Experience-dependent changes in cerebellar contributions to motor sequence learning

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Contributed by Leslie G. Ungerleider, November 19, 2001

Studies in experimental animals and humans have stressed the role of the cerebellum in motor skill learning. Yet, the relative importance of the cerebellar cortex and deep nuclei, as well as the nature of the dynamic functional changes occurring between these and other motor-related structures during learning, remains in dispute. Using functional magnetic resonance imaging and a motor sequence learning paradigm in humans, we found evidence of an experience-dependent shift of activation from the cerebellar cortex to the dentate nucleus during early learning, and from a cerebellar–cortical to a striatal–cortical network with extended practice. The results indicate that intrinsic modulation within the cerebellum, in concert with activation of motor-related cortical regions, serves to set up a procedurally acquired sequence of movements that is then maintained elsewhere in the brain.

Converging evidence indicates that the cerebellum participates in the formation of procedural memories, the learning and retention of skills, habits, and conditioned responses (1–6). Cerebellar lesions impair the acquisition of a variety of skilled behaviors (7–9), and single-unit recording studies have demonstrated dynamic changes in cerebellar activity associated with the acquisition of both conditioned responses and the learning of movement sequences (2, 5, 10, 11). In addition, functional brain imaging studies have reported changes in activation of the cerebellum when subjects acquire a sequence of movements (motor sequence learning) or compensate their movements in response to changes in the mapping of sensorimotor coordinates (motor adaptation) (see refs. 4 and 12–15 for reviews).

Controversy remains, however, regarding the contributions of the cerebellum during both acquisition and retention of motor abilities. It has been argued, for example, that the cerebellar cortex and deep cerebellar nuclei act in concert to establish the motor engrams necessary to execute a motor skill, inasmuch as changes in neuronal activity associated with the acquisition of conditioned responses have been reported to be similar in both cerebellar sites (2). By contrast, others have reported that changes in neuronal activity associated with learning in the cerebellar cortex precede those in the deep nuclei (6, 16), suggesting that there may be a transfer of experience-dependent changes during learning from the cerebellar cortex, the part that receives cortical projections via the pons, to the nuclei, the part that projects back to the cerebral cortex via the thalamus (17). There is also dispute concerning whether the cerebellum constitutes the necessary and sufficient site for the retention of learned behaviors. Some investigators have suggested that long-term representations of motor skills are stored within the cerebellum (3, 18), whereas others have reported findings indicating that a distributed network of motor-related structures outside the cerebellum is sufficient to retain and express well-learned behaviors (2, 4, 15, 19). The present study was therefore undertaken to examine these issues.

In the present study, we used functional MRI (fMRI) in humans to track the time course of changes of activation in the cerebellar cortex and nuclei, as well as in motor-related structures outside the cerebellum during the acquisition of a sequence of movements. Additionally, because we wanted to examine the relationship between dynamic changes in activation and improvements in motor performance as a consequence of motor practice, unconfounded by cognitive influences, all subjects explicitly memorized the sequence of movements before scanning. Thus, improvements in performance in our paradigm reflect learning that is implicitly acquired (see ref. 20 for discussion of this issue).

Methods

Subjects. Nine right-handed, normal individuals served as subjects (six male, three female; mean age = 26.7 years; mean years of education = 15.8). The protocol for this study was approved by the National Institute of Mental Health Institutional Review Board. All subjects gave informed written consent.

Experimental Paradigm. Subjects were scanned during motor sequence learning as they performed a version of the Serial Reaction Time Task. A standard block design was used (perceptual–motor–perceptual–motor–perceptual) with each epoch lasting 40 sec. Each trial block was preceded by 4 sec during which the subjects read the instructions before the condition began. In the Perceptual condition (P), subjects were instructed to look at, but not respond to, the location of red circles that appeared at random above one of four blue squares (see Fig. 1*a*). By contrast, in the motor conditions, subjects were instructed to press as quickly as possible one of four buttons corresponding to the location of the red circle. In the latter conditions, the stimuli were either presented in an unpredictable order [Random condition (R)] or followed a repeating 10-item sequence of movements, memorized by each subject before scanning [Learning condition (L)]. The L condition enabled us to explore the cerebral plasticity associated with the incremental (implicit) automatization of an explicitly known motor sequence as a consequence of practice. Presentation of the L and R conditions was counterbalanced on each run ($n = 4$ per session) and within each scanning session. Two sequences, the reverse of each other, were used: D–B–C–A–C–B–D–C–B–A and A–B–C–D–B–C–A–C–B–D, where A refers to the far left blue box and D refers to the far right blue box. One of these two sequences was selected for the L condition, and the choice of the sequence for any given subject was counterbalanced within the group.

On each trial during training, the subject's task was to press, as quickly as possible while making minimal errors, the button of a custom built response box with fiber-optic technology that corresponded to the location of the red circle. As soon as the subject pressed the appropriate button, the red circle disap-

Abbreviations: L, Learning; P, perceptual; R, random; SMA, supplementary motor area; fMRI, functional MRI; BOLD, blood-oxygen level dependent; ROI, region of interest.

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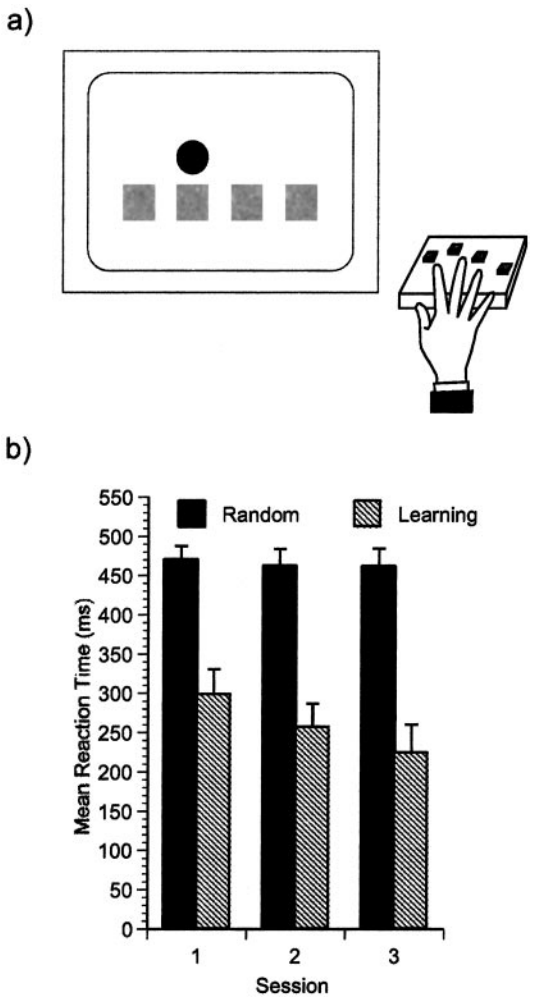

Fig. 1. (*a*) Materials and stimuli used in the motor sequence learning task (7, 8). The stimuli consisted of four blue boxes that were aligned in a horizontal row and a red circle that appeared above one of the boxes on each trial. These stimuli were projected on a screen located in front of the subject, and were reflected through a mirror embedded within the head coil. (*b*) Subjects' mean reaction time in both Random (R) and Learning (L) conditions across the three scanning sessions.

peared. A total of four repetitions of the sequence in the L condition, or 40 randomly presented stimuli in both the R and P conditions, were administered. The trials were presented at a fixed interstimulus interval of 1,000 msec to control the number of responses, thereby ensuring that the increase in signal observed during skill acquisition would reflect the learning process *per se*, and not merely a concomitant increase in the number of responses that are inevitably made during acquisition of any highly learned motor task. Each stimulus was displayed until a response was made, and no feedback regarding reaction time or accuracy was given. Between each response, subjects were asked to keep their fingers on the buttons of the response box in preparation for the next response.

Subjects were scanned on three separate sessions, which lasted approximately 2 h each. Periods of practice (30 min long) of the learning sequence were administered between sessions 1 and 2, as well as between sessions 2 and 3. In each of these periods, the subjects completed 12 blocks of 120 trials each (i.e., 144 presentations of the 10-item repeating sequence), without any demarcation between the end of one sequence and the beginning of the next, such that each block appeared as a continuous series of 120 trials. The number of blocks was chosen on the basis of our previous findings with a similar version of this task (7, 8, 12). Learning was measured by comparing the mean reaction time across blocks of trials. During the practice sessions, a rest period of 20 sec was given between each block, and a 2-min break was allowed between blocks 6 and 7.

Image Acquisition. Blood oxygenation level dependent (BOLD) signals were acquired by using single-shot, gradient-recalled echo-planar imaging [repetition time (TR) = 4,000 msec, echo time (TE) = 40 msec, flip angle = 90°, matrix 64 × 64 voxels] on a 1.5-T GE Signa Horizon scanner. A total of 58 whole-brain echo-planar volume images were collected for each of four scan series per scanning session. Each volume consisted of 28 contiguous axial, 5-mm thick slices (in plane resolution, 3.75 × 3.75 mm). The functional volumes were then registered to high-resolution coplanar anatomical images taken during the same scanning session (three-dimensional, spoiled gradient echo sequence; 28 slices, slice thickness = 5 mm, TR = 22 msec, TE = 4 msec, flip angle = 30°, matrix 256 × 256 voxels).

Data Analysis. Brain activations were detected by means of multiple regression analysis of the fMRI time series at every voxel (21), using a response function of interest corresponding to the contrast between the L and the R conditions. This contrast allowed localization of the functional changes associated with learning *per se*, and not with motor performance because both R and L conditions required subjects to produce movements that were similar, and because they were both triggered by identical visual cues. Additional regressors were used to factor out variance caused by between-run changes in mean intensity and within-run linear changes. Resulting maps from the multiple regression analysis were converted into *z* score maps for significance. Individual z score maps of the L–R regressor and the coplanar MRI anatomical scans were warped into Talairach stereotaxic space (22) by using a template provided by S. T. Grafton (Dartmouth College, Hanover, NH). Group fMRI results for each session were computed by averaging the warped individual *z* score maps. To determine the voxels that were activated within sessions, a stringent α level ($P < 0.001$) was used to guard against the type-I error generated by multiple tests. Comparisons of the functional data between two sessions were assessed statistically ($P < 0.05$) by subtracting *z* score maps using the formula (session b − session a)/square root of 2.

The differential pattern of activation within the cerebellum across the three sessions was analyzed based on functional regions of interest (ROIs) of the right cerebellar cortex and nuclei for the L-R regressor. These ROIs were created by segmenting the extent of the statistically activated regions ($P < 0.001$) observed in the entire group of subjects. Statistical comparison of the level of activation between cerebellar ROIs across sessions was then conducted on the average *z* scores of the activated voxels by using a repeated-measures ANOVA with trend contrasts to determine the nature of the interaction in the pattern of activations within this structure.

Results

Behavioral Findings. As a group, the subjects showed consistent improvement in executing the sequence of finger movements across scanning sessions (Fig. 1*b*). An ANOVA for repeated measures on the mean reaction time data in the two motor conditions revealed that subjects were faster to respond in the L than in the R condition [$F(1,8) = 62.8$, $P < 0.0001$]. There was a significant main effect of session [$F(2,16) = 7.5$, $P < 0.01$], and the interaction condition × session reached significance [$F(2,16) = 5.8$, $P < 0.02$], indicating that the intervening practice sessions improved the execution of the trained motor sequence.

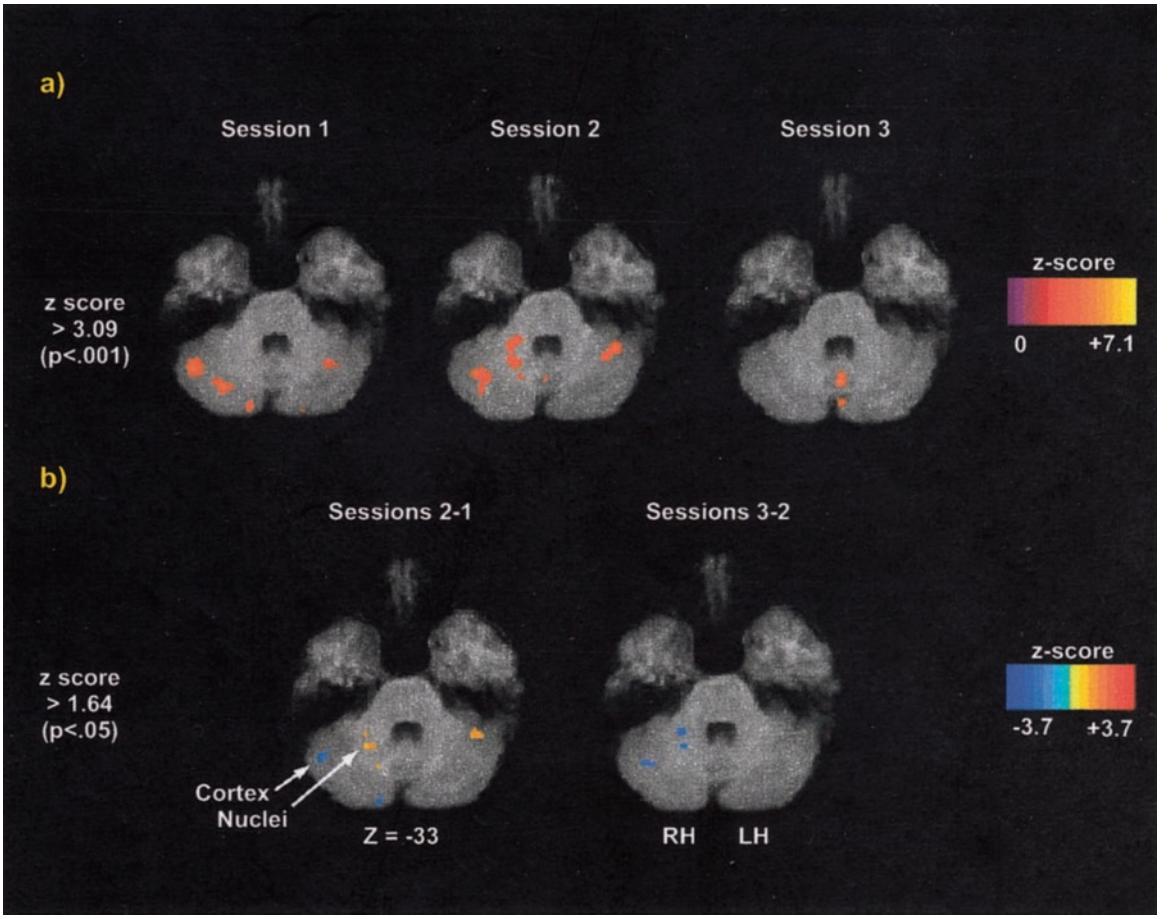

Fig. 2. Merged fMRI–MRI horizontal sections through the cerebellum ($z = -33$) illustrating the results of the multiple regression analysis for the L–R regressor averaged over the nine subjects. The results are shown as *z* score maps and reveal both increases (orange) and decreases (blue) in BOLD signal over the three scanning sessions, and are displayed overlaid on a coplanar, high-resolution MRI scan of a single subject. In the horizontal sections, the *z* coordinate represents the position of the section relative to the anterior–posterior commissure line. The subject's right cerebellar hemisphere is on the left. (*a*) Significant increases and decreases of activation (*z* score > 3.09, $P < 0.001$) in both the cerebellar cortex (lobule V and crus 1) and deep nuclei across sessions. (*b*) Results of the subtraction analysis comparing the *z* score maps obtained in session 2 vs. session 1, and in session 3 vs. session 2.

Imaging Findings. As a group, the results of the contrast between the L and R conditions across sessions revealed the existence of dynamic changes in activation within the cerebellum and other motor-related structures. First, a significant activation in lobule V and crus 1 of the cerebellar cortex ($P < 0.001$), mainly on the right, was seen in both sessions 1 and 2, but not in session 3 (Fig. 2*a*). Furthermore, comparisons between sessions demonstrated that the extent of the area activated in the cerebellar cortex declined significantly from session 1 to session 2 ($P < 0.05$), and again from session 2 to session 3 ($P < 0.05$) (Fig. 2*b*). By contrast, activations in the deep cerebellar nuclei, and in the right dentate nucleus in particular, were observed in session 2 only ($P < 0.001$; Fig. 2*a*), thereby yielding a significant increase in activation from session 1 to session 2 ($P < 0.05$), followed by a significant decline in activation in session 3 ($P < 0.05$; Fig. 2*b*). To test whether this differential pattern of activations in the right cerebellar cortex and deep nuclei was significant, the average *z* scores of the functionally activated areas within these two regions were analyzed by using a trend analysis repeated-measures ANOVA (see *Methods*) over the three scanning sessions (Fig. 3). The results of this analysis revealed a significant quadratic × linear interaction [$F(1,16) = 4.6$, $P < 0.05$]. Thus, although the cerebellar cortex was activated at the beginning of learning, involvement of the dentate nucleus was seen only later in the acquisition process, suggesting that the contributions of the cerebellar cortex and deep nuclei differ in time as a function of the amount of motor sequence practice.

In addition to the experience-dependent shifts of activation in

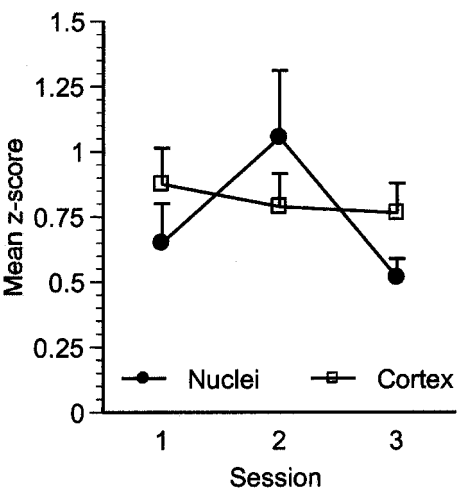

Fig. 3. Mean *z* scores of the subjects across the three sessions derived from functionally defined, activated ROIs within the cerebellar cortex and deep nuclei.

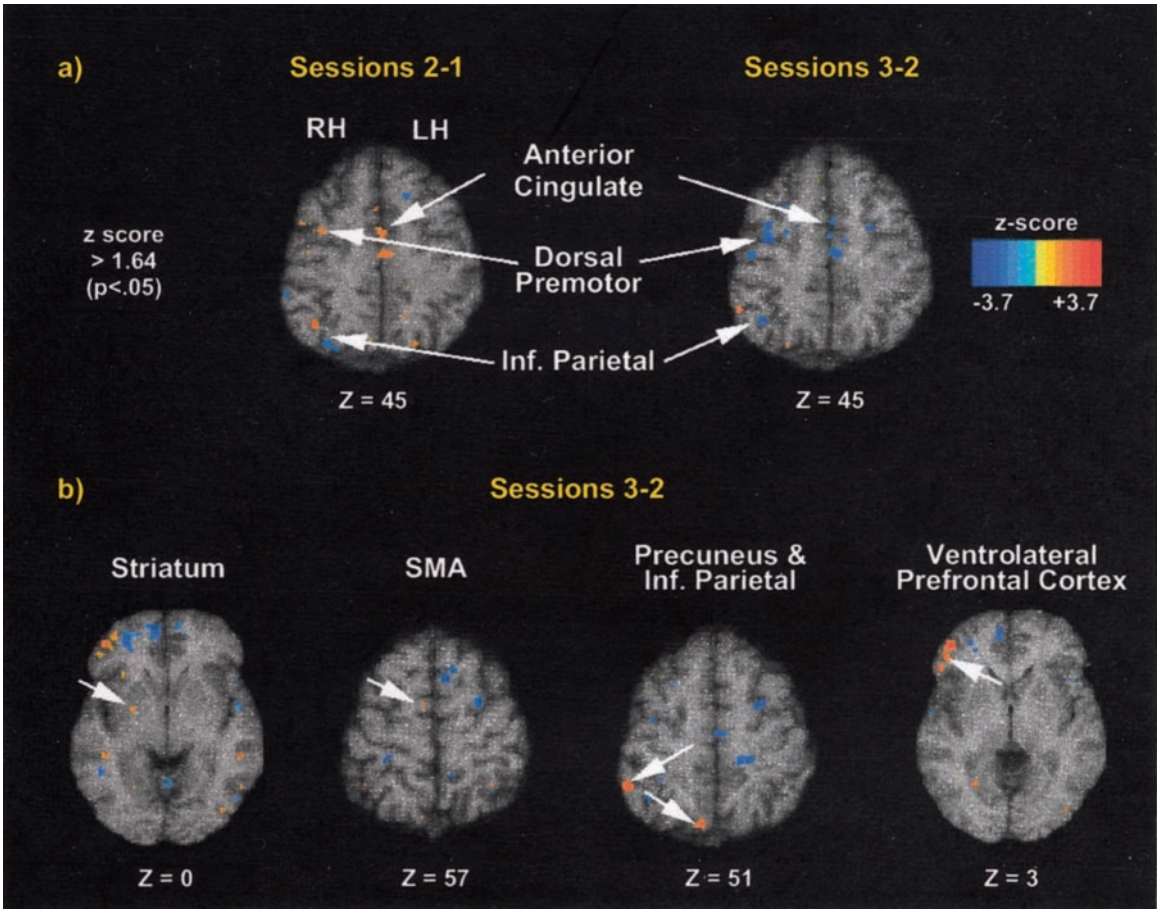

Fig. 4. Merged fMRI–MRI horizontal sections illustrating the results of the subtraction of *z* score maps at the level of the cortex and striatum. (*a*) Session 2 − session 1, the results yielded an increase (z score > 1.64, $P < 0.05$) in BOLD signal from session 1 to session 2 in the right anterior cingulate ($x = 3$; $y = 2$, $z = 45$) and dorsal premotor region ($x = 38$; $y = 3$, $z = 45$). Both an increase and a decrease (z score < -1.64, $P < 0.05$) in activation was also seen in the right inferior parietal cortex ($x = 40$; $y = -53$, $z = 45$). Session 3 − session 2, by contrast, activations within both the right anterior cingulate and premotor regions subsequently declined (blue) in session 3, whereas a further increase in activation was observed in the right inferior parietal region ($x = 56$; $y = -5$, $z = 45$); this activation was located in a slightly more superior region. (*b*) Horizontal sections illustrate the significant increase in BOLD signal in the striatum ($x = 23$; $y = 0$, $z = 0$), supplementary motor area (SMA; $x = 9$; $y = -2$, $z = 57$), precuneus ($x = 9$; $y = -68$, $z = 51$), inferior parietal cortex ($x = 50$; $y = -45$, $z = 51$), and ventrolateral prefrontal cortex ($x = 45$; $y = 36$, $z = 3$).

the cerebellum, plastic changes across sessions were also seen in the cerebral cortex and striatum, another subcortical structure frequently associated with motor sequence learning (e.g., refs. 4, 15, and 23–26). From session 1 to session 2, increases in BOLD signal ($P < 0.05$) were observed in anterior cingulate and dorsal premotor cortex, with the activated regions located predominantly on the right (Fig. 4*a*). A complex pattern of change was seen in the right inferior parietal cortex when sessions 1 and 2 were compared directly, with some voxels showing an increase in signal but others showing a decrease. Activations within both the right anterior cingulate and premotor regions subsequently declined in session 3, whereas a further increase in activation ($P < 0.05$) was observed in the right inferior parietal region; this activation was located in a slightly more superior region than the one found in the subtraction between sessions 2 and 1. Thus, changes in activation within the anterior cingulate and dorsal premotor cortex followed the same temporal pattern during learning as found in the dentate nucleus. This suggests that, like the cerebellum, these frontal regions participate in the formation of motor routines that mediate the implicit learning associated with practice of an explicitly known sequence of movements.

The drop in activation in the anterior cingulate and dorsal premotor regions in session 3 was accompanied by increased activation ($P < 0.05$) in the striatum (in particular, the putamen), supplementary motor area (SMA), precuneus, and ventrolateral prefrontal cortex in the right hemisphere (Fig. 4*b*). Increases in activation from session1 to session 2 ($P < 0.05$), and from session 2 to session 3 ($P < 0.05$) were also observed in the inferior parietal cortex (Fig. 4*a*). These results indicate that an experience-related functional reorganization develops within the striatum and specific motor-related and association cortical areas when subjects have achieved asymptotic performance of a motor sequence.

Discussion

The results of the present study demonstrated dynamic changes in activation in the cerebellar cortex and deep cerebellar nuclei during the acquisition of a sequence of finger movements. The fact that activity increased in the deep cerebellar nuclei from session 1 to session 2, but decreased in the cerebellar cortex demonstrates that learning a complex sequence of movements does not evoke parallel plastic changes in both sites (2). Instead, our results suggest that, early in sequence learning, there is recruitment of the cerebellar cortex, mainly ipsilateral to the hand used, but that its contribution then declines as proficiency at performing the task improves. By contrast, this improved performance is associated with recruitment of the dentate nucleus, suggesting a transfer of plasticity in the neural repre-

sentation of the motor sequence from the cerebellar cortex to the deep cerebellar nuclei. This reverse profile of activations was also observed in a recent imaging study of motor adaptation by Shadmehr and colleagues (27). These investigators found that activity in the cerebellar cortex decreased early in the acquisition phase, whereas, activity increased in the deep nuclei as subjects learned to point to a target with a robotic arm to which different force fields had been applied. Both sets of imaging data in humans thus support the proposal of Mauk and colleagues (6, 11), based on data from conditioning experiments in rats, of distributed plasticity within the cerebellum during motor learning. According to this proposal, early motor learning first induces plasticity at granule–Purkinje cells synapses within cerebellar cortex, with further improvement in performance inducing plastic reorganization at mossy fiber synapses in the deep nuclei (6).

It is important to note that the increase in activation seen in the dentate nucleus in session 2 was followed by a decrease in session 3, suggesting that the role of this structure during learning declines when subjects reach asymptotic performance on the task. This finding is consistent with neurophysiological results from Bloedel and collaborators (2), who recorded the modulation of activity within the deep cerebellar nuclei of the cat during operant learning of complex volitional forelimb movements (moving a manipulandum through the grooves of a maze). These investigators showed that the amplitude of cellular responses in the fastigial, interpositus, and dentate nuclei increased until the time the animal began to produce smooth movements, and then progressively decreased with extended practice. This result suggests, and our findings support, the idea that although the deep cerebellar nuclei contribute to the establishment of motor routines necessary to execute the motor task, the long-term representation of the motor sequence is unlikely to be stored at this site.

The changes in activation we observed in the dentate nucleus were paralleled by changes in activation in both the anterior cingulate and dorsal premotor cortex. Although neurophysiological studies in monkeys and imaging experiments in humans have reported experience-associated changes of activation in anterior cingulate and premotor regions (e.g., refs. 12, 24, and 28), our study associates the activation in these regions with that in the dentate nucleus, and suggests that, together, they form a cerebellar–cortical circuit involved in the early stage of learning when the motor routine is first established.

Prior models of motor skill learning have suggested that, with extended practice, the neural representation of a sequence of movements becomes gradually less dependent on the cerebellum and more dependent on the cortex (e.g., refs. 2 and 19). Our findings showed that, indeed, most activation in the cerebellum was no longer significant by session 3. This reduction in activation was accompanied by an increase in activation in the right striatum, SMA, inferior parietal, precuneus, and ventrolateral prefrontal cortex. These results suggest that, rather than shifting from cerebellum to cortex, the neural representation of a motor sequence becomes gradually less dependent on a cerebellar–cortical circuit and more dependent on a striatal–cortical circuit (15).

The pattern of activations observed in session 3 is consistent with prior work. For example, Graybiel and colleagues (e.g., ref. 29) have found that tonically active striatal neurons in monkeys change their responsiveness during the incremental learning of a task that requires the development of stimulus–response associations similar to those in the present paradigm. Further, after extensive training of monkeys on motor sequence tasks, neurons in the vicinity of SMA come to represent those sequences (30). The results of imaging studies comparing tasks that are well trained to those that are not also support the idea that SMA contributes to the representation of well-learned skilled movements (31, 32). Finally, lesions of SMA have been reported to impair performance on motor sequence learning tasks (33).

Given that the major output of the striatum, the putamen in particular, is mainly directed to motor-related structures in the frontal lobes (e.g., ref. 34), it is not surprising that both the striatum and SMA were active simultaneously in session 3. One can only speculate, however, why the ventrolateral prefrontal, precuneus, and inferior parietal regions were also activated in this late stage of learning. It may be that activation in these regions was related to the specific demands of the task, with inferior parietal cortex contributing to its visuospatial aspect, precuneus contributing to the need for visual–sensorimotor integration, and ventrolateral prefrontal cortex contributing to maintenance of the sequence of movements in their correct temporal order (12, 35, 36). Thus, our findings suggest that when a sequence of finger movements is well learned and its execution becomes automatic, a distributed neural system composed of the right striatum, SMA, and task-dependent cortical association regions is sufficient to express and retain the learned motor behavior. Finally, it is noteworthy that the latter activations were predominantly located in the right hemisphere. This is in accord with a proposal by Doyon and colleagues (12) that the right hemisphere dominance in this type of motor learning may be caused by its demands on spatial processes, such as visually guided attention, as well as the need to monitor externally ordered events that proceed rapidly one after another.

One puzzling finding in our study was the absence of activation in the primary motor cortex (M1), as several imaging studies that were not confounded with changes in kinematics have reported significant increases in M1 activations during motor learning (37–40). It may be that the presence of M1 changes in these studies, and the absence of M1 activation in ours, is caused by the degree of practice; that is, activity-related learning in M1 may be apparent only when subjects are over-trained on a task. An alternative possibility is that, although we assumed that improvement in executing the sequence reflected implicit learning, subjects may instead have learned to retrieve explicitly the next response in the sequence and to prepare for an upcoming movement, two motor functions known to elicit activations outside of motor cortex (37). Finally, M1 activation has also been reported early in learning, i.e., on the first day of training (37). Such activation may have occurred on session 1 of our study, but we did not analyze within session changes.

In conclusion, the model of cerebral plasticity for motor learning we propose here suggests that dynamic changes in the neural representation of a motor sequence depend in part on the stage of learning. Early in learning, there is transfer of experience-dependent changes from the cerebellar cortex to the dentate nucleus, and then later with extended practice, from a cerebellar–cortical to a striatal–cortical network. This model, however, may apply only to the acquisition of movement sequences. For other motor tasks, a different pattern of plasticity may apply. Indeed, during motor adaptation, one typically sees striatal activation during the early phase of learning and more prominent cerebellar activation only later in the acquisition process (41). These findings have recently led to the idea that, in contrast to motor sequence learning, during motor adaptation there is a transfer of plasticity from a striatal–cortical to a cerebellar–cortical network (15). At present, however, this remains a working hypothesis, awaiting further experimental investigation.

We thank Drs. Keith J. Worsley and Karl J. Friston for statistical advice, and Ms. M. K. Hanratty for assistance in preparing the figures. This work was supported, in part, by grants from the Natural Sciences and Engineering Research Council of Canada and the Medical Research Council of Canada (to J.D.) and through funding from the National Institutes of Mental Health Intramural Research Program (to L.G.U.).

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