Robot-Aided Functional Imaging: Application to a Motor Learning Study

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Abstract: The purpose of this study was to examine the neural activity underlying an implicit motor learning task. In particular, our goals were to determine whether initial phases of procedural learning of a motor task involve areas of the brain distinct from those involved in later phases of learning the task, and what changes in neural activity coincide with performance improvement. We describe a novel integration of robotic technology with functional brain imaging and its use in this study of implicit motor learning. A portable robotic device was used to generate forces that disturbed the subjects' arm movements, thereby generating a "virtual mechanical environment" that the subjects learned to manipulate. Positron emission tomography (PET) was used to measure indices of neural activity underlying learning of the motor task. Eight healthy, right-handed male subjects participated in the study. Results support the hypothesis that different stages of implicit learning (early and late implicit learning) occur in an orderly fashion, and that distinct neural structures may be involved in these different stages. In particular, neuroimaging results indicate that the cortico-striatal loop may play a significant role during early learning, and that the cortico-cerebellar loop may play a significant role during late learning. *Hum. Brain Mapping* 6:59–72, 1998. © 1998 Wiley-Liss, Inc.

Key words: robot-aided; functional imaging; motor learning; arm movement

INTRODUCTION

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We have been investigating "explicit and implicit learning and memory" [Rauch et al., 1995, 1997]. Explicit learning and memory refer to the acquisition and retrieval of information accompanied by awareness of the learned information and its influence. Implicit learning and memory refer to similar acquisition without awareness of the learned information and

its influence. In particular, we have been investigating explicit learning and memory and “procedural learning,” which is a form of implicit learning where skill improves over repetitive trials. In our previous study, we reported neuroimaging results on these functionally distinct forms of learning and memory using a serial reaction time (SRT) paradigm [Nissen and Bullemer, 1987]. The paradigm consisted of showing an asterisk in one of four locations arranged in a single row in a computer monitor. Subjects used the index and middle fingers of both hands to press one of four response keys, each corresponding to one position in the computer monitor. Subjects were instructed to press the key below the location of the asterisk as quickly as possible without making errors. The procedure consisted of nine blocks of 144 trials with 12 repetitions of a 12-item sequence. Subjects were blind to the presence of the sequence during the implicit blocks, and were informed of the sequence prior to the explicit blocks, with implicit blocks bracketed by random blocks. Neuroimaging results indicated increased regional cerebral blood flow (rCBF) in structures which constitute key elements of the corticostriatal loop, thus supporting models that posit the corticostriatal loop as playing a significant role during implicit learning.

Other models for procedural learning emphasize the role of motor execution areas. For example, Grafton et al. [1994] studied procedural motor learning in a pursuit rotor task. Their comparison of three sequential scans during motor skill acquisition showed an increase of activity in the cortico-cerebellar loop.

Current theories of human learning and memory consider that the brain is composed of fundamentally and anatomically separate but interacting learning and memory systems [Schacter and Tulving, 1994]. We speculated that the alternate preeminent role played by the two brain loops in different paradigms could be related to the different mechanisms associated with procedural learning in a task with prominent motor demands (rotor pursuit) vs. a task with more cognitive-perceptual demands (sequence learning). Therefore, we set the goal of designing a procedural learning paradigm where the learning process might shift from perceptual to motor, to test the hypothesis that the corticostriatal and cortico-cerebellar circuits change as the demands of the learning task change.

An elegant line of study, incorporating an idea expressed by the Russian physiologist Bernstein, served as an inspirational guide. Bernstein suggested that since we cannot directly access the inputs to the human motor system, we have to “fool it.” Experiments first reported by Shadmehr and Mussa-Ivaldi

[1994] used a robotic device to generate a force field that responded to the subjects’ arm movements, thereby generating a “haptic virtual environment” that subjects learned to manipulate. Because of its prominent motor phase and because it has been used extensively in previous motor learning research, we chose an experimental design similar to that of Shadmehr and Mussa-Ivaldi [1994; Brashers-Krug et al., 1996].

Here we report on the combination of two well-established and validated technologies, positron emission tomography (PET) and the Massachusetts Institute of Technology (MIT) robotic manipulanda, to study the neural activity underlying the force field dynamic implicit motor learning task. In particular, our goals were to determine whether initial phases of procedural learning of a motor task involve areas of the brain distinct from those involved in later learning phases of the same task, and what changes in neural activity coincide with performance improvement [Krebs et al., 1995].

METHODS

Apparatus

This study used a novel robot, MIT-MANUS, designed for clinical neurological applications [Hogan et al., 1995; Krebs et al., 1996]. Unlike most industrial robots, MIT-MANUS is configured for safe, stable, and compliant operation in close physical contact with humans. This is achieved using impedance control, a key feature of the robot control system. MIT-MANUS can move, guide, or perturb the movement of a subject’s or patient’s upper limb and can record motions and mechanical quantities such as position, velocity, and forces applied. The present design is portable and meets or exceeds applicable safety standards for operation in a clinical environment. MIT-MANUS has completed its first pilot clinical trial in the Burke Rehabilitation Hospital to determine its applicability to rehabilitation of stroke patients [Aisen et al., 1997; Krebs, 1997], and a second pilot clinical trial is underway. MIT-MANUS presently has two modules. The “2-dof” module provides two translational degrees of freedom for elbow and forearm motion. The “3-dof” module provides three degrees of freedom for wrist motion. In this study, only the 2-dof module was required. The 2-dof module is lightweight (88 lb), low-friction, and back-drivable, consisting of a direct-drive five bar-linkage SCARA (selective compliance assembly robotic arm) mechanism with 16-bit high-resolution resolvers for position and velocity measurements. Redundant velocity sensing is provided by

DC-tachometers with a range of 14 mV output at 0.008 rad/sec. Torque sensors with a range of 22.6 N.m are mounted on the brushless motor output shafts. The brushless motors are rated to 7.86 N.m of continuous stall torque. The robot control architecture is implemented in a standard personal computer (486 CPU, 66 MHz). This computer also displays the task to be performed to both the operator and subject via a video-splitter with dedicated monitors. The subject's monitor rests in a custom-made holder located close to the ceiling above the PET table. This allows the subject, while supine on the PET table, to view the monitor and access the handle on the end of the robot.

Subjects

Eight healthy male subjects participated in this study after written consent was obtained. All procedures were in accordance with the guidelines and approval of the MIT Committee on the Use of Human Experimental Subjects and the Massachusetts General Hospital (MGH) Subcommittee on Human Studies. The subjects were between 21–35 years old (mean age 24), right-handed (with a handedness quotient >75% by the Edinburgh Inventory [Oldfield, 1971]), and native English speakers. All subjects were naive to the motor learning task.

Motor learning task

The visually-evoked and visually-guided task consisted of moving the robot end-effector from its initial position towards a target, in a point-to-point movement. The target set had a fixed number of positions in a horizontal two-dimensional (2D) plane, as shown in Figure 1.

The outward targets 1–4 were randomly presented. The inward homing target 0 was presented following each of the outward targets. Every outward target was presented an equal number of times. Note that the hand coordinates were different from the visual coordinates, in order to compensate for the rectangularity of the monitor. The subject, while supine on the PET table, grasped a handle on the end-effector of the robot, as illustrated in Figure 2. He was instructed to move the end-effector to the presented target within 0.8 sec. The color of the target changed for the subsequent 0.8 sec, and a new target was presented. Note that the monitor screen was positioned perpendicular to the subject's line of sight, and therefore moving the end-effector handle towards the subject's head corresponded to moving up on the monitor. The subject's movement was performed predominantly with the arm and forearm.

The robot measured the kinematics and dynamics of the subject's hand motions, and imposed perturbation forces as follows. Condition 1 involved motor performance: the robot generated no perturbation, but recorded the behavior of the subject (blocks 1 and 2). The subject practiced as needed to become fully comfortable with the task. Condition 2 involved early motor learning: the robot measured the behavior, and also perturbed the movement of the subject (blocks 3 and 4). Condition 3 involved late motor learning: the robot measured the behavior, and also perturbed the movement of the subject (blocks 5 and 6, and practice sessions A and B). This condition differed from condition 2 by the degree of smoothness of the motor response. Condition 4 involved negative transfer: the characteristic of the perturbation forces was reversed (blocks 7 and 8).

The perturbation forces were velocity-dependent, generating a conservative force field ($\vec{F}^T \cdot \vec{V} = 0$) according to the following relations:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \begin{bmatrix} 0 & -B \\ B & 0 \end{bmatrix} \begin{bmatrix} V_x \\ V_y \end{bmatrix}$$

where B is a coefficient equal to 12 or -12 N.sec/m; the velocity in X-Y direction (V_x, V_y) is given in m/sec; and the forces in the X-Y direction (F_x, F_y) are in Newtons with X-Y directions indicated in Figure 1.

Imaging

PET facilities and procedures were similar to those previously described in the literature [e.g., Kosslyn et al., 1994; Rauch et al., 1995]. A detailed report on the physical properties and reconstruction software of the MGH PET facility used in this study was published elsewhere [Kops et al., 1990]. This facility includes a GE Scanditronix PC4096 15-slice whole-body tomograph. Experimental subjects inhaled tracer ^{15}O -CO₂ gas via a nasal cannula underneath a vacuum face mask to measure rCBF, while performing a specified motor task. Gas concentration was 2,960 MBq/l with a flow rate of 2 l/min, diluted in the face mask with room air. Previous work in our laboratory has demonstrated that this approach eliminates the requirement for an arterial line [N.M. Alpert, unpublished data]. The PET camera field of view allowed us to cover most of the brain territories specified in our a priori hypotheses, i.e., the primary motor (MI) and sensorimotor (SI) cortex, the supplementary (SMA) and premotor cortex (PMC), the basal ganglia, and the thalamus. Nonetheless, it precluded total brain coverage; in particular, the inferior portions of the cerebellum were not visualized.

Figure 1.

Visual and spatial target range. Subject, while supine, has to move robot's end-effector (world coordinates) to targets shown on computer monitor.

All conditions described above were divided into two blocks. Each block entailed a total of 80 movements (40 movements to the outward positions and 40 movements to the homing position). Each practice session entailed a total of 160 movements (80 movements to the outward positions and 80 movements to the homing position). Prior to emission scanning, transmission measurements were made using an orbiting pin source to correct for attenuation. Scanning lasted for a total of 90 sec. Experimental subjects began to inhale the tracer $^{15}\text{O}\text{-CO}_2$ 30 sec after the PET scan, and the movement tasks were initiated. Frames during the last 60 sec of acquisition were summed after

reconstruction to form the rCBF images. There was a 10-min tracer washout period following each PET scan, except that there was a longer washout period following blocks 4 and 5 (to allow for practice sessions). The 10-min washout period between scans corresponded to the desired movement resting period between blocks. The PET 15-slice image set for each scan was generated using the MGH procedure [e.g., Rauch et al., 1995]. Reconstruction was performed with a standard convolution-backpropagation algorithm, resulting in an in-plane resolution after reconstruction of 8 mm (computed attenuation correction and hanning-weighted reconstruction filter). Addi-

Figure 2.

General arrangement and force fields in different conditions. Subject, while supine on the PET table, moved the robot end-effector in a point-to-point task in a virtual haptic environment with different force fields in each condition.

tional corrections were applied to the propagated data to account for scattered radiation, random coincidences, and electronics dead time. The brain images were coregistered to correct for interscan movement [Woods et al., 1992] and then transformed to the standard 1988 Talairach coordinate system, using a least-squares fitting program [Alpert et al., 1993; Talairach and Tournoux, 1988]. The resulting data array comprised 30 contiguous, 4-mm-thick horizontal slices. The horizontal reference plane was at the intercommissural plane. Statistical parametric maps (SPM) were generated with units in z-score. The threshold for significance was set at $z = 3.00$, which corresponds to a probability threshold of a false indication of approximately $P < 0.001$, uncorrected for multiple comparisons, i.e., many pixels [Friston et al., 1991]. As dis-

cussed in previous work, there is an open debate regarding the selection of the threshold for statistical significance. The threshold adopted in the current study is somewhat liberal while remaining unbiased with respect to the a priori hypotheses [Rauch et al., 1995].

Kinematic data from a prior experiment using a similar learning task were used to design the motor learning paradigm and to determine how to aggregate the PET scans to increase the number of degrees of freedom of the statistical parametric analysis [Brashers-Krug et al., 1996]. The blocks were aggregated as follows: block 1 + 2 (baseline), 3 + 4 (early learning), 5 + 6 (late learning), and 7 + 8 (negative transfer). Motor performance scans (baseline) were subtracted from the scans acquired in the early learning, late learning, and negative transfer conditions. Likewise, a

TABLE Ia. Early motor learning minus motor performance PET activation (blocks 3 and 4 minus blocks 1 and 2)

Max pix coordinates ^a			z-score/max pixel value ^b	Region of activation
X	Y	Z		
15	6	-8	3.78	Right ventral striatum
-24	-27	-4	3.71	Left hippocampal formation
35	29	12	3.20	Right insula
49	-23	16	3.36	Right postcentral gyrus (area 40)
48	-41	16	4.21	Right superior temporal gyrus (area 22)
-50	-22	24	3.15	Left supramarginal gyrus (area 40)
-45	-23	48	3.00	Left postcentral gyrus (areas 1 and 2)
13	-49	60	4.06	Right precuneus (area 7)

^a Coordinates defining the location of the maximum pixel values from the statistical parametric maps in Talairach space [Talairach and Tournoux, 1988] are expressed as "x, y, z"; x > 0 to the right of the midsagittal plane, y > 0 anterior to the anterior commissure, and z > 0 superior to the AC-PC plane.

^b Values represent the actual maximum pixel value (in z-score units) from the statistical parametric map. Regional activations with z-score ≥ 3.00 correspond approximately to $P \leq 0.001$, uncorrected for multiple comparisons.

longitudinal comparison between conditions was performed. These results indicated the areas with significant increases in rCBF during different phases of motor learning. Areas of neural activation associated with specific stages in the acquisition of a complex motor skill were identified via the PET results and behavioral measures of learning. Only the imaging results encompassing early learning and late learning conditions are presented in this paper. Results of the negative transfer condition are being analyzed and will be reported separately elsewhere.

RESULTS

Normal subjects typically make point-to-point movements in an approximately straight line. Kinematic analysis of the lateral deviation of subjects' movements from a straight line connecting the targets showed a consistent pattern while learning the task. Using the mean squared lateral deviation as a numerical measure of performance, the baseline condition 1 (blocks 1 and 2) was followed by deterioration of performance as the force field was applied (block 3). The subsequent results showed a progressive reduction on the lateral deviation mean, indicating learning

TABLE Ib. Motor performance minus early motor learning PET activation (blocks 1 and 2 minus blocks 3 and 4)

Max pix coordinates ^a			z-score/max pixel value ^b	Region of activation
X	Y	Z		
-25	44	-12	3.99	Left superior frontal gyrus (area 11)
61	-42	-8	3.27	Right middle temporal gyrus (area 21)
-62	-46	-8	3.90	Left inferior temporal gyrus (area 37)
-7	-73	0	4.13	Left lingual gyrus (area 18)
-49	-37	4	3.25	Left middle temporal gyrus (area 22)
-18	62	8	4.00	Left superior frontal gyrus (area 10)
-7	-37	24	3.24	Left posterior cingulate (area 23)
-31	51	24	4.12	Left middle frontal gyrus (area 10)
1	-27	28	3.39	Right posterior cingulate (area 23)
-11	-54	28	3.25	Left posterior cingulate (area 31)
-18	38	32	3.25	Left superior frontal gyrus (area 9)
39	-64	32	3.04	Right angular gyrus (area 39)
-36	-65	36	4.11	Left angular gyrus (area 39)
8	-35	36	3.04	Right posterior cingulate (area 31)
-18	7	56	3.44	Left superior frontal gyrus (area 6)

^a Coordinates defining the location of the maximum pixel values from the statistical parametric maps in Talairach space [Talairach and Tournoux, 1988] are expressed as "x, y, z"; x > 0 to the right of the midsagittal plane, y > 0 anterior to the anterior commissure, and z > 0 superior to the AC-PC plane.

^b Values represent the actual maximum pixel value (in z-score units) from the statistical parametric map. Regional activations with z-scores ≥ 3.00 correspond approximately to $P \leq 0.001$, uncorrected for multiple comparisons.

(block 4, practice session A, block 5, practice session B, and block 6). Similar patterns could be observed as subjects were challenged with a new force field with reverse characteristics (blocks 7 and 8), as shown in Figures 4 and 5.

The early learning condition was associated with activation in bilateral parietal association areas, the left primary sensory cortex, and the right ventral (inferior) striatum. There was a significant decrease in rCBF in the left premotor area, as shown in Table Ia,b. As

TABLE IIa. Late motor learning minus motor performance PET activation (blocks 5 and 6 minus blocks 1 and 2)

Max pix coordinates ^a			z-score/max pixel value ^b	Region of activation
X	Y	Z		
-21	-18	-8	3.37	Left hippocampal formation
4	-62	-4	3.03	Right cerebellum
2	-82	-4	3.96	Right lingual gyrus (area 18)
-31	43	0	3.19	Left mid-frontal gyrus (area 10)
-24	-62	4	3.26	Left lingual gyrus (area 18)
2	-72	12	4.11	Right cuneus (area 17)
61	-22	16	3.01	Right postcentral gyrus (area 40)
30	-85	20	3.50	Right middle occipital gyrus (area 19)
-49	-13	40	3.76	Left precentral/postcentral gyrus (area 3/4)
-41	-22	48	4.93	Left postcentral gyrus (area 1/2/3)
-35	9	48	4.04	Left mid-frontal gyrus (area 6)
-36	-34	52	3.73	Left inferior parietal lobule (area 40)
-8	-25	52	3.36	Left paracentral lobular (area 5)
-4	-48	60	3.90	Left precuneus (area 7)
-24	-22	60	4.20	Left precentral gyrus (area 4)

^a Coordinates defining the location of the maximum pixel values from the statistical parametric maps in Talairach space [Talairach and Tournoux, 1988] are expressed as "x, y, z"; x > 0 to the right of the midsagittal plane, y > 0 anterior to the anterior commissure, and z > 0 superior to the AC-PC plane.

^b Values represent the actual maximum pixel value (in z-score units) from the statistical parametric map. Regional activations with z-score ≥ 3.00 correspond approximately to $P \leq 0.001$, uncorrected for multiple comparisons.

subjects became skilled at the motor task during late learning, foci of increased rCBF shifted from the right ventral striatum and right parietal areas to the left motor and premotor cortex, as well as the right cerebellar cortex, as shown in Tables IIa,b and IIIa,b. A notable difference between our results and those of other motor studies was the lack of statistically significant differential activation in the supplementary motor area.

To illustrate the behavioral data and the functional imaging results, we present the following: a) examples of one movement of one subject at the beginning of each block. The movement corresponds to the return movement from position (x, y) = (0.135, 0.01) in meters to the homing position (0.01, 0.01) (Fig. 3). This single example is representative of the class of movements, and the velocity profile shapes are typical for each condition, e.g., baseline, early learning, late learning,

TABLE IIb. Motor performance minus early motor learning PET activation (blocks 1 and 2 minus blocks 5 and 6)

Max pix coordinates ^a			z-score/max pixel value ^b	Region of activation
X	Y	Z		
29	35	-12	3.36	Right middle frontal gyrus (area 47/11)
-21	43	-8	3.04	Left medial frontal gyrus (area 32/10)
48	-50	-8	3.24	Right middle temporal gyrus (area 37)
43	-69	-4	5.29	Right middle occipital gyrus (area 19)
43	14	0	3.16	Right insula
52	-55	0	3.72	Right middle temporal gyrus (area 37)
44	-71	0	3.36	Right inferior temporal gyrus (area 19)
38	5	4	3.51	Right insula
-36	6	4	3.13	Left insula
-33	58	8	3.15	Left middle frontal gyrus (area 10)
45	12	8	3.03	Right precentral gyrus (area 44)
53	-48	8	3.85	Right middle temporal gyrus (area 21)
38	-69	8	4.25	Right middle occipital gyrus (area 19/39)
52	-40	12	3.74	Right superior temporal gyrus (area 22)
43	-64	12	3.87	Right middle temporal (area 39/19)
54	-54	20	4.62	Right superior temporal gyrus (area 39/22)
50	-55	24	3.51	Right inferior parietal lobule (area 39/40)
-22	46	28	3.22	Left superior frontal gyrus (area 9)
-3	-44	32	3.73	Left posterior cingulate (area 31)

^a Coordinates defining the location of the maximum pixel values from the statistical parametric maps in Talairach space [Talairach and Tournoux, 1988] are expressed as "x, y, z"; x > 0 to the right of the midsagittal plane, y > 0 anterior to the anterior commissure, and z > 0 superior to the AC-PC plane.

^b Values represent the actual maximum pixel value (in z-score units) from the statistical parametric map. Regional activations with z-scores ≥ 3.00 correspond approximately to $P \leq 0.001$, uncorrected for multiple comparisons.

and negative transfer; b) mean-squared lateral deviation of the hand (end-effector) from the straight line connecting the homing target with the outbound targets averaged across subjects (Fig. 4). Note the consis-

TABLE IIIa. Late motor learning minus early motor performance PET activation (blocks 5 and 6 minus blocks 3 and 4)

Max pix coordinates ^a			z-score/max pixel value ^b	Region of activation
X	Y	Z		
6	-73	-12	3.00	Right cerebellum
-59	-27	-12	3.25	Left middle temporal gyrus (area 20)
1	-83	-8	3.54	Right lingual gyrus (area 18)
-54	-41	-8	3.79	Left middle temporal gyrus (area 21)
-3	-83	-4	3.78	Left lingual gyrus (area 18)
-59	-49	-4	4.03	Left middle/inferior temporal gyrus (area 21)
-64	-46	0	3.44	Left middle temporal gyrus (area 21)
6	-65	8	3.13	Right cuneus (area 31)
6	-74	12	3.16	Right cuneus (area 17)
-16	-65	16	3.05	Left cuneus (area 18/31)
35	12	36	3.92	Right middle frontal gyrus (area 9)
-35	16	40	3.22	Left middle frontal gyrus (area 9/8)
-17	5	52	3.03	Left medial frontal gyrus (area 6)
-26	9	56	3.51	Left middle frontal gyrus (area 6)

^a Coordinates defining the location of the maximum pixel values from the statistical parametric maps in Talairach space [Talairach and Tournoux, 1988] are expressed as “x, y, z”; x > 0 to the right of the midsagittal plane, y > 0 anterior to the anterior commissure, and z > 0 superior to the AC-PC plane.

^b Values represent the actual maximum pixel value (in z-score units) from the statistical parametric map. Regional activations with z-score ≥ 3.00 correspond approximately to $P \leq 0.001$, uncorrected for multiple comparisons.

tent pattern of performance improvement with exposure to the novel mechanical environment across subjects, while learning the task; c) an example of a typical subject’s mean-squared deviation from the straight line connecting the homing target with the outbound targets (Fig. 5). Even for this simple numerical measure of kinematic performance, we can cluster the different movement phases, i.e., motor performance, learning, and negative transfer. Note that block 2 is statistically different from block 3, and block 6 from block 7, and that there is a consistent trend within the learning phase. Moreover, there is no statistical difference between blocks 1 vs. 2, blocks 3 vs. 4, blocks 5 vs. 6, or blocks 7 vs. 8. These results are in consonance with kinematic data from a prior experiment using a

TABLE IIIb. Early motor performance minus late motor learning PET activation (blocks 3 and 4 minus blocks 5 and 6)

Max pix coordinates ^a			z-score/max pixel value ^b	Region of activation
X	Y	Z		
12	56	0	3.53	Right cinguli gyrus (area 32)
43	-48	8	3.07	Right middle temporal gyrus (area 37/21)
47	20	12	3.39	Right inferior temporal gyrus (area 44/45)
48	-48	12	3.58	Right superior temporal gyrus (area 22)
44	17	16	3.13	Right inferior temporal gyrus (area 44/45)
52	-31	16	3.30	Right superior temporal gyrus (area 42/22)
48	-50	16	3.42	Right superior temporal gyrus (area 22)
50	-27	20	4.75	Right postcentral gyrus (area 40)
52	-27	24	4.64	Right postcentral gyrus (area 40)
49	-27	28	3.62	Right inferior parietal lobule (area 40)

^a Coordinates defining the location of the maximum pixel values from the statistical parametric maps in Talairach space [Talairach and Tournoux, 1988] are expressed as “x, y, z”; x > 0 to the right of the midsagittal plane, y > 0 anterior to the anterior commissure, and z > 0 superior to the AC-PC plane.

^b Values represent the actual maximum pixel value (in z-score units) from the statistical parametric map. Regional activations with z-scores ≥ 3.00 correspond approximately to $P \leq 0.001$, uncorrected for multiple comparisons.

similar learning task, used to design the motor learning paradigm and to determine how to aggregate the PET scans [Brashers-Krug et al., 1996]; d) significant activations in *early learning* minus *motor performance* condition (Table Ia); e) significant activations in *motor performance* minus *early learning* condition (Table Ib); f) significant activations in *late learning* minus *motor performance* condition (Table IIa); g) significant activations in *motor performance* minus *late learning* condition (Table IIb); h) significant activations in *late learning* minus *early learning* condition (Table IIIa); and i) significant activations in *early learning* minus *late learning* condition (Table IIIb).

DISCUSSION

These patterns of neural activity are distinct, as are the corresponding patterns of motor activity. This

Figure 3.

Example of velocity record for subject DS. Shown are the x-direction trace and velocity records at the beginning of each block. The Movement corresponds to the return movement from position $(x, y) = (0.135, 0.01)$ in meters to the homing position $(0.01, 0.01)$. Blocks 1-4 are at left, blocks 5-8 at right. Left columns show x-direction trace, and right columns show x-direction velocity.

suggests that the two measures, rCBF and kinematic data, reveal different facets of the same underlying phenomenon and may afford deeper insight than either alone. For example, the behavioral data permit a quantitative measure of the rate of motor learning during each phase, as illustrated in Figure 4. Note in Figure 4 that the learning rate can be assessed by the slope of the regression, with task difficulty measured by extrapolating the regression line to estimate performance at, e.g., the tenth trial ($\log_{10} \text{trial \#} = 1$).

Similarly, the pattern of neural activity suggests that early motor learning (early learning) involves the right striatum (Table Ia and Fig. 6) and right parietal cortex

(Tables Ia, IIIb). Note that the behavioral data indicate that the subjects undergo a great deal of motor learning during this condition (Figs. 4, 5). Yet, there is no evidence of activation in the left motor execution areas [Grafton et al., 1994], but only in the right striatum and right parietal cortex. The increase in rCBF in the right parietal area during early learning is consistent with its purported role in spatial tasks [Mesulam, 1985]. Likewise, the activation in the right ventral striatum is consistent with previous findings in implicit sequence learning [Rauch et al., 1995, 1997; Grafton et al., 1995; Doyon et al., 1996; Berns et al., 1997]. In fact, the reported right striatal loci are very close to each other

Figure 4.

Mean lateral deviation from a straight line averaged across eight normal subjects. The plot shows the mean-squared deviation for each block, with the inner plot showing the learning rate assessed by the slope of the regression during early learning and negative

transfer, as well as for the overall learning phase (early + late), with task difficulty measured by extrapolating the regression line to estimate performance at, e.g., the tenth trial ($\log_{10}$ trial # = 1).

within the spatial resolution of the imaging technique, e.g., (x, y, z = 15, 15, -7), [Grafton et al., 1995] (x, y, z = 10, 11, -8) [Rauch et al., 1995, 1997], (x, y, z = 4, 10, -4) [Berns et al., 1997], and the current study (x, y, z = 15, 6, -8). Indeed, psychophysical experiments with the right hand of a left hemiparetic stroke victim with a right striatal lesion suggested his inability to learn this task, further suggesting the focal character of right striatal activation during early learning [Krebs, 1997]. These results are in agreement with current views on the purported role of the striatum [Graybiel, 1995] and posit the cortico-striatal loop as playing a significant role during early learning of this task. Further experiments are required to determine if this finding is specific to the right hemisphere or due to details of our experimental design (e.g., a right-handed task performed by right-handed subjects). Note, however, that right striatal activation has been shown and replicated in the context of implicit sequence learning paradigms that employed a bimanual task [Rauch et al., 1995, 1997].

In the current study, there was a decrease of activity in the premotor area during early learning (Tables Ib, IIIa). It has been shown that the direction of the intended hand path is encoded by a task-related pool of neurons in the motor areas [Georgopoulos et al., 1984; Kalaska et al., 1989]. We speculate that during early learning, the direction of the intended hand path is yet to be determined [Mitz et al., 1991]. Likewise, it has been shown that the supplementary motor area is involved in multijoint movements imagined but not executed [Roland et al., 1980]. Although other authors have subsequently shown that the SMA is also involved in the execution of movement, the fact that we did not see activation in the SMA deserves mention (Tables Ia,b, IIa,b), particularly considering that others (like Grafton et al. [1995]) did see activation in their rotor pursuit task.

As subjects became skilled at the motor task (late learning), the pattern of neural activity shifted to the cortico-cerebellar feedback loop (Tables IIa, IIIa). This result parallels those of other motor learning studies,

block	1	2	3	4	5	6	7	8
1	1	0.91	0.41*	0.50*	0.57*	0.63*	0.29*	0.43*
2		1	0.45*	0.55*	0.63*	0.70	0.32*	0.48*
3			1	1.22	1.40	1.54*	0.70	1.05
4				1	1.15	1.26	0.58*	0.86
5					1	1.10	0.50*	0.75
6						1	0.46*	0.68
7							1	1.49
8								1

(*)Statistically significant [level 0.05 in 80 trials -- $0.65 < F\text{-value} < 1.53$]

Figure 5.

Mean lateral deviation from a straight line for subject DD. The plot shows the mean-squared deviation for each block, with the inner plot showing the learning rate assessed by the slope of the regression during early learning and negative transfer, as well as for the overall learning phase (early + late), with task difficulty

measured by extrapolating the regression line to estimate performance at e.g., the tenth trial ($\log_{10} \text{trial \#} = 1$). The table shows for reference a statistical test (F-test) to test the hypothesis that the means of different batches are equal.

e.g., Grafton et al. [1994] studied procedural motor learning in a pursuit rotor task (implicit motor learning) focusing on the transition of unskilled to skilled performance. Their comparison of three sequential scans during motor skill acquisition also showed an increase in the cortico-cerebellar loop. Our results in

the late learning phase are consistent with the hypothesis that procedural learning takes place in motor execution areas. Yet our results also suggest that different stages of implicit learning (early and late implicit learning) occur in an orderly fashion at different rates, and that distinct neural structures may be

Figure 6.

Example of relative increase in regional cerebral blood flow during early learning phase (vs. baseline motor performance). PET data indicated a relative increase in activity in the right ventral striatum during this task phase. The example reflects composite data across all subjects ($N = 8$; 16 scans/condition), and it is displayed with a Sokoloff color scale in units of z-score. Dashed lines indicate boundaries of the region of interest as defined via a digitized

version of the Talairich Atlas [1967], while solid line indicates brain slice outline. The image is a transverse section parallel to the AC-PC plane and is shown in conventional neuroimaging orientation, i.e., the top is the anterior part of the brain, the bottom is the posterior, the right is the left, and the left is the right. The section is labeled with its z coordinate, denoting its position with respect to the AC-PC plane (superior > 0).

involved in these different stages. In particular, our results support the view that the cortico-striatal loop plays a preeminent role during early implicit motor learning and that the cortico-cerebellar loop plays a preeminent role during late implicit motor learning.

In addition, the behavioral data may reveal details of the process of motor learning. During early learning a multi-peaked velocity profile is evident (Fig. 3, right column, block 3) that is quite different from the single-peaked profile seen in the unperturbed motor performance case (Fig. 3, right column, blocks 1 and 2). With learning, the secondary peaks become progressively less evident (Fig. 3, right column, blocks 4–6). A similar pattern can be observed during negative transfer (Fig. 3, right column, blocks 7 and 8). This suggests that this motor learning task may be performed initially using a sequence of overlapping segments, which are then progressively tuned and “blended” as motor

learning proceeds. Further investigation is in progress to extract and segregate these segments from the system’s mechanical response [Krebs, 1997].

CONCLUSIONS

We used a novel integration of robotic technology with functional brain imaging to study whether the unskilled phase of procedural learning of a motor task (early learning) involves areas of the brain distinct from those involved in a more skilled learning phase of the task (late learning). PET was used to measure aspects of neural activity underlying learning of the motor task, while a portable robotic device was used to generate a “virtual mechanical environment” that subjects learned to manipulate. We found that early learning activated the right striatum and right parietal area, as well as the left parietal and primary sensory

area, and that there was a deactivation of the left premotor area. As subjects became skilled at the motor task (late learning), the pattern of neural activity shifted to the cortico-cerebellar feedback loop, i.e., there was significant activation in the left premotor, left primary motor, and sensory areas, and in the right cerebellar cortex. These results support the notion of different stages of implicit learning (early and late implicit learning), occurring in an orderly fashion at different rates. Moreover, these findings indicate that the cortico-striatal loop plays a significant role during early implicit motor learning, whereas the cortico-cerebellar loop plays a significant role during late implicit motor learning.

Regarding methodology, this study may herald potential new medical applications of virtual environment technologies. As implemented here, the robot served as a "haptic virtual environment" that provided a mechanism for manipulating the motor-sensory environment. This capability should prompt future studies that can better distinguish between the different roles of specific brain regions and clarify the effects of specific traumas or treatments.

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