Imaging Brain Plasticity during Motor Skill Learning

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The search for the neural substrates mediating the incremental acquisition of skilled motor behaviors has been the focus of a large body of animal and human studies in the past decade. Much less is known, however, with regard to the dynamic neural changes that occur in the motor system during the different phases of learning. In this paper, we review recent findings, mainly from our own work using fMRI, which suggest that: (i) the learning of sequential finger movements produces a slowly evolving reorganization within primary motor cortex (M1) over the course of weeks and (ii) this change in M1 follows more dynamic, rapid changes in the cerebellum, striatum, and other motor-related cortical areas over the course of days. We also briefly review neurophysiological and psychophysical evidence for the consolidation of motor skills, and we propose a working hypothesis of its underlying neural substrate in motor sequence learning. © 2002 Elsevier Science (USA)

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In everyday life, we go about activities using a variety of motor skills that have been acquired gradually through practice and interactions with our environment. These include, for example, the use of smooth coarticulation of finger movements into a specific sequence (e.g., when playing a musical instrument like the piano), of regular multijoint movement synergies (e.g., during reaching and grasping of small objects), and of smoothly executed

eye–body coordinated actions (e.g., as in playing sports such as golf). To study the cognitive processes and the neural substrates mediating our ability to learn such skilled behaviors in the laboratory, investigators have used experimental paradigms that fall into two categories: the first measures the incremental acquisition of movements into a well-executed behavior (motor sequence learning), whereas the second tests our capacity to compensate for environmental changes (motor adaptation) (e.g., Karni et al., 1995, 1998; Doyon et al., 1996; Shadmehr & Holcomb, 1997). Operationally defined, these two forms of motor skills refer to the process by which movements, produced either alone or in a sequence, come to be performed effortlessly through repeated practice.

In both animals and humans, motor skill learning is usually measured by a reduction in reaction time and the number of errors and/or by a change in movement synergy and kinematics (e.g., Doyon et al., 1997; Shadmehr & Holcomb, 1997; for reviews, see Karni, 1996; Doyon, 1997). For some skills, such as learning to play a new melody on a musical instrument, early learning can be facilitated using explicit knowledge (i.e., requiring thought). For most motor skills, however, motor performance is ultimately overlearned to a point where it can be performed implicitly (i.e., without thought). As opposed to other forms of memory (e.g., episodic memory), these changes in performance are known to evolve slowly, requiring many repetitions over several training sessions (Karni, 1996). Indeed, psychophysical studies have demonstrated that the incremental acquisition of motor skills follows two distinct stages: first, an early, fast learning stage in which considerable improvement in performance can be seen within a single training session and second, a later, slow learning stage in which further gains can be observed across several sessions (and even weeks) of practice (Nudo et al., 1996; Karni et al., 1998). In addition to these two stages, an intermediate phase corresponding to a consolidation period of the motor routine has been proposed (Karni & Sagi, 1993; Brashers-Krug et al., 1996; Karni et al., 1998). Finally, with extended practice, the skilled behavior is thought to become resistant to both interference and the simple passage of time. Once overlearned, a motor skill can thus be readily retrieved with reasonable performance despite long periods without practice.

Based on work in animals and humans, several brain structures, including the striatum, cerebellum, and motor cortical regions of the frontal lobe, have been thought to be critical for the acquisition and/or retention of skilled motor behaviors (for reviews, see Karni, 1996; Doyon, 1997; Sanes & Donoghue, 2000). Anatomical studies have demonstrated that these structures form two distinct cortical–subcortical circuits: a cortico-striato-thalamo-cortical loop and a cortico-cerebello-thalamo-cortical loop (Middleton & Strick, 1997) (Fig. 1). Evidence supporting the roles of these cortical–subcortical systems in motor skill learning has come from impairments found in patients with striatal dysfunction (e.g., in Parkinson's or Huntington's disease), with damage to the cerebellum, or with a circumscribed lesion involving frontal motor cortical areas (e.g., Doyon et al., 1997). Further support has come from neurophysiological studies, as well as from lesion experiments, in rodents and nonhuman primates. More recently, modern brain imaging techniques, like positron emission tomography and functional magnetic resonance imaging (fMRI), have allowed us to identify the neural substrates mediating this type of memory in normal, healthy humans and to explore the functional dynamic changes that occur over the entire course of the acquisition process (for reviews, see Karni, 1996; Doyon, 1997; Doyon & Ungerleider, 2002).
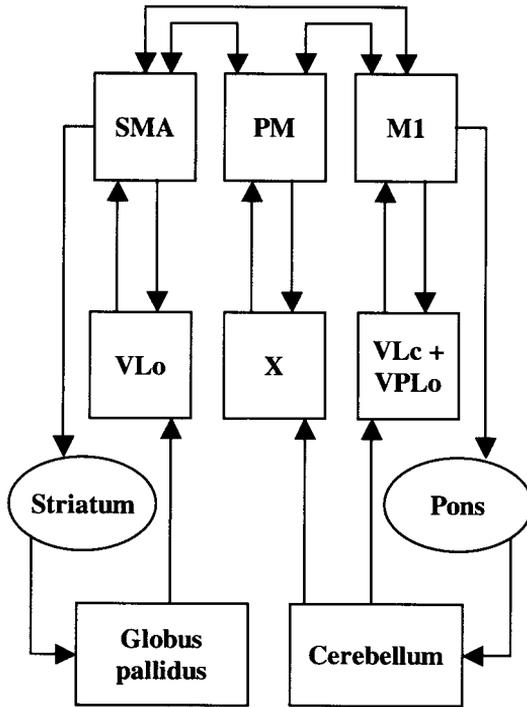
FIG. 1. Diagram illustrating the major cortical and subcortical structures involved in motor skill learning and their interconnections. These structures are organized into two main circuits: a cortico-striato-thalamo-cortical loop and a cortico-cerebello-thalamo-cortical loop. Dynamic changes within these loops occur during motor sequence learning and motor adaptation. Cortical regions: SMA, supplementary motor area; PM, premotor cortex; M1, primary motor cortex. Thalamic nuclei: VLo, ventrolateral nucleus, oral division; X, area X; VLc, ventrolateral nucleus, caudal division; VPLo, ventroposterior nucleus, oral division.

In the following sections, we review recent findings, mainly from our own work using fMRI, which suggest that: (i) the learning of sequential finger movements produces a slowly evolving reorganization within primary motor cortex (M1) over the course of weeks and (ii) this change in M1 follows more dynamic, rapid changes in the cerebellum, striatum, and other motor-related cortical areas over the course of days. We also briefly review neurophysiological and psychophysical evidence for the consolidation of motor skills, and we propose a working hypothesis of its underlying neural substrate in motor sequence learning.

SLOWLY EVOLVING REORGANIZATION OF M1

In the past decade, the learning of sequential finger movements—related to skills such as writing and typing—has become an important paradigm for studying the acquisition of motor skills using imaging techniques. These studies, however, were not designed to look at the effects of long-term training. To examine these effects, we used a simple finger-opposition task in which normal, healthy subjects were trained and tested over the course of several weeks and were scanned using fMRI at weekly intervals to image their brains (Karni et al., 1995).

In this task, subjects were instructed to oppose the fingers of the nondominant hand to the thumb in one of two given sequences (Fig. 2A). The sequences were composed of five component movements or their mirror-reversed counterparts. Subjects were required to tap each sequence, with no visual feedback, as accurately and rapidly as possible. While initial performance of the two sequences, in terms of speed and accuracy, did not differ (Figs. 2B and 2C), 10–20 min of daily practice, during which subjects were instructed to repeatedly tap a given sequence (the other sequence served as the unpracticed control) in a rapid self-paced and accurate manner induced large gains in performance across weekly test sessions. Performance improvement reached an asymptote after about 3 weeks of training with more than a doubling of the initial rate (Fig. 2B). The improvement was specific to the trained hand and did not generalize to the performance of the control sequence. These behavioral results suggest that a specific representation of the trained sequence of movements (rather than a representation of the individual component opposition movements) had developed as a function of training.

In the scan sessions, we measured motor-activity-evoked signal changes at weekly intervals using a 4-T MRI system and a surface coil placed over M1's hand representation in the central sulcus of the contralateral hemisphere. We focused on M1 because this area has been indicated by studies in adult monkeys as a locus of manual skill learning, and it is thought to be important in the initiation of voluntary motor actions, especially those associated with fine manipulative abilities (Schieber, 1995). Additionally, we considered a possible analogy to the results of several basic perceptual tasks, in which primary cortical representations have been shown to reorganize as a function of training and learning (Merzenich & Sameshima, 1993). During scanning, both the trained and the untrained control sequence were performed at a fixed, comfortable rate of 2 Hz, paced by the magnetic field gradient switch noise. Thus both rate and component movements were matched, and the only difference between the two sequences during scanning was the difference in practice histories. The results showed that in the first scan session, performed before any training was given, a comparable extent of the contralateral M1 was activated by the execution of both sequences. However, by Session 4, which corresponded to 3 weeks of daily practice on the designated training sequence, and in all subsequent sessions, the extent of activation evoked by the trained sequence in M1 was significantly larger compared to the extent of activation evoked by the control, untrained sequence (Fig. 2D).

It is important to note that in the initial, naive state the activation in M1 was somewhat patchy; it remained so by Session 4, but to a lesser degree. Control experiments showed that it did not extend beyond the hand representation itself, indicating that an expansion of the total hand representation area had not occurred. Thus, the differential activation was accounted for by a subpopulation of pixels, in the hand area, that showed a significant response to performance of the trained sequence, but little or no response to the performance of the untrained sequence. The more extensive activation evoked by the trained compared to the untrained sequence persisted in M1 weeks after training was discontinued (Fig. 2E). There was also no significant decrease in performance and, in fact, 1 year after training was stopped, there was still significant retention of the skill (results not shown here).

These imaging data suggest that long-term practice results in a gradually evolving, specific, and more extensive representation of the trained sequence of movements in M1. The results are compatible with the idea that motor practice induces the recruitment of
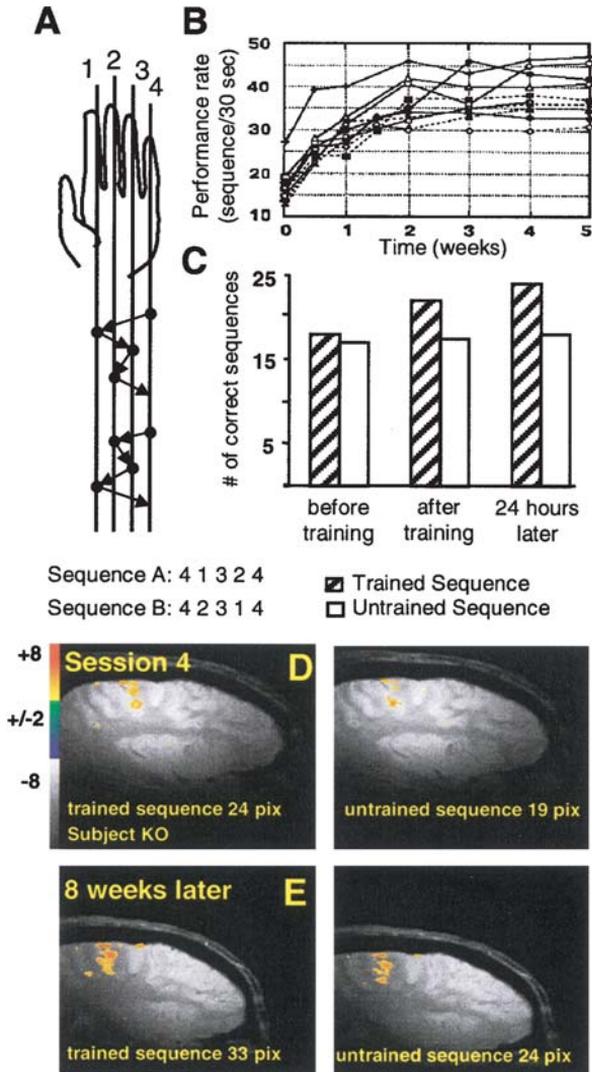
FIG. 2. The effects of long-term practice of a motor sequence. (A) The two sequences of finger-to-thumb opposition movements used in our study (Karni et al., 1995). In Sequence A the order of finger movements was 4, 1, 3, 2, 4 (numbering the fingers from index to little), and in Sequence B the order was 4, 2, 3, 1, 4, as indicated by the arrows (matched, mirror-reversed sequences). (B) Learning curves. Each curve depicts the performance of a single subject as a function of time. Pretraining is time point 0. Subjects reached asymptotic performance after about 3 weeks of training, at which point they had doubled the rate at which they could perform the trained sequence. (C) Behavioral evidence for consolidation of the motor sequence. Number of correct sequences performed during a test interval of 30 s for the two sequences (randomly assigned to be the trained or the untrained control): before training, after a few minutes of externally paced performance of the randomly assigned trained sequence, 24 h later, with no additional training in the interval. (D) Emergence of differential activation in M1 evoked by the trained compared to the untrained (control) sequence following 2 weeks of daily practice on the designated trained sequence. Data are from a single subject. (E) Maintained differential activation 8 weeks later with no additional training in the interval. Sagittal sections in D and E are through the right hemisphere centered ~35 mm from midline. A surface coil was used, which had the advantage of providing enhanced signal-to-noise ratios, but at the cost of resolution.

additional M1 units into a local network specifically representing the trained motor sequence. This interpretation is in agreement with the recent finding, in monkeys, of practice-dependent plastic changes in the functional topography of M1. Nudo et al. (1996) found that following a few weeks of training on a task, which developed skilled manipulation, the evoked-movement digit representation as well as the representation of task-related movement combinations in M1 were gradually expanded. Thus, M1 may code not just single movements, but rather complex movement sequences. This too is supported by the finding in monkeys that, following long-term practice, cocontracting muscles used in the task come to be represented together in motor cortex, with those movement combinations that were used more frequently in training more extensively corepresented (Nudo et al., 1996). That different subpopulations of neurons within a representational domain, such as the hand, participate in the representation of different movement sequences suggests a potential for the learning of many parallel skills within a given representation, rather than an enlargement in the representation of a specific body part.

We think it is likely that kinematic changes may explain why identical component movements are differentially represented in M1 when arranged in a trained sequence versus an untrained sequence. There is evidence from monkeys showing that fingers do not move independent of each other and that each instructed movement is generated by combined activation of several muscles, many acting on more than one digit (Schieber, 1995). Additionally, there is evidence demonstrating the complex overlapping representations of movements in maps of M1 (Schieber, 1995). Thus, the implementation of a sequence in M1 may be related to the representation of transitional movements (switching from one digit to the other) and temporally correlated movements (Nudo et al., 1996), which would be dependent on the particular temporal ordering of the component movements in the sequence. Our results (Karni et al., 1995, 1998) suggest that this order-specific aspect of the representation may be enhanced, extended, and consolidated by practice.

DYNAMIC PLASTICITY IN CEREBELLAR AND STRIATAL CIRCUITS

Although the evolution of a sequence-specific differential pattern of activation in M1 required extended practice over several weeks to be evident, changes in M1 activity were observed as early as the first scan session (Karni et al., 1995, 1998). In particular, there was an initial habituation-like effect, in which the second sequence performed in a set (independent of whether it was to become the trained or untrained sequence) evoked a smaller response than the first sequence performed. Later in the first scan session, however, this effect reversed, such that the second sequence performed now evoked a larger response. We reasoned that these early changes in M1 activity might reflect dynamic events occurring elsewhere in the motor system, perhaps on the order of days instead of weeks.

To test this possibility, we designed another fMRI experiment of motor sequence learning using a version of the serial reaction time task, in which healthy subjects were required to press as quickly as possible one of four buttons corresponding to the location of a red circle that appeared on a screen (Fig. 3A) (Doyon & Ungerleider, 2002). The stimuli were either presented in an unpredictable order (random condition) or followed a repeating 10-item sequence of movements that was taught to each subject explicitly prior to scanning (learning condition). Subjects were scanned at 1.5 T over three separate sessions with intervening 1-h periods of practice of the 10-item sequence administered just prior to the
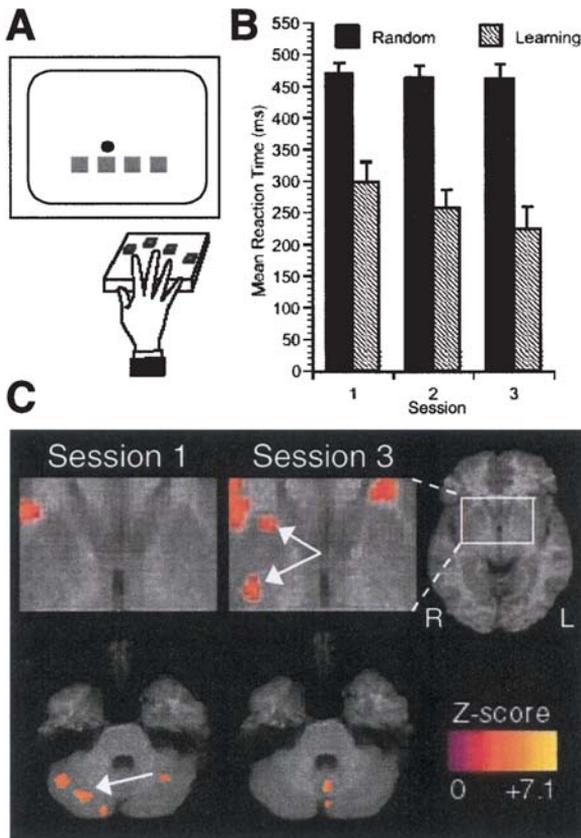
FIG. 3. (A) Diagram illustrating the materials and stimuli used in the motor sequence learning task. Sequence learning was tested using a modified, computerized version of the Serial Reaction Time task. The stimuli consisted of four blue boxes that were aligned in a horizontal row and of a red circle that appeared above one of the boxes on each trial. These stimuli were generated using dedicated software (SuperLab) that allowed measurements of reaction times with millisecond accuracy. They were projected onto a screen located in front of the subject and were visualized through the reflection of mirrors embedded within the head coil. In this task, the subjects were asked to press as quickly as possible one of four buttons corresponding to the location of a visual stimulus that appeared, either randomly or in a repeating sequence that they knew explicitly prior to scanning (see text for more details). The subjects were scanned over three separate sessions with intervening periods of practice administered just before the second and third scan sessions. (B) Bar graph illustrating the subjects' mean reaction time in both Random and Learning conditions across the three scanning sessions. A repeated analysis of variance revealed that subjects improved their ability to execute the finger sequence in both the Learning and the Random conditions ($p < .01$), but that their level of improvement in reaction time across sessions was greater in the Learning than in the Random condition ($p < .05$). (C) Z-score maps showing the dynamic changes in activity in the striatum and cerebellum from Session 1 to Session 3. Significant activity in the striatum was observed in Session 3 only, when subjects attained high levels of performance on this task. By sharp contrast, a decrease in fMRI signal was seen in the cerebellar cortex from Session 1 to Session 3.

second and third scan session. Importantly, during scanning, we used a head coil rather than a surface coil, as used in our first study (Karni et al., 1995), so that changes in patterns of activation across the whole brain could be observed. The behavioral results demonstrated that, as a group, the subjects showed consistent improvement in executing the sequence of finger movements across scanning sessions (Fig. 3B) and attained the slow learning phase, as their level of performance became stable in Session 3. Analysis

of the fMRI data in the early phase of learning (i.e., Session 1) revealed activations in the cerebellum (Fig. 3C), as well as in the right anterior cingulate, dorsal premotor, and inferior parietal regions. At the end of Session 3, however, these cerebellar and cortical regions showed significant reductions in activity. By contrast, right hemispheric activations were now observed in the striatum (see Fig. 3C), as well as in the supplementary motor area, ventrolateral prefrontal cortex, precuneus, and inferior parietal area. The latter findings suggest that when a sequence of movements is well learned and its execution has become "automatic," a distributed neural system composed of the striatum and related motor cortical regions, but not the cerebellum, may be sufficient to express and retain the learned behavior (Doyon, 1997; Doyon & Ungerleider, 2002).

Prior imaging studies of motor sequence learning are consistent with these findings. Such studies have revealed that the cerebellum is active during the fast learning phase when the initial motor routine is being established (e.g., Jenkins et al., 1994; Doyon et al., 1996), but that this activity decreases with practice and may become undetectable when the sequential movements are well learned (Grafton et al., 1994; for review, see Doyon & Ungerleider, 2002). Some investigators have also reported striatal activations in the early acquisition phase of motor sequence learning, when subjects have to rely more strongly on the use of cognitive strategies and working memory (Jenkins et al., 1994). However, the results of other studies have shown that the striatum is significantly more activated when subjects have reached asymptotic performance on the task than when they are at the beginning of the acquisition process (e.g., Grafton et al., 1994; Doyon et al., 1996). Furthermore, unlike the pattern of activity changes in the cerebellum, no decrease in striatal activity is observed with extended practice. The latter findings suggest that the striatum (in concert with the motor cortical areas discussed below) may be critical for the long-term storage of well-learned sequences of movements (Doyon & Ungerleider, 2002).

At the level of the cortex, the evidence thus far indicates that significant experience-related functional reorganization develops within specific motor and associative areas (e.g., Karni et al., 1995, 1998; Classen et al., 1998). Indeed, the creation of a long-term representation of this skill appears to necessitate, at the very least, the contribution of both the SMA and M1 (Karni et al., 1995, 1998; Classen et al., 1998; Gordon et al., 1998). The presence of M1 changes in our first fMRI study, but not in our second, likely reflects the degree of practice subjects received; that is, activity-related learning in M1 may be apparent only when subjects are overlearned on a task.

HOW ARE MOTOR EXPERIENCES CONSOLIDATED?

As first demonstrated during perceptual skill learning, some performance gains become apparent only after a period of time has elapsed following the end of practice. For example, on a simple visual detection task, Karni and Sagi (1993) have described gains in performance emerging after a minimum of 6–8 h following training on the task. This finding has suggested that there may be a process of consolidation, which is initiated by the practice session and spans several hours before becoming evident at the behavioral level. Evidence for a similar process of consolidation in the motor system comes, in part, from a physiological study by Wise et al. (1998) who recorded neuronal activity while monkeys adapted to visuomotor transforms between a joystick and the cursor on a screen

it controlled. Not only did task-related activity change in M1 and premotor cortex during motor adaptation, but changes in activity continued for dozens of trials after performance reached a plateau. Furthermore, there was no clear asymptote of this activity change up to the 30-min limit of the monitoring time, hence suggesting that the continued change of activity in motor cortex reflected the early stages of consolidation. Based on such findings, we looked for behavioral evidence of consolidation by examining whether delayed gains in performance might occur after training on a motor sequence task.

Subjects were trained on the same finger-to-thumb opposition sequential movement task used in our original imaging study of M1 (Fig. 2A). Performance was tested before, immediately after, and then 24 h after a single training session on one of the two sequences. During testing, subjects were required to tap each sequence as accurately and rapidly as possible over a test interval of 30 s. In the training session, one of the sequences, randomly chosen, was tapped at a rate of 2 Hz, paced by a metronome, in six short training intervals of 40 s each, separated by 2–3 min of rest. Motor performance for the two sequences before, immediately after, and on the day following training is shown in Fig. 2C. Initial performance of the two sequences did not differ in terms of either speed or accuracy. Training, however, induced a significant gain in speed for the trained sequence, with no change in accuracy. Little improvement was found for the untrained sequence. On the following day, with no additional training, a significant gain in speed, compared to the immediate posttraining performance level, was found for the trained sequence only (Fig. 2C). These findings demonstrate that not all learning in a sequential finger-opposition task is concurrent with practice. A limited amount of paced opposition movements was sufficient, not only to improve performance during the session, but also to initiate significant additional gains that affected performance by the next day. These results, together with the physiological findings in monkeys described above (Wise et al., 1998), support the idea that some gains require time to become effective and continue to develop after motor practice has ended.

Additional psychophysical evidence for the existence of consolidation for motor learning comes from a motor adaptation study by Brashers-Krug et al. (1996). These investigators trained subjects to move a manipulandum against a force field and then, at varying intervals after training was terminated, introduced a second task. If the second task was introduced 4–6 h after the first, interference was produced. By contrast, beyond a time window of about 6 h, introduction of the second task had no effect. These results, and those of Karni and Sagi (1993), thus point to a window of about 6 h for consolidation to occur. We have repeated this interference experiment using a motor sequence instead of a motor adaptation task and obtained essentially the same results (Rey-Hipolito et al., 1997). Thus, altogether, the behavioral data indicate that human motor memory continues to evolve after the training session and, with the passage of time, is transformed into a long-term trace.

NEURAL CORRELATES OF FUNCTIONAL REORGANIZATION

In the motor system, the neural correlates of functional reorganization have been most extensively studied in M1. Animal work by Donoghue and colleagues, as well as several other investigators, has demonstrated that M1 plasticity depends upon the integrity of the horizontal connections that span the entire region and that this cortical substrate works

by associating M1 neurons into functional assemblies, which are then involved in constructing new motor maps (Donoghue, 1995; Donoghue et al.,1996; Huntley, 1997; Sanes & Donoghue, 2000).

Evidence supporting the role of the horizontal connections as a substrate for cortical plasticity comes from several sources. First, intracellular analyses and field-potential recordings of in vitro slice preparations have revealed the existence of horizontal connections throughout M1, especially in superficial layers II and III and in deep layer V (Donoghue et al., 1996; see Sanes & Donoghue, 2000, for review). Second, Jacobs and Donoghue (1991) have shown that local blockade of GABAergic inhibition in one part of M1 unmasks existing horizontal connections that then reveal the existence of hidden representations of limb movements in other parts of M1. Third, Huntley (1997) has demonstrated that the extent of early M1 reorganization is related to the distribution of the intrinsic horizontal connections within M1. This investigator showed that cutting the motor nerve of rats' whiskers produced significant expansions of the forelimb area into the former vibrissa territory; however, this reorganization was apparent only in areas that contained strong horizontal connections between the whiskers and the forelimb areas. Importantly, no change in movement representation was observed in regions in which these connections were either absent or sparse.

It has been proposed that rapid cortical plasticity can occur through synaptic modification of the local horizontal circuitry, which is modulated via N-methyl-D-aspartate receptors (Nudo et al., 1997; Sanes & Donoghue, 2000). However, persistent changes in the efficacy of this horizontal circuit have been proposed to result from synaptic modifications through mechanisms like long-term potentiation and long-term depression. These mechanisms are believed to up- or down-regulate the strength of the horizontal connections depending on the pattern of activity (context) (Hess et al., 1996; Hess & Donoghue, 1996a,b).

Along with these physiological changes in the horizontal circuit, neurobiological alterations have also been reported following motor learning. Indeed, behavioral training is known to induce changes in gene expression (Kleim et al., 1996), protein synthesis (Hyden & Lange, 1983), and neuron morphology, as measured by dendritic density (Greenough et al., 1985; Kolb et al., 1994; Withers & Greenough, 1989). Interestingly, Kleim et al. (2002) have demonstrated not only that motor learning produces changes in synaptogenesis, but also that these structural changes are colocalized to the region within which alterations in learning-dependent representational maps are observed following extended practice. These researchers have demonstrated that, compared to control animals, rats trained to reach and grasp food pellets through a slot have significantly more synapses per neuron within layer V, specifically in the caudal forelimb area. Such findings indicate, for the first time, that both functional and structural plasticity occurs simultaneously within the same cortical region and thus provide strong evidence that morphological changes contribute to the slow learning phase of a skilled motor behavior.

FUTURE DIRECTIONS

A key unresolved issue still facing neuroscientists concerns the neural site (or sites) mediating the consolidation of new sequences of movements. Results from Shadmehr and Holcomb (1997) have shown that the cerebellum is critical for consolidating motor adaptation learning, and those from Imamizu et al. (2000) have demonstrated that this

structure constitutes a storage site for this form of motor memory. One might therefore expect that the striatum (Doyon & Ungerleider, 2002) and possibly the motor cortex (Wise et al., 1998) would play an equally important role in the consolidation of movement sequences, as these structures contribute to the development and maintenance of the final representation of this type of motor skill. At present, however, this remains a working hypothesis, awaiting experimental investigation.

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