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Motor sequence learning with the nondominant left hand

A PET functional imaging study

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Abstract Whereas the human right hemisphere is active during execution of contralateral hand movements, the left hemisphere is engaged for both contra- and ipsilateral movements, at least for right-handed subjects. Whether this asymmetry is also found during motor learning remains unknown. Implicit sequence learning by the nondominant left hand was examined with the serial reaction time (SRT) task during functional brain imaging. As learning progressed, increases in brain activity were observed in left lateral premotor cortex (PMC) and bilaterally in supplementary motor areas (SMA), with the increase significantly greater in the left hemisphere. The left SMA site was similar to one previously identified with right-hand learning, suggesting that this region is critical for representing a sequence independent of effector. Learning with the left hand also recruited a widespread set of temporal and frontal regions, suggesting that motor skill learning with the nondominant hand develops within both cognitive and motor-related functional networks. After skill acquisition, subjects performed the SRT task with their right hands, and sequence transfer was tested with the original and a mirror-ordered sequence. With the original sequence, the stimulus sequence and series of response locations remained unchanged, but the finger movements were different. With the mirror-ordered sequence, the response sequence involved finger movements homologous to those used during training. Performance of the original and mirror sequence by the right hand was significantly better than

with random stimuli. Mirror transformation of the sequence by the right hand was associated with a marked increase in regional activity in the left motor cortex, consistent with a role for sequential transformation at this level of the motor output pathway.

Keywords Blood flow · Imaging · Laterality · Brain · Human

Introduction

Hand preference exemplifies hemispheric specialization. In right-handed men this preference is reflected in both anatomic (Amunts et al. 1996, 2000) and behavioral (Schmidt et al. 2000) asymmetries. There is also an association between left hemisphere language dominance and the control of movements by either hand (Liepmann 1908; Heilman et al. 1973; McManus 1983; Annett 1985; Geschwind and Galaburda 1987). In right-handed subjects, left hemisphere function is associated with both right and left hand movements, suggesting that this hemisphere has bilateral involvement in motor control. This conclusion was originally motivated by observations on the differential deficits observed in postural, unimanual, and bimanual movements resulting from lesions in the two hemispheres (Wyke 1966, 1967, 1971b; Kimura and Archibald 1974; Haaland et al. 1987; Kashiwagi et al. 1989; Haaland and Harrington 1996). Provided that the motor cortex is spared, more profound deficits are observed for both right and left hand movements following left hemisphere lesions.

Consistent with these observations, functional brain imaging studies of right-handed subjects performing simple motor tasks show that there is a greater likelihood for bilateral motor cortical activation during movements produced with the nondominant left hand. In contrast, activation is generally restricted to the left hemisphere during the production of right hand movements (Kawashima et al. 1993; Kim et al. 1993). Similarly, transcranial magnetic stimulation applied over the right PMC during

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choice reaction time tasks impairs performance with the left hand, whereas left PMC stimulation impairs performance with either hand (Schluter et al. 1998). These asymmetries of function for movement selection are also reflected in functional imaging results (Schluter et al. 2001).

While these studies have focused on motor execution or selection, the clinical literature also suggests that a similar asymmetry may exist for motor learning. Patients with left hemisphere lesions are impaired in the acquisition and subsequent performance of a skill requiring sequential hand movements and limb postures, even when tested with their ipsilesional hands (Kimura 1977). Similarly, Haaland and Harrington (1996) have observed greater variability in their patients with left-sided brain damage when performing a novel sequential task, whereas patients with right-sided brain damage are unimpaired at the task. Acquisition of new bimanual motor skills is also impaired by left-sided brain damage (Wyke 1971a). Similarly, deficits of apraxia are more common and severe with left hemisphere lesions (De Renzi et al. 1980; Haaland et al. 2000) and these patients may show concomitant motor learning deficits (Heilman et al. 1975; Jason 1985; Rushworth et al. 1998). In a direct test of sequence learning, Boyd and Winstein (2001) have reported that patients with sensorimotor stroke are unable to learn movement sequences implicitly even when tested with their ipsilesional hand. Given that most of the patients had damage to the left hemisphere, the results are consistent with the hypothesis that the left hemisphere is critical for sequence learning. However, the study included a few patients with right hemisphere lesions and the results are combined over the different patient groups.

Nonetheless, it is unclear whether these impairments are related to a problem in motor learning per se or reflect problems associated with impaired response selection and/or the coordination of movement kinematics (Rushworth et al. 1998). Moreover, some neuropsychological studies have failed to support a lateralized learning hypothesis (Canavan et al. 1989; Winstein et al. 1999).

The lesion-based evidence for lateralization of motor learning motivated us to examine the functional anatomy of sequence learning with the nondominant hand in neurologically healthy, right-handed individuals. We focus exclusively on right-handed individuals because of the greater consistency of motor and language dominance compared with left-handed individuals. We used the serial reaction time (SRT) task in which the subjects responded on four keys with the fingers of one hand (Nissen and Bullemer 1987). Responses were indicated by spatial visual cues. When stimuli are presented in a sequential order, there is a reduction in reaction time compared with when the stimuli are presented in a random order. In previous imaging studies with this task, participants have usually been asked to respond with their right hand. Under conditions of implicit learning, imaging studies have consistently demonstrated increasing activity in left hemisphere motor cortex, PMC, and supplementary

motor area (SMA) as subjects learn a new sequential motor pattern with the right hand (Grafton et al. 1995, 1998; Sadato et al. 1996; Hazeltine et al. 1997).

In the present study, the participants performed the task with the left hand, and cerebral blood flow (CBF) was measured using positron emission tomography (PET). As in previous studies, a distracter task was performed concurrently with the SRT task to ensure that learning was implicit. A high- or low-pitched tone was presented after each visual stimulus and participants were required to keep an internal count of the low-pitch tones. Such a manipulation blocks awareness of the sequence. In this manner, we could test alternative hypotheses of nondominant-hand implicit skill learning. Sequence acquisition could be accompanied by blood flow increases predominately within (1) the contralateral, (2) the bilateral, or (3) the ipsilateral primary and secondary motor areas. We were particularly interested in determining activation patterns in areas previously shown to be associated with right-hand learning. Increased relative CBF (rCBF) in such sites would provide a substrate for sequential knowledge independent of effector (see Grafton et al. 1998). We were also interested in determining whether sequence learning with the nondominant hand engaged neural regions not observed during sequence learning with the dominant hand.

A second important question addressed by the present study involves the characterization of the acquired representation following sequence learning. A movement sequence learned with the left hand can readily transfer to the right hand (Keele et al. 1995). Immediately upon transfer, reaction times are significantly faster during sequence blocks compared with blocks of randomly ordered stimuli. This finding supports the hypothesis that at least some learning occurs at a level independent of the motor effectors. Behavioral studies designed to determine the representational basis for such transfer effects suggest that learning is neither purely stimulus nor response-based but, rather, reflects a level in which the stimuli are mapped onto abstract response goals. These goals have been defined in a variety of ways. In spatial tasks, they may correspond to categorical spatial positions (Keele et al. 1995; Grafton et al. 1998). In nonspatial tasks, they may correspond to expected perceptual events such as maintaining a melody across different "instruments" (Palmer and Meyer 2000).

Particularly relevant for the present study is mirror transfer, in which a sequence of movements with one hand is then reproduced with the homologous movements of the other hand. Two hypotheses may account for mirror transfer. First, mirror learning may reflect activation of homologous movements for the other hand during training, a hypothesis that emphasizes the development of effector-specific representations. Alternatively, mirror performance may require an on-line transformation of a learned sequence to the appropriate homologue. During implicit sequence learning, reaction time benefits have been observed for both the original and the mirror sequences (Chan et al. 2001). In the present study, we

Table 2 Motor sequence learning with left hand and distraction of attention. Locations of all areas with a learning-related changed of relative cerebral blood flow (CBF) during the acquisition of a motor sequence with the left hand

	Anatomic area	Brodmann's area	Talairach coordinates (mm)			Change of CBF during acquisition (%)	Significance	Right hand study	Activation volume (mm ³)
			x	y	z				
Increasing CBF	R dorsal frontal gyrus	11	1	45	-10	3.4	**		317
	R middle temporal	21	65	-40	-4	4.3	**	&	847
	R middle temporal	21	41	-36	-4	3.6	**		334
	R mesial temporal	27	20	-35	-1	3.5	**		165
	R middle frontal	10	12	54	1	3.4	**	&	388
	R putamen		19	15	2	3.0	**		223
	R middle frontal gyrus	10	40	46	11	2.9	**		84
	Bilaterl parieto-occipital fissure	31	0	-68	18	2.9	**		199
	R dorsolateral frontal	46	38	33	27	2.6	**	&	365
	R superior frontal	6/8	14	32	40	5.8	**	&	442
	R central sulcus	4	35	-19	49	5.0	*		155
	R superior parietal lobule	7	22	-56	54	5.8	**		182
	R dorsal frontal gyrus sma	6	16	-16	57	1.9	*		280
	L middle temporal gyrus	21	-49	-35	-5	3.1	**		442
	L rostral putamen		-22	11	3	3.0	*		135
	L thalamus		-9	-6	5	2.5	**		98
	L mesial frontal gyrus	10	-2	54	12	3.6	**		236
	L anterior frontal	10	-14	36	19	7.0	**	a	1596
	L inferior frontal gyrus	44	-45	13	27	2.9	**		476
	L posterior cingulate gyrus	23	-2	-23	29	2.3	**		334
L inferior parietal lobule	40	-38	-66	39	3.6	**		152	
L dorsal frontal gyrus ^b	6	-16	0	52	8.5	**	a	1488	
Decreasing rCBF	L inferior cerebellar cortex		-14	-62	-33	-2.0	**		12866
	L inferior temporal gyrus	20	-41	-16	-27	-5.3	**		263
	L cuneate	18	-8	-83	13	-2.3	**		250
	L inferior frontal gyrus	44	-58	9	20	-1.8	**		165
	R inferior cerebellar cortex		31	-66	-28	-3.9	**		5454
	R inferior temporal gyrus	20	36	-14	-27	-4.6	**		145
	R inferior temporal sulcus	20/21	44	-1	-26	-4.6	**		540
	R hippocampus		30	-42	-4	-2.2	**		142
	R inferior parietal lobule	40	46	-30	28	-3.2	**		135

Significance was determined with a repeated-measures ANOVA between PET scans 3, 4, 5, and 6

** $P < 0.05$ after correction for multiple comparisons

* $P < 0.01$ uncorrected for multiple comparisons

^aA similar site was identified by Grafton et al. (1995) during dual-task sequence acquisition with the right hand

^bSMA superior frontal/precentral sulcus premotor

Table 3 Mirror transformation of sequential order. Location of areas with significant differences of relative cerebral blood flow between the two conditions (Mirror > Original) after transfer to the right hand

Anatomic area	Brodmann's area	Talairach coordinates (mm)			rCBF (ml/min per 100 g)		Activation volume (mm ³)
		x	y	z	Mirror		
					Sequence	SD	
L central sulcus	4	-36	-21	63	69.0	4.4	1630
L fusiform gyrus	38	-39	-49	-18	73.8	8.0	253
R cuneate	18	27	-84	34	54.8	3.7	182
R inferior frontal gyrus	44	55	16	13	60.0	3.6	155

Significance (ANOVA) of $P < 0.05$ after correction for multiple comparisons

told that some subjects were given a sequential pattern, some were not. They were asked to estimate which group they were in. If they thought they were in the sequence group, they were asked to generate the sequence.

Scanning was performed during every other block. To identify the neural correlates of left-hand sequence learning, we focused on scans 3–6. For the transfer conditions, we compared scans in the original sequence and mirror transfer conditions.

rCBF was determined using the PET autoradiographic method (Grafton et al. 1995). A bolus of 25 mCi of $H_2^{15}O$ was injected intravenously at task onset. An 80-s scan in "3D mode" was begun when cranial radioactivity was first detected. PET scans were coregistered to each other, averaged to form a mean image. The mean PET was coregistered using first affine and then nonlinear algorithms to a PET target atlas centered and rescaled to the Talairach atlas. Images were smoothed to a final image resolution of 14.8 mm FWHM and globally normalized.

A model of learning was tested that assumes that areas involved in the initial encoding of a movement sequence should demonstrate progressive increases or decreases in brain activity as learning takes place. This was tested with a repeated-measures ANOVA design and linear contrasts. The weights -3, -1.1, and 3, were assigned to activation values for trial blocks 6, 8, 10, and 12, respectively, corresponding to a linear increase in CBF over time in scans 3–6. This approach had been used previously in a study of SRT learning with the dominant right hand (Grafton et al. 1995). The resultant t -statistic image was generated at a threshold of $P < 0.005$. Areas achieving this threshold were further evaluated for significance after correcting for multiple comparisons using all gray matter as a volume of interest (Friston et al. 1994). Sites with a volume of 125 mm or more are listed in Tables 2 and 3. Areas showing an inverse linear relationship were similarly identified. For the transfer tasks, 2-way ANOVA (task, subject effects) with task repetition (2/task) treated as replication was calculated on a pixel-by-pixel basis. Significance of the resultant t -image was calculated as for the acquisition analysis. For all analyses, areas reaching significance were superimposed on a reference MRI atlas comprised of the mean of the eight subjects.

Results

All subjects performed the task with less than 5% tone counting and tapping errors per block. Figure 1 presents the median RTs over the first 14 blocks, when the sequence was learned. The first 5 blocks show changes related to task familiarization with either hand, as no sequence was present. Upon introduction of the sequence at block S1 and performance with only the left hand, there is a progressive and significant improvement of RT ($F_{6,36}=5.76$, $P < 0.0003$). The shape of the curve is best fit by a linear model ($F_{1,6}=9.79$, $P < 0.025$). The strongest test of sequence learning is provided by the inclusion of a random block of trials between sequence blocks S7 and S8. The mean RT for the random probe was slower than on the preceding (1-way paired- t -test: $t_6=2.96$, $P < 0.02$) and following (one-way paired- t -test: $t_6=2.99$, $P < 0.02$) sequence blocks.

At the end of the study, seven of the eight subjects were unaware of a sequence; they thought they were in a group given all randomly ordered stimuli. The eighth subject reported that there had been a sequence but he was unable to reproduce any of it. These results establish that subjects were implicitly learning a motor sequence with the left hand.

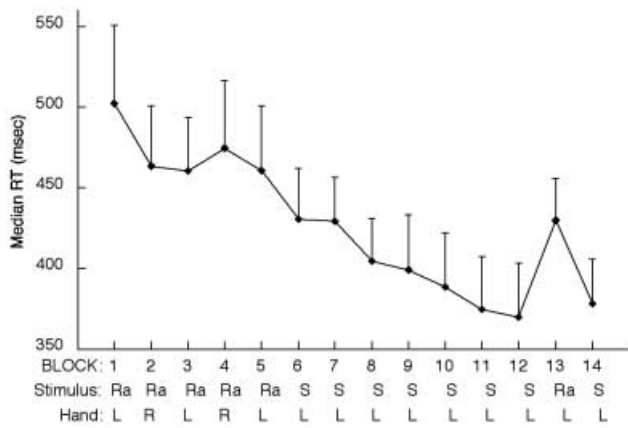


Fig. 1 Left hand sequence acquisition. Median reaction times (RT), averaged across subjects during the initial 14 blocks of the experiment, when the sequence was learned with the left hand. Six-element sequences were repeated in randomly ordered (RA) or stimuli-structured (S) blocks. There was a progressive decrease in median RTs when the sequence was repeated from blocks 6 to 12. Insertion of a random sequence at block 13 led to a performance decrement that was restored when the sequence was reintroduced at block 14, consistent with sequence-specific learning

To identify learning related brain areas, we tested for changes of rCBF during presentation of the sequence blocks (blocks 6–12, scans 3–6). Linear increases and decreases of brain activity were identified by repeated-measures ANOVA. This approach is identical to methods previously employed in experiments of right-hand learning (Grafton et al. 1995, 1998; Hazeltine et al. 1997).

The most prominent learning related changes over these scans was a longitudinal increase in rCBF in the *left* SMA, extending from the medial frontal cortex and dorsal cingulate cortex into the depths of the adjacent precentral and superior frontal sulci. A second left hemisphere site was located more posterior within the superior frontal gyrus and adjacent precentral sulcus, i.e., the dorsal PMC (Brodmann's area 6) as shown in Fig. 2. These sites were significant after correction for multiple comparisons, using a whole-brain search volume. Locations of these sites in Talairach coordinates are summarized in Table 2. Of note, the SMA site was close to one identified in a previous study of SRT learning with the right hand under similar conditions (Grafton et al. 1995).

When we corrected for multiple comparisons, no changes were observed in motor or premotor areas of the right hemisphere. It is possible that the lack of change in right hemisphere motor areas was due to overly stringent statistical criteria. When the statistical threshold was made less conservative ($P < 0.01$ uncorrected for multiple comparisons), a small increase in rCBF could also be identified in the bilateral sensorimotor cortex (SMC) and right SMA. No changes were found in the right PMC even with the adjusted criterion.

Figure 3 plots the rCBF values from bilateral SMC and SMA, as well as left PMC during skill acquisition. The figure does not include a plot for right PMC, since no learning-related activity was detected within this region.

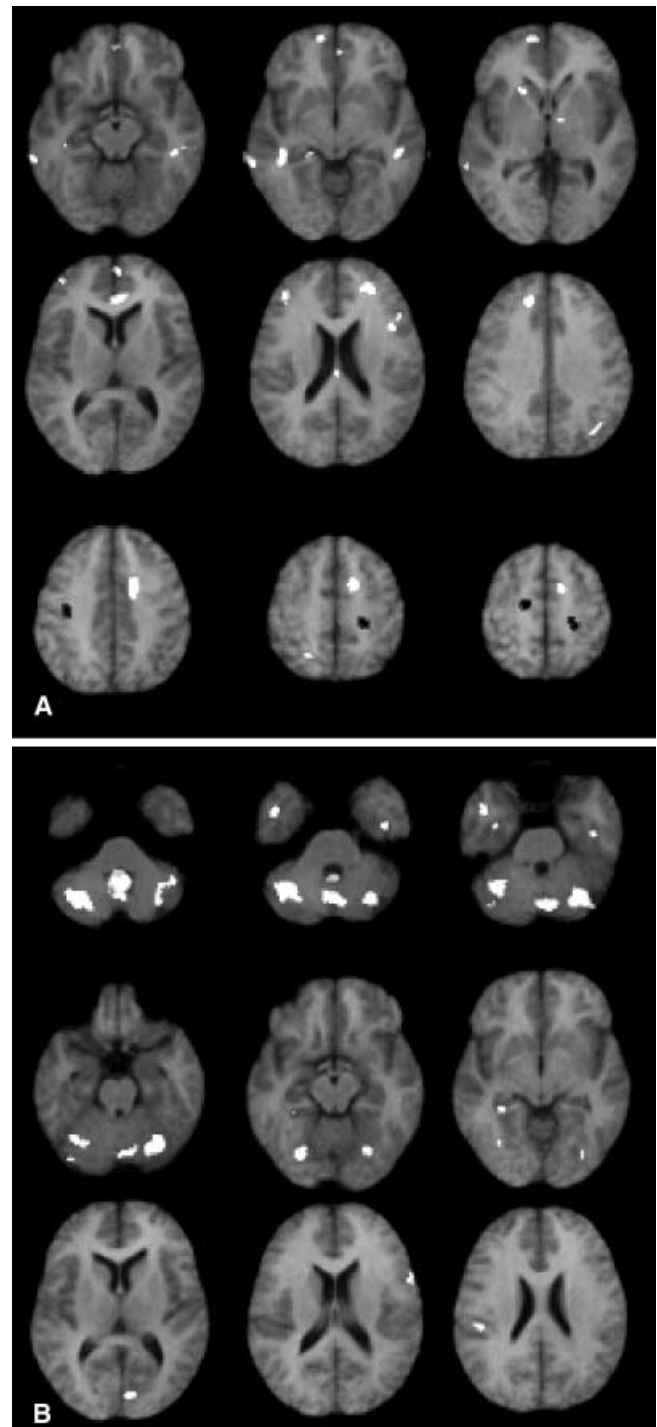


Fig. 2A, B Functional changes during left hand sequence learning. **A** Areas of increasing of relative CBF (rCBF) across the four PET scans obtained during presentation of a repeating sequence in behavioral blocks 6, 8, 10, and 12. Axial slices correspond to Talairach z -axis: -15 , -6 , 0 , 9 , 21 , 36 , 45 , 54 , and 57 . CBF increases include the left premotor cortex, middle frontal cortex, bilateral supplementary motor area, and motor cortex. **B** Areas of decreasing rCBF over the same scans. Slices correspond to Talairach z -axis: -36 , -30 , -24 , -18 , -9 , -3 , 12 , 21 , and 27 . Prominent decreases are observed in cerebellum. Areas in *white* represent threshold of $P < 0.05$ adjusted for multiple comparisons, in *black*, $P < 0.01$ uncorrected

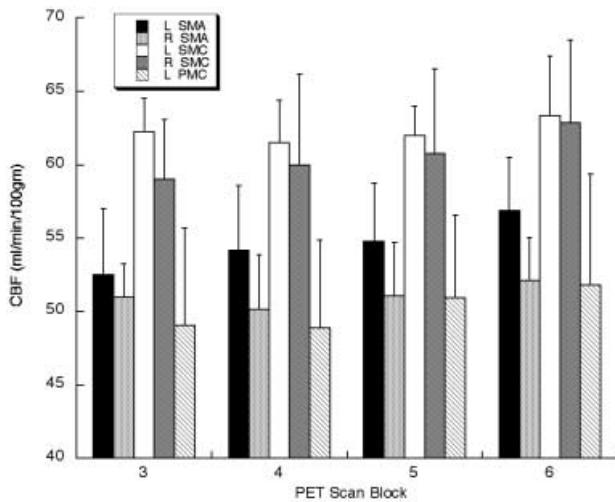


Fig. 3 Serial changes of brain activity in motor areas during left hand sequence acquisition. When a sequence was presented during behavioral blocks 6, 8, 10, 12 (corresponding to PET scans 3–6), there was significant increasing activity (after correction for multiple comparisons) in left premotor (*PMC*) and supplementary motor area (*SMA*). At an uncorrected threshold of $P < 0.01$, increases were also observed in right *SMA* and bilateral sensorimotor cortex (*SMC*). Blood flow (*CBF*) values correspond to a spherical, 1.5-cm-diameter region of interest centered on the local statistical maxima (from the repeated-measures ANOVA) of the unsmoothed PET data

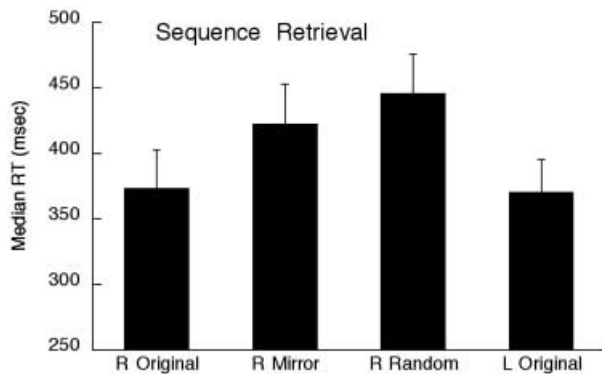


Fig. 4 Right hand performance of the serial reaction time (*RT*) task after sequence learning by the left hand. Performance with the right hand and original sequence was similar to performance at the end of sequence learning with the left hand, and significantly better than a block of randomly ordered stimuli. Presentation of a mirror sequence led to performance improvement relative to the random condition that was not as great as the original sequence

Starting with the onset of sequence learning at block 6 (scan 3), the increase in rCBF was greater in the left *SMA* than in the right *SMA* (Scan block \times Side interaction: $F_{1,14} = 6.88$, $P < 0.02$). Although the Scan \times Side interaction in *SMC* is not significant, the absolute rCBF increase across the four learning blocks is numerically greater in the right hemisphere.

In addition to changes in *SMA*, premotor and motor areas, increases and decreases in rCBF were observed in other cortical and subcortical sites. Sequence learning was also accompanied by recruitment of multiple areas in

temporal and prefrontal cortex. Changes in most of these sites were not observed in our previous study of right-hand sequence learning with the serial reaction time task (Grafton et al. 1995). It is possible they reflect effects associated with performance by the nondominant hand or the use of nonmotor networks for representing sequential information. They may also simply be a result of greater sensitivity with the 3D imaging method of the current study.

Two points of special interest can be seen in Table 2 and Fig. 2. First, some of the right hemisphere cortical foci are similar to those recruited during SRT learning with the right hand in the absence of a distracter task (Grafton et al. 1995). Second, there was a dramatic decrease in activity in bilateral cerebellum over the course of the four scans during sequence learning. Decreases in cerebellar activity during motor learning have been reported in previous imaging studies, including some involving the SRT task (Friston et al. 1992; Flament et al. 1994; Grafton et al. 1994; Jenkins et al. 1994; Ebner et al. 1996).

Intermanual transfer

After the sequence acquisition phase, blocks were performed with the left and right hands in an alternating fashion. As shown in Table 1, during the left-hand blocks, the stimuli were ordered with the original sequence. Right-hand blocks were performed with either random, original sequence, or mirror sequences. Median RTs for right hand responses during random, original sequence, and mirror sequence blocks were compared after averaging the two repetitions of each task. Significant transfer was found when the original sequence was performed with the right hand; RTs were considerably faster than on the random blocks (paired-*t*-test: $t_6 = 5.58$, $P < 0.002$), as shown in Fig. 4. Although caution is required when comparing performance between hands, no significant difference was observed between left and right hand performance on the sequence blocks. Transfer in the mirror condition was less dramatic but nonetheless significant compared with the random block (paired-*t*-test: $t_6 = 5.500$, $P < 0.002$). When the original and mirror conditions were directly compared, RTs were significantly faster in the former condition, (paired-*t*-test: $t_6 = 4.57$, $P < 0.004$). Thus, consistent with previous behavioral studies, intermanual transfer is excellent when the stimulus sequence and environmentally defined response sequence is maintained. In addition, we also observed significant transfer when the right hand produced a sequence of finger movements homologous to those used during left hand training, the mirror transfer condition.

Regions playing a specific role in the mirror transformation of the sequence representation were identified by subtracting activation during right-hand blocks with the original sequence from that observed during right-hand blocks with the mirror sequence. Given the transfer results, both of these conditions presumably involve

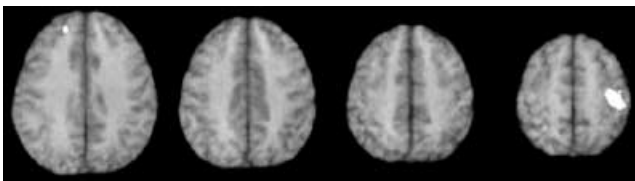


Fig. 5 Localization of mirror sequence transformation. Sites where the mirror sequence task (right hand) was greater than the original sequence (right hand) are shown in *white* ($P < 0.05$, corrected for multiple comparisons). There is markedly increased activity within the left primary motor cortex

retrieval of the learned sequence. The mirror condition, however, must also involve a remapping of this sequence into transformed coordinates. The main finding from this analysis was more activity in left sensorimotor cortex in the mirror condition compared with the original sequence (Fig. 5, Table 3). An increase in activation in left fusiform, right cuneate, and right inferior frontal gyrus was also observed in the mirror transformation condition. Activation within left motor cortex suggests that the recoding of the sequence as a mirror pattern engages the motor cortex, perhaps in combination with secondary visual areas.

We also performed the reverse analysis, subtracting activation in the mirror transfer condition from that observed in the original sequence transfer condition. No significant differences were obtained for this analysis. While we cannot draw strong conclusions from null results, this finding is consistent with the hypothesis that performance during the mirror task is supported by the same underlying representation as the original sequence, and additional processes are also recruited to perform the transformation.

Discussion

We examined the neural correlates of sequence learning with the nondominant left hand. The results indicate that the left lateral PMC and adjacent left SMA are critical for acquiring visually cued sequential movements of the ipsilateral nondominant hand. The SMA, dorsal premotor, and cingulate cortex all demonstrated longitudinal increases in activity over the course of sequence learning. At a very weak statistical threshold, changes were also observed in the contralateral right hemisphere. However, these right hemisphere effects were considerably weaker. There was considerable overlap between the left-sided foci observed in the present experiment and those identified by previous studies requiring right-handed movements (Grafton et al. 1995, 1998). This similarity suggests that the PMC and SMA in the left hemisphere are dominant for the acquisition of new sequences, regardless of whether the new skill is performed with the left or right hand. Since these experiments have only tested right-handed subjects, the functional findings cannot be generalized to left-handed individuals.

Our findings are tempered by two methodological limitations of the study. There was no parallel group of subjects performing the SRT task with only randomly ordered trials or randomly intermixed trials. Thus, the present results cannot dissociate general time effects from sequence-specific learning. However, subjects had practiced the randomly ordered left-hand task in blocks prior to presentation of the sequence and their behavior on random blocks was no longer improving at the time the sequence was presented. Thus, the proportion of behavioral improvement observed on subsequent trials was in large part related to the sequence rather than general practice effects. A second concern is that the changes could be due to an effect of task difficulty with the nondominant hand. However, the main statistical measure of learning tested for a within task change over time rather than a direct comparison of left and right hand performance. Changes of brain activity during left hand sequence learning paralleled improvements of response latency.

Left hemisphere dominance for sequence learning is consistent with clinical studies that assess the effects of unilateral brain damage on motor performance. Localization within left SMA and lateral PMC has also been observed in many imaging studies of either implicit or explicit sequence learning by the dominant hand under a variety of experimental conditions. We assume that the left SMA develops effector-independent representations of the movement sequence (see also Grafton et al. 1998). The most probable pathway linking the left SMA to right primary motor cortex is via the right SMA. Although there are direct connections between the left premotor areas and right motor cortex, they are modest in density compared with the rich interhemispheric connection of bilateral SMA (Rouiller et al. 1994). Consistent with this hypothesis, we did observe a small increase in activation within both right SMA and motor cortex across the left-hand learning blocks.

Unlike our previous studies of sequence acquisition with the right hand, results of left-hand learning demonstrate recruitment of many additional brain areas outside of the motor system, particularly in prefrontal and bilateral temporal cortex. Interestingly, some of these areas had also shown learning-related increases in rCBF under single-task conditions in which the distracter task is eliminated (Grafton et al. 1995; Hazeltine et al. 1997). The functionality of these areas remains unclear. We had proposed in our previous work that these areas might be associated with memory processes that provide an alternative representation of the sequence, one that is less closely tied with an action system; for example, a representation based on expectations of the next event in a sequence rather than anticipation of the next movement or target location for a response. Perhaps similar representational changes occur during nondominant hand learning because this hand is more weakly associated with neural regions involved in producing sequential movements.

After transfer to the right hand, responses were fastest when subjects responded to the original, environmentally

consistent sequence. In fact, performance was nearly equivalent to nondominant left hand performance. Response times were significantly slower when the sequence (both stimulus sequence and response sequence) was mirror-reversed. However, positive transfer was obtained in the mirror transformation condition, since response times here were faster than on random blocks with the right hand. These behavioral findings suggest subjects are learning the sequence with respect to an environmental reference frame rather than specific effectors. The mirror task may then require an additional transformation of the goal to the new pattern of motor responses. Compared with the original sequence, the transformation of a sequence into its mirror image recruited markedly greater activity within secondary visual areas and the left motor cortex. Consistent with the latter result, single-neuron recording studies in nonhuman primates suggest a role of sequencing as well as sensorimotor remapping of responses in the motor cortex (Shen and Alexander 1997; Carpenter et al. 1999). Alternatively, the increased left motor cortex activation might reflect parallel activation of responses for both the original sequence and its mirror transform.

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