Motor Learning of Compatible and Incompatible Visuomotor Maps

Scott T. Grafton\(^1\), Joanna Salidis\(^2\), and Daniel B. Willingham\(^2\)

Abstract

Brain imaging studies demonstrate increasing activity in limb motor areas during early motor skill learning, consistent with functional reorganization occurring at the motor output level. Nevertheless, behavioral studies reveal that visually guided skills can also be learned with respect to target location or possibly eye movements. The current experiments examined motor learning under compatible and incompatible perceptual/motor conditions to identify brain areas involved in different perceptual–motor transformations. Subjects tracked a continuously moving target with a joystick-controlled cursor. The target moved in a repeating sequence embedded within random movements to block sequence awareness. Psychophysical studies of behavioral transfer from incompatible (joystick and cursor moving in opposite directions) to compatible tracking established that incompatible learning was occurring with respect to target location. Positron emission tomography (PET) functional imaging of compatible learning identified increasing activity throughout the precentral gyrus, maximal in the arm area. Incompatible learning also led to increasing activity in the precentral gyrus, maximal in the putative frontal eye fields. When the incompatible task was switched to a compatible response and the previously learned sequence was reintroduced, there was an increase in arm motor cortex. The results show that learning-related increases of brain activity are dynamic, with recruitment of multiple motor output areas, contingent on task demands. Visually guided motor sequences can be linked to either oculomotor or arm motor areas. Rather than identifying changes of motor output maps, the data from imaging experiments may better reflect modulation of inputs to multiple motor areas.

INTRODUCTION

Humans can acquire new skills in a matter of minutes to hours. With sufficient practice, motor skills such as typing or sports are retained lifelong. This ease is remarkable given the complexity involved in the timing and generation of new muscle synergies. A persistent question for functional mapping is where a new motor skill is represented in the brain. Converging evidence from invasive and noninvasive brain mapping techniques have begun to identify a set of sensory and motor areas where learning-related changes might occur.

Previous imaging studies of procedural motor learning from our laboratory examined the pursuit rotor task (Grafton et al., 1992). This is a prototypical procedural task in which subjects hold a stylus and chase a small target positioned on the outer edge of a rapidly rotating disc (Ammons, 1947). Over the course of 20–40 min the time on target, a measure of accuracy and learning, increases dramatically. The skill can be retained over many years (Ammons et al., 1958). As subjects learn this skill, imaging studies identify progressive increases of activity in contralateral motor cortex and the supplementary motor area. With additional practice on a second day there is evidence for a further increase of activity in contralateral putamen (Grafton, Woods, & Tyszka, 1994). This basic observation of enhanced activity in the motor circuit with practice has been observed with many other procedural and implicit sequence learning tasks when studied in the initial period of skill learning (Hazeltine, Grafton, & Ivry, 1997; Jueptner et al., 1997; Shadmehr & Holcomb, 1997; Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Flament, Ellermann, Kim, Ugurbil, & Ebner, 1996; Karna et al., 1995, 1998; Rauch et al., 1995; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Schlaug, Knorr, & Seitz, 1994; Seitz et al., 1994; Grafton et al., 1992, 1994; Grafton, Hazeltine, & Ivry, 1995; Haier et al., 1992; Roland, Gulyas, & Seitz, 1991; Lang et al., 1988; Saint-Cyr, Taylor, & Lang, 1988). Complementary methods, such as transcranial magnetic stimulation, have identified analogous learning-related increases of the relevant digit representations in human motor cortex during implicit sequence learning (Clasen, Liepert, Wise, Hallett, & Cohen, 1998; Pascual-Leone, Grafman, & Hallett, 1994).

Interpretation of motor learning-related changes of brain activity requires a thorough identification of what skill or knowledge is actually acquired by a subject.

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RESULTS

Experiment 1a: Psychophysics of Spatially Compatible Procedural Learning

This experiment validated a procedure that leads to implicit motor skill learning under spatially compatible conditions with respect to limb, target, and cursor movement directions. The task, a modification of the pursuit tracking task originally developed by Pew (1974), is more kinematically constrained than other learning procedures such as mirror writing or pursuit rotor. Unlike pursuit rotor, there is no explicit representation of the spatial sequence that could define movement. From observations made during pilot experiments with videotaping it is apparent that subjects consistently follow the moving target with the eyes. Thus, there is a general congruency between eye movement and target movement in this task.

Subjects tracked a target that moved across the screen in the horizontal direction only. There were two kinds of trials, sequence and random. In random trials, the target reversed direction at randomly generated screen positions. In sequence trials, the target reversed at random positions for the first last and middle 10 sec of each trial; during the remaining 60 sec the target turned at points determined by a sequence. Figure 1A shows the horizontal position of the target through the 90-sec trial and Figure 1B shows a repeating 10-sec movement pattern. In each trial throughout the experiment, the same 10-
sec sequential pattern of target movement was repeated three times in a row, followed by the middle 10 sec of random turns, followed by the remaining three repetitions of the sequence.

After each of 28 trials, the screen displayed the participant’s root mean square error (RMSE—a measure of the average distance of the cursor from the target) for that trial. Participants were told to try to minimize the RMSE.

Figure 2 shows the mean RMSE for each trial. The figure indicates that RMSEs decreased over the course of the experiment, as expected with learning. Some of this learning may be due to learning the parameters of the task, such as the target speed and the relationship between joystick movement and cursor movement, rather than the sequence per se. Indeed, learning was reliable over the first nine random trials \(F(8,48) = 5.04, p < .01, \text{MSE} = 16.90\). As Figure 2 indicates, this result is largely due to learning in the initial four trials; performance was constant for the rest of the random trials. Two aspects of the data suggest that participants also learned the specific sequence along with general parameters of the task. First, when the sequence trials were introduced, participants improved further \(F(17,102) = 4.44, p < .01, \text{MSE} = 10.75\). Secondly, the RMSE increased when participants were switched back to random tracking in the last trial \(F(1,6) = 10.42, p < .01, \text{MSE} = 2.59\).

Rating and recognition scores for explicit knowledge indicated that some participants may have been aware of the sequence, but their recognition scores were quite low. The mean rating for the “Which group do you think you were in?” question was 4.14 (SE = 0.63), where 5 was “no idea.” Only two participants gave ratings above 5. Participants rated the sequences in the recognition test on a scale of 1 to 99, where 1 indicated certainty that the present sequence was not the practiced sequence and 99 indicated certainty that it was. The recognition score was calculated as the rating given to the sequence minus the mean of the ratings given to the distracters. This score \(M = 15.29, \text{SE} = 7.88\) was significantly greater than 0 \(t(6) = 1.94, p < .05\), indicating that participants could recognize the pattern in a recognition performance task.

This experiment established that a spatially compatible visually guided learning task could be used to study motor skill learning. The test of explicit recognition suggests that subjects were unaware of a sequence and the task was successful at minimizing strategic learning. The contribution of “top-down” mental processes to skill acquisition could be treated as temporally constant in the subsequent imaging study. The significant recognition scores suggest the presence of some form of implicit recognition or perceptual fluency. Furthermore, the leveling off of performance during the early all-random trials establishes that nonspecific learning of the apparatus and general task requirements had reached a plateau prior to the subsequent sequence-related learning.

**Experiment 1b: Functional Imaging of Spatially Compatible Procedural Learning**

The spatially compatible learning task of Experiment 1a was examined during positron emission tomography (PET) imaging to identify longitudinal changes of brain activity associated with the acquisition of a new

| Block | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
| PET scan | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
| Stimulus | R | R | R | R | R | R | R | S | S | S | S | S | S | S | S | S | S | S | S | S | S | S | S | R | R | R | R | R | R |
| Mapping | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C |

R = stimuli presented as random pattern; S = stimuli presented as a repeating spatial pattern; C = compatible mapping between cursor and joystick direction.
motor sequence. The primary prediction was an increase of activity in the motor cortex during learning, analogous to results obtained with the pursuit rotor task. The experiment structure is shown in Table 1.

Subject performance while tracking in the PET scanner for six subjects is shown in Figure 3. Mean RMSEs decreased over the course of the experiment when the sequence was presented. Improvement over the sequence trials with PET scanning was marginally significant [F(1,5) = 5.686, p < .06]. More importantly, this behavioral change was specific to sequence learning because the RMSE increased when participants were switched back to random tracking in the last trials: Scan 9 vs. Scan 10 [F(1,5) = 20.744, p < .006].

The ratings scores were all low, indicating that participants were not aware of the presence of a sequence. As in Experiment 1a, there was evidence for recognition when the sequence was presented to the subjects [M = 35.66, SE = 10.36, t(6) = 3.44]. This mixed pattern of results suggests a form of awareness that may be associated with implicit rather than explicit recognition.

As summarized in Table 2, the functional imaging data revealed significant longitudinal increases of activity during skill acquisition in the superior aspect of the contralateral (left) sensorimotor cortex and adjacent precentral and dorsal frontal gyrus. The latter two areas encompassed a portion of the premotor cortex and supplementary motor area, respectively. The site of motor cortex activation shown in Figure 4A was superior, in a region associated with proximal arm

<table>
<thead>
<tr>
<th>Table 2. Experiment 1b: Localization of Compatible Pattern Encoding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomic location</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Increasing activity</td>
</tr>
<tr>
<td>Right globus pallidus</td>
</tr>
<tr>
<td>Left thalamus</td>
</tr>
<tr>
<td>Left parieto-occipital fissure (18/31)</td>
</tr>
<tr>
<td>Left postcentral gyrus (40)</td>
</tr>
<tr>
<td>Left precuneate cortex (7)</td>
</tr>
<tr>
<td>Right anterior cingulate gyrus (32)</td>
</tr>
<tr>
<td>Left central sulcus/precentral gyrus</td>
</tr>
<tr>
<td>Dorsal frontal gyrus</td>
</tr>
<tr>
<td>Decreasing activity</td>
</tr>
<tr>
<td>Right posterior cerebellum*</td>
</tr>
<tr>
<td>Right lateral cerebellum*</td>
</tr>
<tr>
<td>Right fusiform gyrus (20)*</td>
</tr>
</tbody>
</table>

Locations were determined by repeated measures ANOVA and linear contrasts on CBF values, corrected for multiple comparisons. Anatomic locations in parenthesis are Brodmann’s areas according to the atlas of Talairach and Tournoux (1988).

*Significant at p < .001, uncorrected for multiple comparisons.

**Significant (p < .05) changes at this site were also observed in subjects of Experiment 2b.
The joystick task we used required more proximal arm movements as well. The next most prominent area showing learning-related changes was the left postcentral sulcus of the inferior parietal lobule. Figure 4A shows this area extending into the postcentral gyrus. The time course of activity in these two areas is shown in Figure 4B. The most significant changes were near the end of the study, when most of the performance gains occurred. Table 2 shows that the percent change of blood flow in all areas during the early random blocks was inconsequential whereas it increased substantially with the sequence trials. At the end of the experiment, all of the sites showed a drop of activity when the random task was reintroduced.

After correcting for multiple comparisons there were no areas demonstrating a progressive decrease of activity during learning. When the data were reexamined without correction for multiple comparisons at a threshold of $p < .001$, there were two sites...

Figure 4. (A) Learning-related increases of CBF during spatially compatible sequential arm movements. Areas of significance ($p < .05$, after correcting for multiple comparisons; in blue) are projected onto an MRI scan from a normal subject. The left hemisphere is displayed in a superior oblique view with a cutout through the arm area of the sensorimotor cortex. The most superior site is located in the arm area of sensorimotor cortex. This activation extends continuously into the left supplementary motor area (partially seen in the interhemispheric fissure). The center of this distributed activation (~13, –30, 64) is summarized in Table 2. The more inferior site is located in the rostral inferior parietal lobule. The area in red is the frontal eye field, which was significant at $p < .01$ without correction for multiple comparisons. (B) CBF plotted as a function of time at the sensorimotor and parietal cortex.

Figure 5. (A) Learning-related decreases of CBF during spatially compatible sequential arm movements. Areas of significance ($p < .001$, uncorrected for multiple comparisons; in white) are projected onto an MRI scan from a normal subject. Two sites in the right cerebellum and an area fusiform gyrus are shown. (B) CBF plotted as a function of time at these three sites.
identified in the right cerebellum and a third site in the right fusiform gyrus, shown in Figure 5A. The time course of activity in these areas is shown in Figure 5B.

The primary observation of Experiment 1b was a progressive increase of activity in the proximal arm area of the primary sensorimotor cortex and SMA with the learning of a sequential arm movement. Less significant changes were also observed in the region of the frontal eye fields. Under spatially compatible conditions the sequence appears to be represented at the level of motor effector (eye and arm) with a predominance of changes occurring in the cortex associated with arm movements. There is an interesting difference between this study and previous imaging studies of sequencing discrete finger movements using the SRT task. When the subjects switch from a sequence to all random block in the present study, there is a drop of activity in the motor cortex and SMA. This drop does not occur in the first block for the discrete case. This could be related to a more rigid internal model for sequences linked to discrete responses, i.e., it simply takes more trials for the activity associated with a sequential representation to attenuate. For continuous movements the error associated with random tracking might be detected sooner.

Increasing activity in the arm motor cortex are probably not related to increases of force, velocity, or amplitude. Although limb kinematics were not measured, the pattern of gross limb movements observed visually were relatively constant. If anything, subjects make less forceful movements with less frequent and smoother corrections over time as they learn this task. The current results also establish that involvement of the SMA can occur with motor learning of continuous sequential movements as has been shown previously with discrete movements. The results also show decreasing activity in the cerebellar cortex ipsilateral to the moving limb that is proportionate to the amount of performance error. This is consistent with a previous fMRI study showing decreasing error-related activity in the cerebellum during a task in which subjects must learn to move a joystick in new directions to control a cursor (Flament et al., 1996). Although it is tempting to infer that this cerebellar decrease could be a direct correlate of an error signal, there are alternative explanations including the coding of a new “internal model” (Imamizu et al., 2000). In the latter case the cerebellum would be more active early by facilitating the development of

Table 3. Experiment 2a: Mean Rating and Recall (Explicit Knowledge)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rating</th>
<th>SE</th>
<th>Recall</th>
<th>SE</th>
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<tbody>
<tr>
<td>Perceptual</td>
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<td>0.44</td>
<td>3.06</td>
<td>0.53</td>
</tr>
<tr>
<td>Motor</td>
<td>5.78</td>
<td>0.48</td>
<td>2.89</td>
<td>0.54</td>
</tr>
<tr>
<td>Random</td>
<td>5.17</td>
<td>0.39</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Identical</td>
<td>5.83</td>
<td>0.36</td>
<td>2.72</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 4. Experiment 2b: Schedule of Incompatible Motor Pattern Learning

<table>
<thead>
<tr>
<th>Block</th>
<th>Practice</th>
<th>1</th>
<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Sp</td>
<td>Sp</td>
<td>Sm</td>
<td>Sm</td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Stimulus</td>
<td></td>
<td>C</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Mapping</td>
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<td></td>
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</tbody>
</table>

R = stimuli presented as random pattern; S = stimuli presented as a repeating spatial pattern; C = compatible mapping between cursor and joystick direction; I = incompatible mapping between cursor and joystick direction; Sp = same pattern reintroduced in perceptual dimension; Sm = same pattern reintroduced in motor response dimension.
a new model. With time the model might be represented in other structures and cerebellar involvement would decrease.

Experiment 2a: Psychophysics of Spatially Incompatible Procedural Learning

Are continuous visuomotor skills represented in a common set of brain structures? This could be investigated using the technique of behavioral transfer between incompatible and compatible visuomotor mappings. To do this, subjects first performed tracking with the joystick reversed. Thus, target and arm move in opposite direction. A sequence was learned in this condition. Then, the joystick was returned to a standard configuration so that target and arm movements were compatible. The previously learned sequence was reintroduced with respect to the pattern of target movements (perceptual group, \( n = 18 \)) or with respect to hand movements (motor group, \( n = 18 \)). If learning occurs with respect to target location (or perhaps eye movements, which are approximately congruent with target movement), only the perceptual group will show performance gains at transfer. If movements are related to motor effector, then only the motor group will show performance gains at transfer. Two additional control groups performed (1) random movements for all trials (‘random,’ \( n = 18 \)) and (2) all compatible trials (‘identical,’ \( n = 18 \)).

The mean RMSE across trials for each condition are summarized in Figure 6. All participants (except those in the Random condition) learned the sequence in the learning phase. The perceptual group demonstrates transfer, as indicated by the similarity between their performance gains at transfer. Two additional control groups performed (1) random movements for all trials (‘random,’ \( n = 18 \)) and (2) all compatible trials (‘identical,’ \( n = 18 \)).

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Table 5. Experiment 2b: Localization of Incompatible Pattern Encoding

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Talairach coordinates (mm)</th>
<th>Percent change of activity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Increasing activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L thalamus/caudate</td>
<td>−9</td>
<td>−15</td>
<td>21</td>
</tr>
<tr>
<td>Right precentral gyrus (6)</td>
<td>43</td>
<td>−7</td>
<td>36</td>
</tr>
<tr>
<td>Left precuneus (7/24)</td>
<td>−12</td>
<td>−24</td>
<td>43</td>
</tr>
<tr>
<td>Left precentral gyrus (4/6)</td>
<td>−42</td>
<td>−15</td>
<td>46</td>
</tr>
<tr>
<td>Right precentral gyrus (4/6)</td>
<td>42</td>
<td>−22</td>
<td>52</td>
</tr>
<tr>
<td>Left dorsal frontal gyrus (6)</td>
<td>−1</td>
<td>−13</td>
<td>69</td>
</tr>
<tr>
<td>Right dorsal frontal gyrus (6)</td>
<td>7</td>
<td>−30</td>
<td>70</td>
</tr>
<tr>
<td>Decreasing activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cerebellar nuclei and cortex</td>
<td>−28</td>
<td>−60</td>
<td>−37</td>
</tr>
<tr>
<td>Right lateral cerebellum</td>
<td>37</td>
<td>−54</td>
<td>−19</td>
</tr>
<tr>
<td>Left middle temporal gyrus (21)</td>
<td>−49</td>
<td>−54</td>
<td>6</td>
</tr>
<tr>
<td>Right middle temporal gyrus (39)</td>
<td>46</td>
<td>−72</td>
<td>16</td>
</tr>
</tbody>
</table>

Locations were determined by repeated measures ANOVA and linear contrasts on CBF values, corrected for multiple comparisons. Anatomic locations in parenthesis are Brodmann’s areas according to the atlas of Talairach and Tournoux (1988).

*Significant \( (p < .05) \) changes at this site were also observed in subjects of Experiment 1b.
performance and the identical group at transfer. In contrast, the motor group does not look different from the random group after transfer.

Initial sequence learning was confirmed with a repeated measures ANOVA on the RMSEs on the first nine blocks with trial as a within- and condition as a between-subjects factor. Most importantly, a significant trial by condition interaction indicated that the learning rates differed between the conditions, as expected if there was sequence-specific learning \( F(24,544) = 4.36, p < .01, \text{MSE} = 109.41 \). Planned contrasts confirmed that the motor and perceptual groups’ rate of learning exceeded that of the random group’s \( F(8,544) = 2.18, p < .05 \). The level of RMSE differed among the four conditions \( F(3,68) = 17.56, p < .01, \text{MSE} = 1494.79 \), at least partially because of the greater difficulty of reversed tracking. The effect of trial was also significant \( F(8,544) = 74.08, p < .01, \text{MSE} = 109.41 \).

An ANOVA on the difference in RMSE between Trials 9 (sequence) and 10 (random) was also conducted to assess sequence-specific learning. As expected, this score differed among the conditions \( F(3,68) = 10.85, p < .01, \text{MSE} = 42.64 \). Planned contrasts showed that the motor, perceptual, and identical difference scores were greater than the random difference scores, \( F \) values > 17), and did not differ from each other (all \( F \) scores < 1.1). This analysis indicates that the initial level of sequence-specific learning among the three sequence learning groups was comparable.

Of course, the purpose of the experiment was not to demonstrate that participants can learn the sequence, but rather to specify exactly what type of sequence they learn. Do they learn the perceptual sequence, the motor sequence, or both? An ANOVA on the difference in RMSE between Trials 12 (sequence) and 13 (random) was conducted to answer this question. Again, this difference score differed among the four conditions \( F(3,68) = 41.26, p < .01, \text{MSE} = 2805.37 \). Planned contrasts revealed that, although the perceptual group differed from the random group \( F(1,68) = 6.25, p < .05 \), the motor group did not \( F(1,68) < 1 \). Furthermore, as expected if participants were entirely relying on a perceptual representation, the perceptual group’s scores did not differ from the identical group’s scores \( F(1,68) < 1 \).

Table 3 shows the mean rating and recall scores for each condition. As in Experiment 1, participants were not aware of the sequence. Participants’ ratings of whether they tracked a sequence or not did not differ by condition \( F(3,68) < 1 \). More focused contrasts comparing each of the sequence groups to the random group also did not indicate any significant differences (all \( F \)s < 2).

The recall task yielded very similar results. The number of segments correctly sequenced, with three in a row correct being the minimum chunk required for scoring, was the measure of awareness. This score did not differ by condition \( F(3,68) < 1 \). Furthermore, none of the sequence conditions differed from the random condition (all \( F \)s < 1).

The main finding indicates that participants learned a visually guided, sequential movement in relationship to...
target location. Because eye movements were probably congruous with target movements across transfer, we cannot determine if the representation is at the level of target location, specific eye movements, or both. The results provide evidence that the motor sequence is probably learned in a perceptual domain. As with compatible learning, subjects were unaware of a sequence. Even when told there was a sequence, they could not recall any of the sequential movement better than a random group. Because a recognition test was not performed, we cannot rule out the possibility of implicit perceptual learning. Nevertheless, the tests of explicit knowledge, mixed as they are, argue against any sort of strategic learning.

Experiment 2b: Functional Imaging of Spatially Incompatible Procedural Learning

The last experiment identified longitudinal changes of brain activity associated with learning the incompatible task. The incompatible task of Experiment 2a was used. Because perceptual transfer was more robust than motor transfer, it was tested first after transfer in all subjects. The experiment timeline is shown in Table 4.

Subject performance (Figure 7) reveals that RMSEs decreased significantly over the initial learning phase of the experiment \(F(8,32) = 5.75, p < .0005\). Most importantly, this improvement can be attributed to sequence learning because the RMSE increased when participants were switched back to random tracking in Trial 10 \(F(1,4) = 16.233, p < .02\) (missing performance data for one subject).

After transfer there was a significant reduction of the RMSE after the previously learned sequence was reintroduced at the perceptual level. This is reflected in the difference between Trials 14 and 15 \(F(1,5) = 47.45, p < .001\). The subsequent transfer to the motor condition did not lead to a significant difference of performance. From Experiment 2a we can deduce that subjects are most likely relearning the sequence as a spatially compatible task during the “Sm” condition. This is supported by the observation that performance deteriorates in the final all random block compared to the “Sm” condition in which the target was presented with respect to movements.

The mean rating (5.33 ± 1.2) and recognition (6.00 ± 10.5) scores indicated that participants were not aware of the sequence.

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Talairach coordinates (mm)</th>
<th>Percent change of activity, random to Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increasing activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L inferior temporal gyrus</td>
<td>(-46)</td>
<td>(-25) (-7)</td>
</tr>
<tr>
<td>L middle temporal gyrus</td>
<td>(-42)</td>
<td>(-79) (10)</td>
</tr>
<tr>
<td>R postcentral gyrus</td>
<td>(58)</td>
<td>(-24) (18)</td>
</tr>
<tr>
<td>L anterior cingulate</td>
<td>(-15)</td>
<td>(43) (22)</td>
</tr>
<tr>
<td>L central sulcus</td>
<td>(-16)</td>
<td>(-31) (67)</td>
</tr>
<tr>
<td><strong>Decreasing activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>(-37)</td>
<td>(39) (12)</td>
</tr>
<tr>
<td>L posterior parietal cortex</td>
<td>(-43)</td>
<td>(-45) (39)</td>
</tr>
<tr>
<td>R middle frontal gyrus</td>
<td>(24)</td>
<td>(22) (37)</td>
</tr>
<tr>
<td>L posterior parietal cortex</td>
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<td>(-43) (36)</td>
</tr>
<tr>
<td>L inferior precentral gyrus</td>
<td>(-31)</td>
<td>(-37) (42)</td>
</tr>
<tr>
<td>L precentral gyrus</td>
<td>(-43)</td>
<td>(15) (43)</td>
</tr>
<tr>
<td>L superior parietal</td>
<td>(-42)</td>
<td>(-42) (54)</td>
</tr>
<tr>
<td>R superior frontal sulcus</td>
<td>(21)</td>
<td>(-15) (57)</td>
</tr>
<tr>
<td>L superior parietal</td>
<td>(-25)</td>
<td>(-57) (61)</td>
</tr>
<tr>
<td>L superior frontal sulcus</td>
<td>(-16)</td>
<td>(-6) (64)</td>
</tr>
</tbody>
</table>

Locations were determined by a comparison of CBF values for Scans 7 and 8 using \(t\) test corrected for multiple comparisons. Anatomic locations in parenthesis are Brodmann’s areas according to the atlas of Talairach and Tournoux (1988).
Changes of brain activity during the initial sequence acquisition are summarized in Table 5. Increases of activity were most prominent in the bilateral precentral gyrus, in the probable location of the frontal eye fields. Bilateral increases were also present in the bilateral mesial frontal cortex within the supplementary motor area. The location of these sites with respect to local gyral anatomy and their time activity profiles are shown in Figure 8. Learning effects in the sensorimotor cortex were also examined without correction for multiple comparisons. In this case, significant increases were also observed in the arm area of the sensorimotor cortex during incompatible learning, although they were of a lesser magnitude than the changes in the frontal eye fields. Relative decreases of activity during sequence learning were observed in the bilateral cerebellum and temporal cortex.

To examine the effect of behavioral transfer, we compared changes of brain activity between Trials 14 and 16. In this case, all subjects had already transferred to trials where the joystick and cursor moved in the same direction. From Experiment 2a it was known that the sequence was initially learned with respect to target movement. When the target sequence was reintroduced in the same way that it was learned (Sp), with respect to the direction of target movement, there was a significant increase of activity in the anterior cingulate, temporal and sensorimotor cortex, as summarized in Table 6.

Figure 9 shows that the location of the sensorimotor site overlaps with the location of maximally increasing relative cerebral blood flow (rCBF) under compatible conditions observed in Experiment 1b, i.e., the arm area. Numerous sites decreased in activity with the reintroduction of the sequence under compatible condition, including the left frontal eye field and bilateral dorsal premotor cortex.

We did not test for transfer effects between the Sp and Sm conditions because of the lack of significant behavioral differences between these two tasks and the ambiguity in interpreting any transfer effects at this point of the experiment.

**GENERAL DISCUSSION**

The primary conclusion of these experiments is that the functional anatomic correlate for learning continuous sequential patterned limb movements depends critically on the specific sensory to motor transformation. Although skill learning in the imaging experiments was accompanied by progressive increases of activity in both the arm region of the sensorimotor cortex and the frontal eye fields, the relative contribution of these two areas depended on the spatial congruency of the task. From the present data it could argued that there is a functional hierarchy in this process. In the congruent case the arm (and cursor) movement is directly tracking target location. Thus, a representation of the sequence linked to the arm cortical area takes precedence. For the incongruent case the arm area is inversely related to target (and cursor) direction. Sequential eye movements, on the other hand, could be congruent to cursor and target and form the next best solution for tracking. Consistent with this hypothesis our results showed maximal learning-related changes in the frontal eye fields and weak activation in the arm area. Although we did not measure eye movements, from pilot studies with videotaping of subject eye movements we found consistent tracking movements of the eyes with the target. As a corollary, we found subjects could not reliably perform this task with the eyes held in fixation. This hierarchical model is also supported by CBF changes that occurred after transfer. With the reintroduction of the sequence under spatially compatible conditions, there was an associated increase of activity in the arm motor area of the sensorimotor cortex and decrease of activity in the frontal eye fields.

A potential pitfall of our study was the use of multiple study populations and experiments to identify areas involved in different forms of motor learning. Nevertheless, we have been cautious in not pooling our data inappropriately and the main conclusions of this study do not rely on negative inferences between populations. It is emphasized that the findings of Experiment 1b, (reorganization in the limb area of the motor cortex) strongly recapitulate what has been observed in many
previous studies of procedural learning. The results from Experiment 2b are strikingly different. It is unlikely that these group differences are related to experimental error. Another potential problem of this study was the rather complex result of testing for explicit recall and recognition in the spatially compatible task (Experiments 1a and 1b). In this task, subjects had no explicit knowledge of the presence of a short, simple repeating sequential pattern. In Experiment 2, none of the subjects, even when instructed there was a sequence, could reliably recall a portion of the sequence. This rules out the presence of conscious awareness in the learning task. Thus, learning-related changes during functional imaging are unlikely to be related to “top-down,” mental, or strategic operations. On the other hand, some of the subjects, after being told of a sequence, had the ability to correctly recognize the movement pattern and only if they actually performed the movements. This is consistent with implicit perceptual (visual or somatosensory) learning. This may represent the main substrate for skill learning in this task.

The dynamic property of learning-related changes observed in the current study is not without precedent (Grafton, Hazeltine, & Ivry, 1998). In a previous intralimb transfer study we observed a transfer of learning-related activity from the finger area to the arm area of the motor cortex when a sequence that was learned with respect to finger movements was reintroduced after subjects had transferred to a large keyboard requiring whole-arm movements. The results suggest that functional imaging may yield a fundamentally different measure of learning than is provided by experiments employing transcranial magnetic stimulation (TMS) or direct physiologic recording (Pascual-Leone et al., 1994). With the TMS method, the size of the representation for individual muscles of the hand can be estimated. With learning, the size of the representation for relevant fingers enlarged whereas it remained constant for irrelevant fingers. In this case the size of the representation is presumed to be linked to the motor cortex output map. A logical interpretation of the TMS data is that the change of activity or size of representation is related to a remodeling of the output map in the motor cortex. This interpretation is supported by physiological studies of rat and monkey showing use dependent, rapid reorganization of forelimb motor output maps, mediated by shifts of inhibitory inputs to the motor cortex (Donoghue, 1995; Jacobs & Donoghue, 1991; Nudo, Jenkins, & Merzenich, 1990; Nudo, Milliken, Jenkins, & Merzenich, 1996).

The functional imaging data identify a transitive process, with shifts of activity across motor output areas that may occur more rapidly than what is observed with TMS or neural recording. These shifts of activity measured by CBF may represent changes of afferent activity projecting into the motor areas. Indeed, it has been shown that metabolic or blood flow activation most strongly reflects a combination of excitatory and inhibitory presynaptic activity (Nudo & Masterton, 1986). What is remarkable from the current study is that the representation of previously learned sequences can “relocate” across motor output areas. This effect begs the question of whether there are unique sites in the cortex or basal ganglia that might be a source for this sequential information. We have previously suspected a critical role for the rostral inferior parietal lobule in representing sequences (Grafton et al., 1998). Learning-related changes were again observed in this area in Experiment 1b, under spatially compatible learning conditions. However, changes were not significant under spatially incompatible conditions. Alternatively, there is remarkable consistency with which the SMA and/or pre-SMA are active during sequence learning, suggesting a critical role for this premotor area. In contrast, we found no learning-related changes in the basal ganglia. From other studies of continuous visually guided tracking with similar methods we can consistently detect significant changes of activity in the globus pallidus, thalamus, and posterior putamen as a function of movement (Winston, Grafton, & Pohl, 1997), movement velocity (Turner, Grafton, Votaw, Delong, & Hoffman, 1998), and movement amplitude (unpublished data). Thus, the lack of learning-related changes in the present study is unlikely to be due to a general inability to detect activation of subcortical structures. Finally, it is possible that a widespread set of cortical areas may share information used to generate sequential information. In such a widely distributed process, no single area may uniquely demonstrate significant increases of blood flow during skill acquisition.

METHODS
Experiment 1a

Subjects
Seven undergraduate students (four male) from the University of Virginia participated to partially fulfill a course requirement.

Stimuli and Apparatus
Participants used an Advanced Gravis optical joystick (Advanced Gravis Computer Technology, Burnaby, Canada) to track a moving target, a 1.06-cm diameter black circle, across a white background (the computer screen). The experiment was conducted on a Macintosh Iici computer.

Throughout each 90-sec trial, the target moved smoothly at a rate of 105.6 mm/sec across the screen in the horizontal direction only. The vertical position was the midpoint of the screen. There were two kinds of trials, sequence and random. In random trials, the target reversed direction at randomly generated screen positions. In sequence trials, the target reversed at random
positions for the first last and middle 10 sec of each trial; during the remaining 60 sec the target turned at points determined by a sequence. Figure 1A shows the horizontal position of the target through the 90-sec trial and Figure 1B shows a repeating 10-sec movement pattern. In each trial throughout the experiment, the same 10-sec sequential pattern of target movement was repeated three times in a row, followed by the middle 10 sec of random turns, followed by the remaining three repetitions of the sequence. There were no breaks in target movement between these segments of the trial. Cursor location (controlled by the subject) and target position were compared by the program 5 times/sec. The frequency with which the target changed directions was the same for the random and sequence trials.

**Procedure**

Each participant performed a total of 28 trials. The first nine trials and the last trial were entirely random. All other trials contained the sequence. Participants were not informed about the repeating nature of the sequence trials. To simulate the body position to be used for PET imaging, a participant tracked the target while lying on the floor on a mat. Their head was supported with a pillow. Each participant was asked to position the joystick so that their grasp was comfortable. The monitor was approximately 75 cm above the participant’s knees, with the screen tilted towards their face.

After each trial, the screen displayed the participant’s RMSE for that trial. Participants were told to try to minimize the RMSE. Rest breaks, provided after every trial, were 2 min long. In addition, after the ninth and eighteenth trials, participants were given 10 min rest breaks during which they were asked to get up, stretch, get a drink of water, etc.

Following the 28 trials, participants were told that the target’s movement was always random for some people (although it was not), but it often moved in a sequence for others. They were asked to indicate which group they believed they were in on a scale of 1 (definitely in the random group) to 9 (definitely in the sequence group). Participants were also asked to track five 10-sec segments of target movement (the sequence and four distracters), and rate the likelihood that each was the segment that was repeated in the earlier task.

**Experiment 1b**

**Subjects**

Six normal young adult subjects (three men and three women), mean age 32 ± 14 years, volunteered for this study under informed consent in accordance with the Emory University Human Investigations Committee. Subjects were judged to be normal by excluding any prior neurologic, psychiatric, or major medical history and no person was on psychoactive medications. All subjects were strongly right handed (decile range 89–100; Oldfield, 1971).

**Behavioral Tasks and Performance Measures**

The pursuit task defined in Experiment 1a was used. A total of 30 trials were presented over the PET scanning session. As shown in Table 1, there were two practice trials between each scan trial and there were three random blocks at the end of the session.

**Imaging**

rCBF was determined using the PET autoradiographic method (Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, & Herscovitch, 1983). For each scan, a bolus of 35 mCi of H$_{2}$^{15}$O was injected intravenously commensurate with the start of the behavioral task. A 90-sec scan was acquired in “2-D mode” beginning 10 sec after tracer administration. Attenuation correction was based on a calculated method using boundaries defined separately on each emission scan coupled with a transmission scan of the PET head-holder. After reconstruction by filtered back-projection, image resolution was 11.8 mm full width at half maximum (FWHM) as verified by a line source. Blood samples were not acquired. Images of radioactive counts were used to estimate rCBF as described previously (Mazziotta et al., 1985; Fox, Mintun, Raichle, & Herscovitch, 1984).

**Image Analysis**

For each subject, all PET scans were coregistered to each other and the mean PET (Woods et al., 1998a) was then coregistered using affine and then nonlinear algorithms to a PET target atlas centered and rescaled to the Talairach atlas (Talairach and Tournoux, 1988; Woods et al., 1998b). The target was comprised of PET scans from 20 normal adult subjects. All PET studies were smoothed with a Gaussian filter to a final image resolution of 14.8 mm FWHM and globally normalized to each other by proportional rescaling. Application of the general linear model of analysis of variance (ANOVA) were used to calculate task differences on a pixel by pixel basis without global pooling of image variance (Woods et al., 1996).

For the given experimental paradigm there were several possible approaches for identifying learning-related changes of brain activity. We used a model of learning predicated on the notion that areas involved in the initial encoding of a movement sequence should demonstrate progressive increases of brain activity as learning takes place. This was tested with an ANOVA design using weighted linear contrasts comparing regional CBF values. In this case, the weights were defined by the mean performance for each of the 10 scan trials. This
statistic would identify areas where blood flow increased at a rate similar to changes of performance. This approach was used previously in studies of pursuit rotor learning (Grafton et al., 1992, 1994). The resultant $t$-statistic image was masked at a threshold of $p < .001$. Areas achieving this threshold were further evaluated for significance after correcting for multiple comparisons (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). Areas showing an inverse relationship between performance and rCBF were similarly identified. Areas reaching significance were superimposed on a reference atlas of MRI anatomy centered in Talairach coordinates with 2-D and 3-D renderings using the Advanced Visualization Systems (AVS) software package. rCBF values showing a significant change at all sites, for all scans and subjects, were obtained and percent change of CBF between tasks were calculated (see Tables 2, 5, and 6).

**Experiment 2a**

**Subjects**

Seventy-two undergraduate students (21 male) from the University of Virginia participated to partially fulfill a course requirement. Participants were randomly assigned to the “random,” “perceptual,” “motor,” or “identical” conditions with the constraint that an equal number of participants were in each condition.

**Stimuli and Apparatus**

The stimuli and apparatus were identical to those used in Experiment 1 except as follows. (1) The sequence involved 5 sec, rather than 10 sec, of target movement. Therefore, each 10-sec sequence segment consisted of two seamless repetitions of the sequence. (2) After behavioral transfer the target sequence was presented in reverse order. A reversed sequence was generated from the original sequence by translation and rotation: 250 pixels were added to each target position and then the direction of movement was reversed. The translation was necessary to keep the sequence on the screen.

Participants in the perceptual, motor, and random groups tracked with a reversed joystick during the first portion of the experiment. The reversed joystick was a joystick with its base turned 180° from the participant. With a reversed joystick there is a spatial 180° incompatibility between joystick and cursor directions. Moving the handle to the right results in the cursor moving to the left, and vice-versa. The “identical” participants used a joystick in standard orientation with compatible movements of joystick and cursor.

**Procedure**

Each participant performed a total of 13 trials, separated by 30-sec rest breaks. All participants were comfortably seated, with their arm resting on a counter with the monitor and joystick.

There were two phases to the procedure, learning and transfer. During the learning phase, participants learned a repeating sequence. During the transfer phase, some aspects of the sequence were kept constant and some changed. Aspects of the sequence were dissociated by changing the stimulus–response mapping so that some participants saw the same perceptual sequence, but made different motoric responses to it (perceptual condition) whereas other participants saw a different perceptual sequence at transfer than they had seen during the learning phase, but made the same sequence of motoric responses that they had during the learning phase (motor condition). Another group saw a different perceptual sequence and made different motor movements (random condition) and for a final group of participants, both the perceptual and motor sequence at transfer matched those seen during training (identical condition). The goal of these transfer conditions was to examine which aspect of the sequence (perceptual or motor) could support good performance during the transfer phase.

The dissociation of the perceptual and motor sequences was made possible by changing the stimulus–response mapping at transfer. During the learning phase, participants tracked the target with an incompatible stimulus–response mapping. When the joystick was moved to the left, the cursor moved to the right, and vice versa. At transfer, the mapping was made compatible. Thus in the perceptual condition participants saw the same perceptual sequence, but a different motor sequence was necessary to track the target. In the motor condition, a different perceptual sequence was used at transfer, constructed so that the motor responses necessary to track it were identical to those used during the learning phase. In the random condition, the sequence used at transfer had not been seen during the learning phase. The identical condition was slightly different; they used the compatible mapping during both the learning and the transfer phase so that the perceptual and motoric sequences would be same in the two phases. Subjects in all conditions saw the identical stimuli during the transfer phase. The difference among the conditions lay in the training during learning phase and how it related to the transfer phase.

The learning phase consisted of nine sequence trials followed by one random trail. The transfer phase was composed of a random trial, a sequenced trial, and then a final random trial.

As in Experiment 1, participant’s awareness of the sequence was assessed with a rating scale. In addition, a recall rather than a recognition test was used. This change was made to avoid the possibility of recognition failure due to idiosyncratic starting points. If participants think the sequence starts in its actual middle, for example, they may fail to recognize it when they see it starting at its beginning. For the recall test, participants
were asked to reconstruct the sequence out of cardboard segments. The pieces were three different lengths with arrows drawn on them. The pieces corresponded to the different segment lengths (the distance the target would travel before turning) of the sequence. Participants were asked to place 10 pieces in order to indicate the direction and distance of the target’s movement in the sequence. They were to use the piece that most closely matched the desired length.

**Experiment 2b**

**Subjects**

Six normal young adult subjects (two men and four women), mean age 30.0 ± 4.2 years, volunteered for this study under informed consent in accordance with the Emory University Human Investigations Committee. Subjects were judged to be normal by excluding any prior neurologic, psychiatric, or major medical history and no person was on psychoactive medications. All subjects were strongly right-handed (decile range 83–100; Oldfield, 1971).

**Behavioral Tasks and Performance Measures**

The task defined in Experiment 2a was used. Each trial lasted 90 sec. A total of 20 trials were presented over the PET scanning session. As shown in Table 4, there was one practice trial between each scan trial. The session began with two trials each of random practice in the compatible and incompatible conditions to familiarize subjects with the apparatus. Then, all subjects learned the sequence with the joystick reversed such that cursor and joystick moved in opposite directions. At transfer, the joystick was rotated 180° so that the cursor and joystick moved in the same direction. After transfer the previously learned target was reintroduced with the target moving in the same sequence as it had prior to transfer (“perceptual transfer, Sp”). Then, the target sequence was reversed leading to identical movements as had been used prior to transfer (“motor transfer, Sm”). Perceptual transfer was tested first as this manipulation demonstrated better evidence for a transfer effect in the psychophysical study 2a.

**Imaging**

Imaging procedures and spatial normalization were identical to Experiment 1b. Learning-related increases of activity were identified using an ANOVA design using weighted linear contrasts. In this case, the weights were defined by the mean performance for the six scan trials prior to behavioral transfer. This statistic would identify areas where blood flow increased at a rate similar to changes of performance. After transfer, areas showing changes of activity in association with the reintroduction of the sequence were identified using a pixel by pixel test comparing Scans 7 and 8. Results were assessed for significance, corrected for multiple comparisons and rendered using the same methods as Experiment 1b.

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