Functional Changes in Brain Activity During Acquisition and Practice of Movement Sequences

Hanneke I. van Mier, Joel S. Perlmutter, and Steven E. Petersen

In the present study, brain activations were measured using positron emission tomography (PET) over the course of practice. Fourteen right-handed participants were scanned during six 1-min periods of practice tracing a cut-out maze design with their eyes closed. Practice-related decreases were found in the right premotor and posterior parietal cortex and left cerebellum, increases in the supplementary motor area (SMA) and primary motor cortex. The decrease in right premotor activity and the increase in SMA was significantly correlated with a decrease in the number of stops, implying involvement in learning and storing the movement sequence. The significant correlation between decreases in errors and left cerebellar and right posterior parietal activity suggests a role in accuracy. Involvement of the primary motor cortex in motor execution is indicated by the correlation of increased activation and movement speed. These results suggest that different neural structures (involving a premotor-parietal-cerebellar circuit) play a role in a sequential maze learning task.

Key Words: practice-related, premotor cortex, supplementary motor area, cerebellum, parietal cortex, primary motor cortex

Behavioral results in motor tasks have shown drastic changes in performance as a result of practice. In most instances, slow, uncoordinated, and inaccurate movements become fast, coordinated, and accurate with practice. These behavioral changes are accompanied by changes in brain activations as shown in numerous imaging studies, supporting the idea of plasticity in the mature brain associated with learning and practice. Results from our and other studies have demonstrated that different brain regions are involved in the performance of unskilled and skilled tasks (Hikosaka et al., 1999; Krebs et al., 1998; Penhune & Doyon, 2002; Petersson et al., 1999; Sakai et al., 1998; Staines et al., 2002; Tracy et al., 2003; van Mier et al., 1998; Weissman et al., 2002).

Earlier results from our lab (van Mier et al., 1998) showed a shift in brain areas.
that were activated before and after practice. It was shown that different brain areas were activated during naive, unskilled motor performance than during practiced, skilled performance. In that study, normal right-handed participants moved a pen continuously in a clockwise direction through a cut-out maze as quickly and accurately as possible with their eyes closed. Skilled performance in this task was accompanied by a decrease in the number of stops between maze segments, a decrease in errors, and an increase in movement velocity. These behavioral changes were accompanied by changes in brain activation. Activation shifted from the right premotor cortex, the right parietal cortex, and the left cerebellum, which were mainly activated during initial unskilled performance, to activation of the supplementary motor area (SMA), which was primarily activated during skilled performance. Neuroimaging results from other groups are consistent with our findings (Decety et al., 1992; Deiber et al., 1996; Ghatan et al., 1995; Grafton et al., 1992; 1994; Jenkins et al., 1994; Jueptner et al., 1997b; Toni et al., 1998) (although not all studies measured or reported changes in all areas mentioned above).

The finding that different behavioral variables and brain areas changed as an effect of practice raises questions about the relationship of different performance parameters both to each other and to the timing and order of functional anatomical changes.

The longstanding idea in motor learning is that the acquisition of skills proceeds in different stages (Anderson, 1982; Fitts, 1964; Pew, 1966). A common view is that during the early stage, task performance is based on the recognition of a certain behavioral demand, which might be explicit (when a participant consciously knows that something needs to be learned), or implicit. Correction of gross performance errors takes place during the next stage. In the final stage, when less effort or attention is needed for task performance, fine adjustments in performance and over learning takes place. It has been suggested that different processes are associated with the different levels of skill, perhaps allowing the performance of a task to be programmed at different levels of complexity (Rosenbaum et al., 1987; van Mier & Hulstijn, 1993; van Mier et al., 1993). Because of this, different levels of performance might be expected to utilize different neural substrates.

Few imaging studies have measured changes in the whole brain over the course of motor practice (Grafton et al., 1994; Mueller et al., 2002; Toni et al., 1998). In the study by Grafton et al. (1994) participants were only scanned during different stages of motor learning and changes in brain activations were only correlated to an overall measure of performance. Toni and colleagues (1998) scanned participants throughout the course of learning but changes in brain activation were not correlated to changes in behavioral measures. Furthermore, in this study only 3 participants were tested and no control for movement execution was included. Although participants were scanned during six learning blocks and changes in errors and reaction time (RT) were measured in the study by Mueller et al. (2002), results from the first and last three blocks were combined, as were behavioral changes in errors and RT. Instead of studying changes over six blocks, combining the blocks left only two learning stages.

In our previous study (van Mier et al., 1998), participants were only scanned during naive and practiced performance and no information was available on the
time course of the practice-related changes. Therefore, the present study was set up to study the relationship between changes in different behavioral variables and changes in brain activations during the course of practicing sequential movements using the abovementioned maze task. Fourteen right-handed participants were scanned during six 1-min periods of practice on a sequential motor task. Participants were instructed to move as quickly and accurately as possible with a pen through a cut-out maze design with their eyes closed.

**Methods**

*Participants*

Fourteen volunteers (6 women and 8 men) participated in the imaging study. They ranged in age from 19 to 27 years, with a mean age of 23.7 years. All participants were strongly right-handed as determined by the Edinburgh Handedness Inventory (Raczkowski et al., 1974). None of the participants had a history of neurological or motor disorders.

The experimental procedure was approved by the Human Studies Committee and the Radioactive Drug Research Committee of Washington University. Before the experiment started, written informed consent, conforming to the guidelines and procedures set forth by both committees, was obtained for all participants. Participants were compensated for taking part in the experiment.

*Material*

One square design and two maze designs were used in the experiment (see Figure 1), consisting of 4 or 8 segments, connected by intersections and a total path length of 24 cm, if traced correctly. When following the mazes in a clockwise direction, each segment ended in a T-split. The designs were cut-out patterns, creating paths for the pen to traverse. Each path had a width of .5 cm and a depth of .15 cm. For the mazes, at each intersection two opposite direction choices could be made, one of which came to a dead end. The latter had a length of .5 cm. The designs could be traced continuously because they formed closed loops, i.e. the end point of one loop was the starting-point of the next loop. Two maze versions were used in the experiment, one version of the 8 segment maze was traced during performance of the naive maze and training sessions, the other 8 segment maze was traced during performance of the novel maze. The version of maze presentation was counterbalanced across participants.

During the experimental scans, the x- and y-coordinates of the pen movements were recorded with a precision of 1 mm and a frequency of 100 Hz using a CalComp 2500 digitizer (GTCO CalComp, Inc., Columbia, MD) and a specially designed pen (Maarse et al., 1988) both connected to an IBM PS2/30 microcomputer (see van Mier et al., 1993; 1998). During each 40 s experimental scan, movements were registered for a period of 1 min, starting 10 s before and finishing 10 s after each scan.
Task Description and Procedure

The designs were fixed on a digitizer, which was placed on a table positioned at the right side of the participant. The table was adjustable in height. Participants traced the designs with eyes closed while lying in the scanner with both arms lying in arm rests. They performed the tasks with their right hand. To minimize movement of the upper arm, shoulder, and head, the right upper arm was fixed with straps. Hand, wrist, and forearm were positioned freely above the writing tablet (See Figure 2). Participants were not allowed to inspect the maze designs by touch. Prior to the start of each experimental scan, the right hand of the participant was positioned at
the proper starting position of the design by the experimenter. Participants were told that the first movement was always upwards and were instructed to trace the designs as quickly as possible, to move continuously in a clockwise direction through the design, and to avoid entering blind alleys and backtracking of a segment. Before participants were placed in the scanner the task was described and a different (six segment) maze was shown as an example to explain the two-choice principle at intersections. During all scans the pen was kept on the writing tablet. Participants were verbally instructed when to start and finish tracing.

Eleven 40-s PET scans were performed for each participant, nine experimental scans and two rest scans, each separated by a 10-min inter-scan interval. All participants were scanned under the following conditions, which were presented in the following fixed order:

1. tracing the square design as quickly as possible, (SQUARE);
2. holding the pen in their hand without moving it (REST);
3. initial unpracticed maze tracing (NAIVE);
4. tracing the same maze during 1 min (TRAIN 1);
5. tracing the same maze during 1 min (TRAIN 2);
6. tracing the same maze during 1 min (TRAIN 3);
7. tracing the same maze during 1 min (TRAIN 4);
8. tracing the same maze during practiced performance (PRAC);
9. holding the pen in their hand without moving it (REST);
10. tracing a novel maze design (NOVEL);
11. tracing the novel maze after 4 min of practice (PRAC NOVEL).

A more detailed description of the abovementioned conditions can be found in van Mier et al., 1998. Participants had not been involved in maze tracing before the first maze condition (scan 3). During the 10-min interval between scans 10 and 11, participants practiced the novel maze continuously for 4 min (with a resting period of 30 s after 2 min of practice to control for effects of fatigue). The last condition was included to check for differences between discontinuous (four periods of 1 min tracing, interspersed with 10-min inter-scan intervals) and continuous practice. Participants were not involved in any task during the other intervals between scans.

It is known that mental practice can enhance performance and can lead to changes in brain activations (Jeannerod, 1995; Laffleur et al., 2002). Our design creates the opportunity to mentally practice the maze during the 10-min inter-scan interval between training sessions. Although experiments by our lab (Reithler et al., 2003; van Mier et al., 2001) in which the effects of mental practice were studied using the maze task showed only marginal effects of mental practice, we tried to exclude this possibility. Therefore, participants were not informed about the training scans, but received a general instruction stating that they would be asked to trace different mazes.
The square and novel mazes were included as control conditions (for the rationale behind including these conditions, see van Mier et al., 1998). The total PET session lasted about 2.5 hr. In a separate session, 1 to 10 days after the PET experiment, participants returned for an anatomical magnetic resonance image (MRI) scan, which lasted about 20 min.

PET and MRI Acquisition

The PET scanning activation methodology developed at Washington University described in van Mier et al. (1998) was used in this experiment. Participants lay supine in the scanner on an adjustable table. Because tracing was done with the right hand, an intravenous catheter was placed in the left arm. An individually molded plastic mask was securely and closely fit over the participant’s face to minimize head movement during the experiment. A lateral skull radiograph permitted assessment of head alignment in the scanner.

A Siemens-CTI 953B PET scanner was used and collected data for 31 axial planes with a center-to-center separation of 3.38 mm. Data were collected in a three-dimensional mode covering an axial field of view of 10.5 cm. Because of this somewhat limited axial field of view, participants were positioned either low or high in the scanner in such a way that the top of the brain and the cerebellum were scanned in at least 8 participants (see also van Mier et al., 1998). Optimized data collection for the whole brain could be obtained in 2 female participants. PET data from all participants were combined to acquire data for the whole brain.

After a 10-min transmission scan, the experimental scans were obtained by administering intravenously water labeled with $^{15}$O as a blood flow tracer. Relative regional cerebral blood flow (rCBF) was estimated using a bolus of 8 to 10 mL of saline containing 15 mCi of $H_2^{15}$O which was injected for each experimental scan. Participants started tracing 10 s before the onset of brain radioactivity. The interval between successive scans was about 10 min. MRI anatomical images were obtained on a Siemens 1.5-Tesla Vision System, using a sagittal MPRAGE T1-weighted sequence to acquire structural images with a voxel size of $1.25 \times 1 \times 1$ mm.

Data Analysis

Behavioral Data. For the behavioral data, the mean tracing velocity was measured for each 1 min period. The tracing period was also checked for the number of stops and errors (incorrect entries in dead alleys and backtracking of a segment; see also van Mier et al., 1993; 1998). Only the behavioral data of the participants in which a particular brain area was scanned were included in the analyses. For each of the dependent variables, repeated measurement ANOVAs were performed to study the effect of all conditions (during the 9 experimental scans). A separate analysis was done to study the effect of practice, including the naive, training, and practiced conditions performed during scans 3 to 8. Probabilities were adjusted using the Greenhouse-Geisser epsilon. When a significant effect of practice was observed in this ANOVA, post hoc comparisons were performed to assess differences between particular scan sessions.
PET Data. Reconstruction of the PET images was done using filtered back projection. The transaxial resolution was 14 mm full width at half maximum after reconstruction with a Butterworth .5 filter with an order of five. A linear normalization was applied to the smoothed images. PET and MRI images were anatomically normalized using automated image registration to transform each participant’s PET and MRI into Talairach space (Talairach & Tournoux, 1988). The structural MRI image was coregistered to the PET image.

For each participant, images were grouped in experimental minus rest pairs and subtracted from each other. No excessive movement artifacts were observed in any of subtractions. To improve signal-to-noise, single subtraction images of identical conditions were averaged across all 14 participants in such a way that the top and the bottom of the brain included data from at least 8 participants, while a small area in the middle of the brain included data from all 14 participants. Averaged subtraction images were then searched by an automatic maximum-detection algorithm to identify and record all maxima by location in stereotaxic coordinates and by magnitude in PET counts. For each region of interest a repeated measurement ANOVA was performed on the magnitudes in all conditions (during the 9 experimental scans). A separate analysis was done to study the effect of practice, including the naive, training, and practiced conditions performed during scans 3 to 8. Probabilities were adjusted using the Greenhouse-Geisser epsilon.

Results

Behavioral Data

We first tested if there were any behavioral differences between the group of participants in which the top of the brain was scanned and those in which the bottom of the brain was scanned. Repeated measurement ANOVAs showed no significant differences between the two groups for any of the dependent variables ($p = .99$ for velocity; $p = .78$ for errors; $p = .87$ for stops). Both groups performed at more or less the same speed, the same accuracy and smoothness.

Secondly, a repeated measurement ANOVA was performed for each dependent variable for all 9 conditions, including only the participants in which particular brain areas were scanned (8 participants for cortical areas, 9 participants for the cerebellum; see Table 1). Note that the participants whose cortical areas were scanned were different from the participants in which the cerebellum was scanned (with two overlapping participants in which the whole brain was scanned). Highly significant conditional effects were found for changes in velocity, errors, and stops ($p < .001$ for velocity and stops, $p < .01$ for errors). Finally, a repeated measurement ANOVA was performed on the 6 conditions related to practice, scans 3 to 8, including the naive, training, and practiced conditions. Changes in stops, errors, and velocity were highly significant ($p < .001$ for velocity and stops, $p < .01$ for errors).

As shown in Figure 3, the behavioral data displayed in the leftmost graphs showed different practice-related effects. While stops and errors decreased with practice, velocity increased. Figure 3 clearly shows that the learning curves have different time courses. The largest decrease in stops was found between Sessions 1 and 2, for errors between Sessions 2 and 3, while the largest increase in velocity was
Table 1  Means and SD (in parentheses) of dependent variables for each experimental condition (averaged over 8 [for cortical areas] or 9 [for cerebellum] participants that contributed to the activations in the brain areas given below) and magnitudes (in PET counts) per condition for areas showing practice-related changes

<table>
<thead>
<tr>
<th>Conditions</th>
<th>n</th>
<th>Naive</th>
<th>Train 1</th>
<th>Train 2</th>
<th>Train 3</th>
<th>Train 4</th>
<th>Prac</th>
<th>Novel</th>
<th>Pr. nov</th>
<th>Sq. fast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stops per loop</td>
<td>8</td>
<td>6.8 (1.6)</td>
<td>5.3 (2.8)</td>
<td>5.0 (3.3)</td>
<td>3.8 (2.9)</td>
<td>2.7 (2.8)</td>
<td>1.5 (2.4)</td>
<td>4.6 (2.5)</td>
<td>1.3 (2.1)</td>
<td>0.3 (0.3)</td>
</tr>
<tr>
<td>Errors per loop</td>
<td>8</td>
<td>7.1 (8.0)</td>
<td>7.7 (10.2)</td>
<td>4.2 (6.1)</td>
<td>2.7 (4.6)</td>
<td>1.7 (2.1)</td>
<td>0.6 (0.7)</td>
<td>2.9 (0.7)</td>
<td>0.1 (2.7)</td>
<td>0.0 (0.2)</td>
</tr>
<tr>
<td>9</td>
<td>6.8 (7.2)</td>
<td>7.4 (8.3)</td>
<td>4.5 (5.6)</td>
<td>2.6 (3.4)</td>
<td>1.4 (1.9)</td>
<td>0.5 (0.8)</td>
<td>3.5 (3.1)</td>
<td>0.3 (0.3)</td>
<td>0.0 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Velocity (cm/sec)</td>
<td>8</td>
<td>4.6 (2.9)</td>
<td>6.2 (5.2)</td>
<td>7.5 (6.1)</td>
<td>8.7 (6.3)</td>
<td>11.3 (6.7)</td>
<td>12.6 (6.1)</td>
<td>8.1 (4.3)</td>
<td>14.2 (5.1)</td>
<td>20.7 (6.9)</td>
</tr>
</tbody>
</table>

Activated area

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>R. premotor cortex (25, -3, 50; BA 6)</td>
<td>8</td>
<td>164</td>
<td>129</td>
<td>118</td>
<td>104</td>
<td>123</td>
<td>95</td>
<td>136</td>
<td>95</td>
<td>75</td>
</tr>
<tr>
<td>SMA (-7, -11, 54; BA 6)</td>
<td>8</td>
<td>12</td>
<td>63</td>
<td>71</td>
<td>73</td>
<td>67</td>
<td>100</td>
<td>63</td>
<td>94</td>
<td>108</td>
</tr>
<tr>
<td>L. cerebellum (-31, -45, -30)</td>
<td>9</td>
<td>138</td>
<td>164</td>
<td>94</td>
<td>101</td>
<td>82</td>
<td>68</td>
<td>129</td>
<td>54</td>
<td>42</td>
</tr>
<tr>
<td>R. pos. parietal cortex (15, -63, 50; BA 7)</td>
<td>8</td>
<td>152</td>
<td>159</td>
<td>101</td>
<td>110</td>
<td>83</td>
<td>75</td>
<td>123</td>
<td>93</td>
<td>13</td>
</tr>
<tr>
<td>L. motor cortex (-31, -23, 54; BA 4)</td>
<td>8</td>
<td>213</td>
<td>229</td>
<td>237</td>
<td>239</td>
<td>280</td>
<td>296</td>
<td>257</td>
<td>302</td>
<td>356</td>
</tr>
</tbody>
</table>

Note. Coordinates are given in Talairach (1988) format in the order x, y, z, where x is the lateral displacement from the midline (- for left hemisphere); y is the anteroposterior displacement relative to the anterior commissure (- for positions posterior to this; and z is the vertical position relative to the AC-PC line (- if below this line). R, right; L, left; BA, Brodmann Area. Train x, Training x; Prac, Practiced; Pr. nov, Practiced novel; Sq. fast, Square fast.

observed on average between Sessions 4 and 5. Post hoc comparisons between the six practice conditions showed that for stops only a significant difference was found between Sessions 1 and 2 (p < .05). Differences between Sessions 2 and 3, 3 and 4, 4 and 5, and 5 and 6 were not significant. As for velocity, a significant difference was only observed between Sessions 4 and 5 (p < .01). None of the other differences between adjacent sessions were significant. For errors a significant difference (p < .05) was found between Sessions 2 and 3 for the participants in which the cerebellum
Figure 3—Effects of practice for number of stops, errors, and mean velocity, and for activations in right premotor cortex, SMA, right posterior parietal cortex, left cerebellum, and left motor cortex (magnitude in PET counts). Note that the errors in the second row are based on the performance of 8 participants in which the top of the brain was scanned, the errors in the third row on performance of 9 participants contributing to the activations in the cerebellum.
Figure 4—Horizontal sections through the top and bottom of the brain showing areas of positive blood-flow changes during maze practice compared to a rest control condition. The subtraction images are horizontal slices through the top (z = 52) and bottom of the brain (z = –28) shown in Talairach space (1988). These sections show the blood flow changes over the course of practice. Left in the images corresponds to the left hemisphere and the top to the front of the brain. Labeled areas: 1 = premotor cortex, 2 = superior parietal cortex, 3 = supplementary motor area, 4 = primary motor cortex, 5 = cerebellum. Note that grey areas with a light colored outline (e.g. areas 1 and 2 in the Naive–Rest condition) represent high activation. A color print or .pdf image of Figure 4 can be obtained by contacting the first author at h.vanmier@psychology.unimaas.nl.
was scanned, a trend \((p < .07)\) was measured for the difference between Sessions 2 and 3 for the participants in which the posterior parietal cortex was scanned with no significant differences between the other adjacent sessions.

Although differences in learning curves between participants were observed, in all participants the sharpest decreases between successive sessions for stops and errors preceded the steepest increase between sessions for velocity.

**Imaging Data**

The right premotor cortex, the SMA, the right posterior parietal cortex, and the left primary motor cortex were completely sampled in 8 participants, the left cerebellum in 9 participants. As can be seen in Figures 3 and 4, practicing traversing the mazes resulted in decreases in brain activations in the right premotor and the right parietal cortex. An area in the left lateral cerebellum also became less activated over the course of practice. In contrast, the SMA and the left primary motor cortex became more involved during practice. Repeated measurement ANOVAs including the naive, training, and practiced conditions revealed significant decreases in brain activations in the right premotor cortex, the right posterior parietal cortex, and the left cerebellum (all \(p < .05\)). On the other hand, significant increases were observed in the supplementary and the primary motor areas (\(p < .05\) and \(p < .01\), respectively).

Repeated measurement ANOVAs including all 9 conditions showed a highly significant effect of condition in the left primary motor cortex, the right premotor cortex, the right posterior parietal cortex, the SMA, and the left cerebellum (all \(p < .01\)). As can be seen in Table 1, when participants were confronted with a second novel maze after having practiced the first maze, activation returned to levels observed during early performance of the first maze. After having practiced this second maze, comparable decreases and increases in brain activations to those found for the first maze were observed. No significant differences were found between the practiced condition of the first and second maze regarding performance measures and magnitudes, suggesting that discontinuous and continuous practice in this task lead to the same results. The activations observed in the square fast

### Table 2  Significance levels of correlations between behavioral measures and brain activations

<table>
<thead>
<tr>
<th></th>
<th>Stops</th>
<th>Errors</th>
<th>Velocity</th>
<th>R. Premotor</th>
<th>SMA</th>
<th>L. Cerebellum</th>
<th>R. Parietal</th>
<th>L. Motor cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stops</td>
<td>p &lt; .001</td>
<td>p &lt; .001</td>
<td>p &lt; .05</td>
<td>p &lt; .05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Errors</td>
<td>p &lt; .01</td>
<td>p &lt; .01</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; .01</td>
<td>p &lt; .01</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Velocity</td>
<td>p &lt; .001</td>
<td>p &lt; .01</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; .05</td>
<td>p &lt; .05</td>
<td>p &lt; .01</td>
<td>n.s.</td>
</tr>
<tr>
<td>R. Premotor</td>
<td>p &lt; .05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; .001</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>SMA</td>
<td>p &lt; .05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; .001</td>
<td>p &lt; .05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>L. Cerebellum</td>
<td>n.s.</td>
<td>p &lt; .01</td>
<td>p &lt; .05</td>
<td>n.s.</td>
<td>p &lt; .05</td>
<td>p &lt; .001</td>
<td>p &lt; .05</td>
<td>n.s.</td>
</tr>
<tr>
<td>R. Parietal</td>
<td>n.s.</td>
<td>p &lt; .01</td>
<td>p &lt; .05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; .001</td>
<td>n.s.</td>
</tr>
<tr>
<td>L. Motor cortex</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; .01</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; .05</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Note:* Contrasts that were correlated negatively are presented in *italic.*
condition were comparable to those reported in earlier studies (van Mier et al., 1998, van Mier & Petersen, 2002).

As shown in Table 2, when time courses in behavioral measures were correlated with those in brain activations, a significant, positive correlation was observed between changes in stops and activations in the right premotor cortex (p < .05), while a significant, negative correlation was found between changes in stops and activations in the SMA (p < .05). Changes in left cerebellar and right posterior parietal activations correlated positively with changes in errors (p < .01), while changes in the primary motor cortex correlated most significantly with changes in velocity (p < .01).

A strong negative correlation of .97 was measured between changes in the right premotor cortex and the SMA, while a strong positive correlation of .92 was found between the left cerebellum and the right posterior parietal cortex (both p < .001). Changes in the left cerebellum also correlated negatively with changes in the SMA and the left primary motor cortex, although to a lesser extent (p < .05). Table 2 presents the p-values of correlations between activations in abovementioned brain areas.

**Discussion**

Changes in blood flow over the course of practice were measured with PET in a group of 14 participants while they traced a maze with their right hand and eyes closed during six separate sessions of 1 min, separated by intervals of 10 min. Practice resulted in faster, more accurate, and coordinated tracing performance, decreased activation in the right premotor, the right posterior parietal cortex, and the left cerebellum, and increased activation in the SMA and the primary motor cortex. Furthermore, differential changes between behavioral parameters and brain areas were found.

We would like to stress that in addition to the abovementioned brain areas, several other areas showed increased activation during maze and square tracing. Cortical, subcortical, and cerebellar areas reported in the study by van Mier et al. (1998; 2002) were also activated in this experiment. In this paper, however, we focus on areas that showed significant practice-related changes over the course of six successive 1-min tracing sessions.

We found that behavioral parameters changed with different time courses during the process of sequential motor learning. This result is in agreement with other studies (Eversheim & Bock, 2001; Flament et al., 1999). In our task, the largest decrease in stops was observed on average between Sessions 1 and 2, the largest decrease in errors between Sessions 2 and 3, while the largest increase in velocity was found between Sessions 4 and 5. Only differences between these sessions were found to be significant or showing a trend (for errors in participants contributing to right parietal activations). Although differences in learning curves between participants were observed, in all participants the largest decrease between adjacent sessions for stops and errors preceded the strongest increase for velocity. The behavioral data showed the same pattern found in earlier experiments in our lab; with practice, participants became faster, more accurate, and stopped less (van Mier et al., 1993; 1998; van Mier & Petersen, 2002). More errors made during early performance in this study compared to our previous study (van Mier et al., 1998) might reflect that in the 1998 study participants had been subjected to a different 10-segment maze before naive performance on the 8-segment maze. As can be seen
in Table 1, fewer errors were made in this study during tracing of the second, novel maze, suggesting that fewer errors are elicited when the overall structure of one of the mazes is known. Yet, the observation that more errors were made during the first training session than during naive tracing is not consistent with this explanation. Keep in mind that participants were not informed that they would be presented successively with the same maze. Most participants reported afterwards that they had expected a different maze and therefore took opposite turns at the end of the segments, producing more errors. During later training sessions participants noted more quickly that the same maze was presented again.

With respect to brain activations, the practice-related changes observed in our earlier PET study (van Mier et al., 1998) were replicated in this experiment; over the 6 sessions we observed that activations in the right premotor cortex, the right posterior parietal cortex, and the left cerebellum decreased while activations in the SMA and the primary motor cortex increased. As was found for the behavioral data, the changes in blood flow also showed different time courses. To determine if specific behavioral measures could be used to parse neural substrates, we correlated the practice-related changes in the behavioral data directly with the changes in brain activations. Changes in activations in the right premotor cortex and the SMA were significantly different between Sessions 1 and 2 and showed a time course that correlated highly significantly with changes in stops at the end of the maze segments. This suggests that the first learning stage in this study entailed the learning of the specific movement sequence. During the next learning stage participants showed a decrease in the number of errors, which correlated significantly with a decrease in activation in the left cerebellum and the right posterior parietal cortex. In both brain areas, the biggest decrease in activation was observed between Sessions 2 and 3 as was found for the decrease in errors. Only when participants had more or less learned the correct path and sequence could they focus on movement execution, resulting in increased speed, with the highest increase between Sessions 4 and 5, being significant. This might indicate that the participants have reached the next learning stage, in which less effort is needed for the more cognitive, higher level aspects of the task and more effort can be directed at lower levels related to the execution of the task. The finding that the activation in the primary motor cortex also showed the largest increase between Sessions 4 and 5 and the significant correlation between increased speed and the primary motor cortex activation suggest involvement of the latter in motor execution.

Premotor Cortex and SMA

Evidence that the premotor cortex and the SMA play a role in sequence learning comes from several other imaging studies (de Weerd et al., 2003; Doyon et al., 2002; Grafton et al., 1994; Lee & Quessy, 2002; Toni et al., 1998; Ullen et al., 2003; for a review see also van Mier, 2000). A study in which monkeys practiced several motor sequences has shown that neurons in the SMA were only active when the monkeys performed the learned sequences (Tanji et al., 1994). Our results suggest that both the premotor cortex and the SMA are involved in sequential processing, however, during different phases. The premotor cortex was mainly activated during naive and early maze practice, conditions during which performance was most likely guided by external cues (bumping into the sides of the maze at the end of the
segment, resulting in a stop). Later in practice, when performance became more coordinated and smoother (participants stopped less at corners and pen trajectories were rounded at the corners, see also van Mier et al., 1993) reliance was on internal cues controlled by the SMA. These results are in agreement with sequential motor learning models proposed by Hikosaka and colleagues (1999; 2002).

Although one might have expected that right hand performance would result in practice-related changes in the left premotor cortex rather than in the right premotor cortex, in our previous study we found that the right premotor was activated in right-handed participants performing the task with the right as well as with the left hand. When we scanned our first group of participants in that study, who performed the task with the right hand, we were surprised to find right premotor activation related to practice. When we scanned a second group of right-handed participants, performing the task with the left hand, however, we found the same practice-related activation in the right premotor cortex. As we concluded in that paper, the right premotor cortex most likely codes information at an abstract level that is distinct from the motor performance of the task itself. This is in accordance with Harrington et al. (2000), who stated that their results in a sequential key press task were consistent with the role of the premotor cortex in the retrieval or preparation of abstract action plans.

In the present study we also observed activation in the left premotor cortex. Changes in activations in this area did not show a practice-related pattern, however. Conditional changes found in the left premotor cortex might have been related to temporal aspects of the task (Halsband et al. 1993; Seitz et al. 1994; van Mier et al., 1998).

Cerebellum

There is growing evidence from neuroimaging studies that the cerebellum is mainly activated during early learning and that this activity decreases with practice (Doyon et al., 2002; 2003; Grafton et al., 1994; Hund-Georgiadis & von Cramon, 1999; Penhune & Doyon, 2002; Toni et al., 1998; van Mier, 2002). Evidence that the cerebellum is involved in motor learning comes also from studies involving patients and animals with cerebellar lesions showing impaired motor and sequence learning in patients (Gebhart & Thach, 1999; Laforce & Doyon, 2002; Molinari et al., 1997; Sanes et al., 1990; Shin & Ivry, 2003) and maze learning in animals (Lalonde & Botez, 1990; Lalonde et al., 1996). The strong correlation between errors and cerebellar activation in our study suggests a role for the cerebellum in error processing. Increased cerebellar activation related to performance errors is also reported by other researchers (Flament et al. 1996; Imamizu et al., 2000; Jenkins, 1994; Miall et al., 2000). Furthermore, others have also proposed cerebellar involvement in error detection or correction (Kawato & Gomi, 1992; Thach, 1998; see also van Mier & Petersen, 2002).

Results from a recent fMRI study by Seidler et al. (2002) suggest that changes in cerebellar activation are related to changes in performance rather than changes associated with motor learning. In their study, participants performed nine blocks of the serial reaction time task in which the stimuli appeared either randomly or in a fixed 12-element sequence. During the first six blocks (two random blocks
and four sequence blocks) participants performed the task concomitantly with a distractor task. Behavioral data showed that performance on the random and sequence blocks was not significantly different. The fMRI data showed no significant cerebellar activation during these six blocks. During the last three blocks (two random and one sequence block) participants performed the task in the absence of the distractor task. Performance was significantly better during the sequence block without the distractor compared to the sequence blocks with the distractor, suggesting that participants had learned the sequence during the latter. Furthermore, better performance in the former was accompanied by significant bilateral cerebellar activation, while the cerebellum was not significantly activated during the random blocks. These data suggest that the cerebellum was not active during the initial learning of the sequence but only when the learned sequence was expressed as shown by improved performance. Our data and those from other imaging studies in which improved performance resulted in decreased cerebellar activation, are in contrast with this hypothesis. It is, however, possible that the cerebellum only contributes to motor learning when certain requirements are met and is not recruited when a movement sequence has to be learned concurrently with a distractor task.

As was the case with the premotor activation, the fact that the left cerebellum showed a practice-related decrease in activation while the right lateral cerebellum did not also assumes abstract coding for the lateral left cerebellum. It should be noted that the right lateral cerebellum was also activated in the present study as was the anterior cerebellum, but these areas showed changes related to timing aspects of the task; the right lateral cerebellum seems to be involved in higher cognitive aspects of motor timing while the ipsilateral anterior cerebellum seems to play a role in timing aspects during movement execution (van Mier & Petersen, 2002).

**Posterior Parietal Cortex**

Numerous imaging studies observed that improved performance as an effect of practice produced decreased activation in the parietal cortex (de Weerd et al., 2003; Jenkins et al., 1994; Jueptner et al. 1997a; Mueller et al., 2002; Poldrack et al., 1998; Toni et al., 1998). Haslinger et al. (2002) found a positive correlation between activation in the parietal cortex and increases in sequence length and complexity. The observed practice-related decrease in parietal activation in our study might reflect chunking of the elements, thus the sequence becomes “shorter” and less complex. Changes in activation in the posterior parietal cortex showed the same practice-related pattern as changes in errors. Because there is no evidence suggesting that the right posterior parietal cortex is directly implicated in error processing, changes in activation are most likely related to different processes, such as kinematic and sensory processing, attention, and/or spatial processing.

It is known that the posterior parietal cortex is involved in kinematic and sensory processing (in humans: Binkofski et al., 1999; Darling et al., 2004; Freund, 2003; Harrington et al., 2000; Rizzolatti et al., 1998; in animals: Klam et al., 2003), and online movement control (Grea et al., 2002). Over the course of practice, participants in our study bumped less into the sides of the maze (see also van Mier et al., 1998) thereby decreasing sensory processing. When a blind alley was entered, however, an error was signaled by bumping into the side.
Another possibility is that when participants encountered an error, they paid more attention to the trajectory of the maze to avoid future errors, which might explain the significant correlation between parietal activation and errors. This is consistent with studies reporting that the posterior parietal cortex is engaged in processes related to attention (Behrmann et al., 2004; Nair et al., 2003; Petersen et al., 1994).

Right parietal involvement can also be related to spatial aspects of the task. When an error is detected, participants likely attend to the spatial aspect of the task, to determine where in the maze they are located and in which direction to continue. Involvement of the parietal cortex in tasks requiring a response based on spatial processing has been reported in several studies (Crowe et al., 2004; Deiber et al., 1996; Jeuptner et al., 1997a; Schumacher et al., 2003; van Mier, 2000).

To summarize, the activations observed in the posterior parietal cortex in the present study and the significant correlation of these activations with changes in the number of errors can be related to several aspects, such as kinematic and somatosensory processing, attention, and spatial processing. Because all these processes might come into play when participants encounter an error, at this point it is hard to identify one specific process to the parietal involvement in our study.

**Primary Motor Cortex**

The significant correlation between increased speed and primary motor cortex activation observed in our study suggests a role for the latter in aspects of motor control related to movement execution. A connection between speed/frequency and activation in the primary motor cortex has been established in several other imaging studies (Jancke et al., 1998; Jenkins et al., 1997; Nakai et al., 2003; Schlaug et al., 1996). Furthermore, in studies where movement rate and amplitude were kept constant between conditions, no differences in primary motor cortex activation were found (Friston et al. 1992; Haslinger et al., 2002; Jenkins et al. 1994; Raichle et al. 1994). There are, however, studies that have shown a progressive increase in motor cortex activations during motor learning, although kinematics were held constant (Hazeltine et al., 1997; Karni et al., 1995; Pascual-Leone et al., 1994). It is possible that in our study both practice and velocity-related effects played a role, but that the former were masked by the latter.

**Conclusion**

Our results have shown that different neural structures (involving a premotor-parietal-cerebellar circuit) play a role in practice-related aspects of our sequential maze learning task, each showing different time frames of learning, being related to different dimensions and stages of the learning process. The right premotor cortex and the SMA appear to play a role in movement sequencing, while the left cerebellum and the right superior parietal cortex seem to be related to accurate performance of the task. The primary motor cortex is most likely involved in aspects of motor execution.

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References


Brain Activity and Movement Sequences


van Mier, Perlmutter, and Petersen


