjects who became aware of the sequence with those who did not suggests that bilateral inferior parietal cortex has a special role in the conscious representation of sequence patterns.

Summary

Motor learning takes place in a rich and dynamic cortical system. Behavioral studies have suggested that attentional manipulations can gate motor sequence learning to separate cognitive systems. Converging evidence is provided by the current study: Sequence learning under different attentional conditions was associated with me-

tabolic changes in distinct neural regions. It is apparent that at least two cerebral systems can be used to represent a motor plan, contingent on the complexity of the attentional demands placed on the brain.

MATERIALS AND METHODS

Healthy subjects performed the SRT task and PET scanning under dual- and single-task conditions. Twelve normal right handed subjects (mean age 22, standard deviation 5 years, 5 men, 7 women) participated after informed consent was obtained in accordance with the U.S.C. Institutional Review Board. Subjects underwent a neurologic history and physical examination to rule out any preexisting condition and completed a handedness questionnaire prior to the study (Raczkowski & Kalat, 1980).

Serial Reaction Time Task

In the basic SRT task, subjects view a display of four LEDs arranged in a row. The LEDs are 4 cm apart and positioned inside the PET scanner gantry, approximately 20 cm from the subjects' eyes and in clear view. When an LED is illuminated the subjects are required to press a response key corresponding to the position of that stimulus as rapidly as possible. All of the subjects used their right, dominant hand. The right arm was extended parallel to the body axis and rested on a table with the index through little finger in contact with four response keys. A fixed interstimulus interval of 1500 msec was used so that the number of movements per block (and PET scan) was held constant. A block of trials consists of 84 responses and the sequence of stimulus locations can either be random or follow a six-element pattern that repeats continuously. An example of a sequence is 1-3-2-4-2-3 where 1, 2, 3, and 4 correspond to the index, middle, ring, and little fingers. On sequence blocks, this pattern would be repeated 14 times with the starting position randomized across blocks. There were four different sequences with two assigned to each subject, one for the dual-task blocks and one for the single-task blocks. On random blocks the stimulus locations were chosen randomly with the constraint that no location be chosen twice in succession. For each of the dual- and single-task conditions subjects performed 7 blocks of random trials, then 8 blocks of sequence trials, and finally 2 blocks of random trials. Behavioral indices of learning were derived by comparing median reaction times of correct responses on sequence blocks with those obtained on random blocks.

In the dual-task condition, the subjects were required to concurrently monitor a stream of audible tones, keeping track of the number of low pitched tones. Targets for the secondary task were 50 msec at 200 Hz pure tones. Distracters were 1000 Hz pure tones. The presentation of the visual and auditory stimuli was made asynchro-

nously by varying the delay between the onset of an LED and the onset of the tones. Intervals of 1100, 1200, or 1300 msec separated the two events. Approximately 50-75% of the tones were targets in the dual task. The number of target tones was randomly varied between blocks eliminating the possibility of a learning effect related to the secondary task. In previous studies with these types of sequences and this secondary task, sequence learning has been found without subjects ever becoming aware of the sequence (Cohen et al., 1990). A significant learning effect without development of awareness was also established for the modified SRT task (with a fixed interstimulus interval) in a series of normal subjects who were tested prior to these imaging experiments.

Tones were also presented in the same manner on the single-task blocks, but only at the distracter frequency. These tones did not follow a pattern or change pitch and were used to counterbalance the auditory stimulation and provide minimal attentional interference. In the single-task condition, the motor sequence task was performed alone and subjects were instructed not to count any tones. Different sequences were used in the single and dual tasks and subjects were always unaware that a sequence would be presented prior to the start of each condition. Since subjects uniformly do not become aware of the stimulus-response sequence in the dual-task condition, they were first tested on this condition. When interviewed at the end of the experiment, none of the subjects reported noticing the sequence during the dual-task phase. In contrast, 7 of 12 subjects became aware of a sequence structure in the single-task condition and reported it with 100% accuracy. The other 5 were completely unaware of a sequence.

Imaging

Images of relative CBF were obtained by bolus intravenous injections of 35 mCi radioactive $H_2^{15}O$ water using a modified autoradiographic method and a Siemens 953/A scanner with a measured in-plane resolution of 7.5 mm and between plane resolution of 5 mm after reconstruction (Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, & Herscovitch, 1983). Twelve sequential PET scans (6 in the dual task, then 6 in the single task) of 90 sec duration were obtained every 10 min. For each scan, tracer injection, imaging, and a block of trials were started simultaneously. Two additional blocks of trials were presented in the 10 min interval between sequential PET scans. The relationship of block type and scanning is summarized in Figure 1. Blood samples were not obtained. Images of radioactive counts were used to estimate relative cerebral blood flow (rCBF) as described previously (Fox, Mintun, Raichle, & Herscovitch, 1984; Mazziotta, Huang, Phelps, Carson, MacDonald, & Mahoney, 1985). Attenuation was corrected with a calcu-

lated method using boundary information from the sinogram of each scan.

Image Analysis

Data processing required three steps: within-subject coregistration of images to remove interscan movement errors; between-subject image coregistration to pool data and provide a common reference space for describing the location of responses; and statistical analysis for identifying learning-related changes of rCBF.

Images from each individual were aligned (within subject) using an automated registration algorithm as previously described (Woods, Cherry, & Mazziotta, 1992). The method is highly accurate and fully reproducible. The 12 coregistered images from each subject were averaged together to generate a mean rCBF image for each individual. These mean images were then coregistered to a reference PET atlas previously centered and scaled to match the Talairach atlas (Talairach & Tournoux, 1988; Grafton et al., 1994). This between-subject coregistration uses an "affine" fitting algorithm incorporating 12 parameters (3 rotations, 3 translations, and 3 scalars along axis specified by an additional 3 parameters) (Woods, Mazziotta, & Cherry, 1993). Validation studies have confirmed this fitting algorithm to be an improvement over manual techniques for transforming one brain to match the global shape of another (Friston, Passingham, Nutt, Heather, Sawle, & Frackowiak, 1989; Minoshima et al., 1993; Grafton et al., 1994). All of the original rCBF scans for each subject were resliced to match the target Talairach atlas. Images were then smoothed to a final image resolution of 20 mm full width at half maximum and were normalized (within subject) to a common global value. After smoothing there were approximately 120 gray matter resolving elements as defined previously (Worsley, Evans, Marrett, & Neelin, 1992).

A specific statistical model was applied for identifying learning-related changes of rCBF. The experimental design was set up so that learning would occur during PET scans 3, 4, and 5 of the dual-task condition and during PET scans 9, 10, and 11 of the single-task condition. As the performance measure demonstrated a longitudinal improvement in reaction time during these sequential scans, we were interested in using a model that would identify longitudinal changes of rCBF over the same trials and scans. In other words, we consider changes of brain activity that correlate best with learning to occur when there are concurrent changes of performance. Changes of rCBF during the 3 scans when learning was occurring were determined on a pixel by pixel basis with a multivariate repeated measures analysis of variance (ANOVA) as described in Maxwell and Delaney (1990). An omnibus F test for changes of rCBF activity during the three sequence scans was calculated and a significance thresh-

old of $p < 0.005$ was selected. A full multivariate F -omnibus was calculated rather than a mixed model F test to avoid errors related to assumptions of compound symmetry that can occur when variance is pooled. Once a pixel location was identified as showing a significant change during the three time points, the next step was to define the nature of the changing rCBF. With only three time points, the number of possible linear contrasts that could best describe the significant differences noted on the omnibus test were limited to two models. A site of significant rCBF change could best be described in terms of a monotonic model ($\text{Scan3} - \text{Scan1} = 0$) or by a quadratic model ($2 \times \text{Scan2} - \text{Scan1} - \text{Scan3} = 0$). Of these, the quadratic model has no measurable performance correlate showing a quadratic change, thus it is not clear what this type of change represents. Therefore, we included only those areas in which the significant change of rCBF was best explained by a monotonic model, analogous to the changes observed in the performance data. To do this, pixels with a significance above the omnibus statistical threshold and where a linear contrast F test for a monotonic contrast was greater than a quadratic model F test were displayed in pseudocolor onto an anatomic reference atlas. Both monotonic increases and decreases were considered for the two conditions. The maximum pixel of significance within each site was identified and used to localize responses with respect to Talairach coordinates. These statistics were performed separately for the single- and dual-task conditions.

To investigate time effects unrelated to the learning of sequences, the three scans obtained during presentation of random trials were compared using the same F -omnibus test. Sites with significant time effects unrelated to learning were excluded from final analysis.

Direct comparisons between specified conditions were determined with a paired t test or unpaired t test, calculated on a pixel by pixel basis, without variance pooling or a Bonferroni correction. A statistical threshold of $p < 0.005$ was used for all t tests.

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