

PLASTICITY AND PRIMARY MOTOR CORTEX

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■ **Abstract** One fundamental function of primary motor cortex (MI) is to control voluntary movements. Recent evidence suggests that this role emerges from distributed networks rather than discrete representations and that in adult mammals these networks are capable of modification. Neuronal recordings and activation patterns revealed with neuroimaging methods have shown considerable plasticity of MI representations and cell properties following pathological or traumatic changes and in relation to everyday experience, including motor-skill learning and cognitive motor actions. The intrinsic horizontal neuronal connections in MI are a strong candidate substrate for map reorganization: They interconnect large regions of MI, they show activity-dependent plasticity, and they modify in association with skill learning. These findings suggest that MI cortex is not simply a static motor control structure. It also contains a dynamic substrate that participates in motor learning and possibly in cognitive events as well.

INTRODUCTION

In the past decade, there have been substantial changes in understanding of the function and the role of motor cortical areas as information processing structures for planning and controlling movements, and new evidence has emerged that these motor cortical areas play a role in learning and cognition. One additional significant advance has been the definition of a number of frontal motor areas, each appearing to have distinctive features (Picard & Strick 1996, Preuss et al 1997). However, the body of new information and insights about the primary motor cortex (MI) alone sufficiently warrants separate consideration. Consequently, this review focuses on advances made in understanding of MI functions. Four important topics have emerged in recent years. First, somatotopy in MI holds only for major body divisions, such as the arm, face, or leg. Internally, each of these subdivisions contains a separate, distributed network for which the traditional concept of somatotopy does not readily apply. Second, MI has a plastic functional organization in adult mammals. This property ostensibly results from a broad connectional organization, and the capacity for activity-driven synaptic

strength changes. Third, in addition to its primary role in muscular control, MI participates in learning. Fourth, MI may participate in cognitive activities as well as motor actions. In this review, we discuss the work that has generated each of these new concepts.

MI FUNCTIONAL ORGANIZATION

Beginning in the mid-twentieth century, work that used low-intensity electrical stimulation to map output functions of MI revealed a somatotopically ordered representational map for movements (or muscles) that resembled a distorted cartoon of the body (Penfield & Rasmussen 1950, Woolsey et al 1952). This map commonly depicted body-part joints or movements as a continuous representation laid out upon the surface of electrically excitable MI. The principal organizing feature incorporated a general medial-to-lateral topography of leg (hindlimb in quadrupedal mammals), arm (forelimb, including digits), and head and face.

Although the general medial-to-lateral leg, arm, and face representation appeared consistently in all early studies, one doubts that the level of somatotopic detail was ever intended by the near omnipresent homunculus cartoon (Schott 1993). Nevertheless, this widely adopted schema has profoundly influenced concepts of motor cortex organization. In particular, the homunculus plan suggests that representations for each body part are orderly and point-to-point and that each part occupies nonoverlapping cortical space. Thus, a highly ordered somatotopy implies dedication of specific neural elements, such as a cortical column, for the control of one body part (Asanuma & Ward 1971), such as an individual finger.

Current data obtained from contemporary methods has upheld the results showing the segregation within MI of functional subregions for legs, arms, and heads but soundly rejects the idea of a precise topography. Instead, the internal organization of each subregion is best described as a network having broadly distributed functions involving large populations of neurons within a subregion (Sanes & Donoghue 1997). The most complete data for this departure from a simple topography has been obtained for the MI arm region, and the most extensive maps of this region have been realized with intracortical electrical stimulation techniques. This influential method, developed by Stoney et al (1968), provided a means to evaluate the movement or muscle coupling of a site focally stimulated by electrical stimulation via a microelectrode inserted among cortical neurons. New movements evoked when the electrode moves in small steps across cortex suggested the existence of an underlying pattern of organization. However, when assembled into a comprehensive map, sites for any particular body part appear widely distributed, multiple, and overlapping (Kwan et al 1978, Sessle & Wiesendanger 1982, Gould et al 1986, Donoghue et al 1992, Nudo et al 1992). It should be noted that even the cruder surface stimulation data derived by Penfield

& Boldrey (1937), albeit at much lower resolution than that possible with intracortical stimulation, also provided support for this form of distributed organization. In addition, the landmark studies of Jankowska et al (1975) also foretold this distributed pattern. From more limited data sets, it appears that MI organization for both the face (Huang et al 1989) and leg areas (Gould et al 1986) shows a similar distributed internal organization while maintaining separation from the adjacent arm region.

Reservations about the artificial nature of electrical stimulation are clearly warranted when defining the organizing features of the motor map. However, evidence from neural recordings, pharmacological inactivation, and connectional studies all reveal that the distributed nature of MI subregion organization is consistent with that identified by intracortical electrical stimulation mapping. Spike-triggered averaging has demonstrated that single neurons in the MI arm area influence multiple arm muscles (Buys et al 1986, Fetz et al 1989), including combinations of proximal with distal muscles (McKiernan et al 1998). In addition, recordings of single MI neurons show that they rarely modulate with the action of a single joint or part; each neuron appears to participate in multiple hand motor actions, and neurons influencing different digits or the wrist appeared to have a seemingly random distribution (Schieber & Hibbard 1993). This pattern does not easily find reconciliation with a discrete, topographically segregated organization for MI. As predicted by the distributed functional relationship of MI to movement and muscle control, focal inactivation of monkey MI produces more global effects on arm actions but does not block the action of individual parts (Schieber & Poliakov 1998).

Contemporary neuroimaging methods that detect local changes in blood flow have also allowed exploration of the organization of human motor cortex. Low-resolution studies with positron emission tomography (PET) found overlapping activation patterns for distal and proximal arm movements within the MI arm area (Colebatch et al 1991, Grafton et al 1991). The higher-resolution functional magnetic resonance imaging (MRI) method has also revealed overlapping, distributed activation in MI for distinctive movements of the fingers, wrist, and elbow (Rao et al 1995, Sanes et al 1995), thus showing consistency with a distributed organization within the MI arm subregion. Finally, all the functional data appear to have an anatomical correlate insofar as the MI arm subregion has vast horizontal interconnectivity without an obvious topographic plan for fingers, wrist, or other parts of the arm (Huntley & Jones 1991).

Taken together, this body of experimental data reveals a pattern of MI organization that has discrete gross subdivisions. However, each subdivision has an internal distributed network in which control emerges from broad activity patterns (Sanes & Donoghue 1997). Not only can this organization provide the immense storage capability and richness of function characteristics of distributed networks, it also provides a basis for flexibility if the organization of this network has modifiability. In the next sections, we provide evidence that MI representations

have plasticity, and we discuss whether a MI propensity to exhibit plasticity has implications for a MI role in motor learning.

DYNAMIC MI ARCHITECTURE: PLASTICITY

One of the most intriguing aspects of the behavior of more encephalized mammals, particularly primates, is their remarkable flexibility in motor behavior. Although many invertebrates with minimal nervous systems exhibit complex motor skills, as in the dance of the honeybee, none matches the combined range of skills, precision, and adaptability of motor control evident in animals with large forebrains. Behavioral flexibility is often attributed to the cerebral cortex (although sometimes without good reason), and this connection suggests that some sort of modifiable architecture exists within motor cortical circuitry. The idea of a dynamic organization in motor cortex is almost as old as the notion of a motor cortex (Brown & Sherrington 1912). Furthermore, the concept of MI flexibility has continually appeared in this century's experimental literature (Lashley 1923, Gellhorn & Hyde 1953). More recently, intracortical electrical stimulation mapping has shown that maps within MI are capable of rapid and long-lasting reorganization. In a series of electrical stimulation mapping experiments, we demonstrated that transection of the facial motor nerve, which supplies rat facial whisker musculature, led to a functional loss of the MI whisker area. This region was supplanted by representations of the adjacent forelimb or eye/eyelid regions (Donoghue et al 1990, Sanes et al 1992). This reorganization emerged abruptly within hours of the nerve lesion, and the basic form of the reorganization revealed soon after the lesion persisted for months (Sanes et al 1990). The ability to evoke movements at similar thresholds in both the reorganized and normal areas of MI suggested that these areas acquired functions of the normal cortex as part of an expanded representation. In experimental animals, this pattern generalizes to peripheral nerve (Sanes et al 1990) or central (Nudo & Milliken 1996) lesions, repetitive MI stimulation (Nudo et al 1990), or changes in limb configuration (Sanes et al 1992). The availability of transcranial stimulation methods has extended MI mapping to humans. Amputations (Hall et al 1990, Cohen et al 1991), spinal cord injury (Topka et al 1991), transient modifications in sensory inputs (Brasil-Neto et al 1992), immobilization (Liepert et al 1995), and repetitive MI stimulation (Berardelli et al 1998) all modify MI movement representations. This diverse set of results establishes the dynamic and adaptive nature of motor maps for humans and nonhuman mammals.

A complex issue of electrical stimulation mapping is defining the site of effect. It is essential to understand the site and basis for map reorganization before concluding that changes observed in a MI map occurred because of neural circuit modifications within MI. Intracortical stimulation in MI activates pyramidal tract neurons that eventually produce the muscular activity with appropriate temporal and spatial summation. However, electrical stimulation also activates intracortical

dendritic and axonal processes in and around the vicinity of the stimulating electrode(s), and perhaps most significantly, stimulation activates the recurrent axon collateral system for each neuron brought to threshold. A striking feature of cerebral cortical pyramidal neurons is that all these projection neurons have extensive local collateral branches in addition to the efferent axon (Ghosh & Porter 1988). The branches synapse in the immediate vicinity of the neuron and typically have substantial horizontal, or lateral, connection systems that can extend upward of 1 cm within MI (DeFelipe et al 1986, Huntley & Jones 1991, Keller 1993a, Hess & Donoghue 1994). Thus, one must acknowledge that projection neurons participate in the internal processing of MI as well as delivering the output message to subcortical systems. Finally, electrical stimulation of pyramidal tract neurons sends signals not only to the spinal cord but also to a vast set of supraspinal, subcortical targets, with the brainstem, striatum, and thalamus (Canedo 1997).

In humans, transcortical stimulation with electrical and magnetic devices has also been used profitably to study MI map plasticity (Hall et al 1990, Cohen et al 1991, Topka et al 1991). These more-global transcranial stimulation methods, in comparison with intracortical electrical stimulation, although essential to study the potential for modification in the human cortex, suffer even more severely from the lack of precise knowledge of which neurons, and their related connections, are activated by stimulation. Transcranial magnetic stimulation (TMS) is assumed to activate neurons superficial to output layer V, whereas transcranial electrical stimulation likely activates neurons mainly in layers V and VI and axons in the underlying white matter. Although the observation that TMS but not transcranial electrical stimulation yields certain types of map reorganization is consistent with an intracortical site for plasticity (Chen et al 1998, Ziemann et al 1998), both TMS and transcranial electrical stimulation would activate immensely complex sets of cortical and subcortical circuits. Thus, it remains unproven that reorganization observed in the cerebral cortex using any of these forms of stimulation necessarily means that the cerebral cortex is the site of modification.

SUBSTRATES AND MECHANISMS FOR PLASTICITY WITHIN MI

Recent evidence has directly demonstrated that MI contains both a substrate for and a mechanism to implement plasticity, thereby placing MI intrinsic circuitry in a key position to account for map organization that stimulation mapping has revealed. The candidate substrate for MI plasticity is the system of horizontal connections that spans MI. Evidence from several sources demonstrates that this system of connections functionally associates MI neurons to form neuronal assemblies that construct dynamic motor maps. The existence of occult motor maps in MI has been revealed using focal and local blockade of GABAergic inhibition that then apparently unmasks existing horizontal connections likely

normally blocked by feed-forward inhibition (Jacobs & Donoghue 1991). Local GABAergic release yielded map changes parallel to those occurring following nerve lesions. This experiment demonstrated that MI has the intrinsic circuitry necessary to support reorganization, and the results further suggested that the details of MI organization likely depended, probably moment to moment, on the precise balance of excitatory and inhibitory influences within the network of MI connections. Corroborative evidence to that from experimental animals has recently been obtained with humans by using the indirect methods of transcranial stimulation and pharmacological manipulation through systemic application (Ziemann et al 1998).

A second important finding that linked MI map reorganization to modification of the horizontal MI circuitry emerged by direct comparison of the distribution of intracortical connections and the sites of map changes (Huntley 1997). In this work, facial nerve lesion in rats yielded MI reorganization at sites having strong horizontal connections that spanned the reorganized facial whisker area and the forelimb areas. No significant reorganization occurred in MI zones having no or sparse connections between the forelimb and whisker regions. This striking finding indicated that MI reorganization revealed by electrical stimulation mapping reflected the architectural pattern of the horizontal connection network in MI and that reorganization could reflect synaptic plasticity of these fibers.

A third important finding supporting the existence of an intracortical substrate to mediate restructuring of MI maps has been obtained from motor cortex slice preparations. Slice preparations can be used to directly evaluate local connections under controlled circumstances using both intracellular and, on a grosser scale, field-potential recordings. Field potentials can reveal summed synaptic effects within a small patch of cortex (Aroniadou & Keller 1993, Donoghue et al 1996). These studies have shown extensive and functionally strong horizontal pathways in MI spanning the superficial layers II and III and the deeper layer V. Pharmacological manipulations demonstrated that glutamate receptors mediate these horizontal excitatory connections (Keller 1993b, Hess et al 1994). Furthermore, feed-forward GABA inhibition likely regulates the strength of excitation, as was predicted by earlier *in vivo* work (Hess et al 1994, 1996; Donoghue et al 1996).

Although these intracortical connections could provide a basis for dynamic, moment-to-moment modulation of the functional architecture of MI, persistent changes in the efficacy of horizontal connections over longer periods would appear to require a stable form of synaptic modification. Activity-dependent modification through processes leading to long-term potentiation (LTP) and depression (LTD), which has been documented extensively in the hippocampus, could also provide a mechanism for long-lasting synaptic modification in the cerebral neocortex. The possibility for activity-dependent synaptic plasticity has been long established and well documented in MI (Baranyi & Feher 1978, Baranyi et al 1991). The horizontal pathways in MI that may mediate formation of new associations among populations of MI neurons have recently been shown to have a capacity for long-lasting synaptic modification (Hess & Donoghue 1994, Aron-

iadou & Keller 1995). Connection strength can be adjusted up with LTP or down with LTD, depending on the pattern of stimulation used; low frequencies typically elicit LTD, whereas high-frequency stimulation results in LTP (Hess & Donoghue 1996b). As in the hippocampal Schaeffer collateral system and in developing neocortex (Bear & Malenka 1994), the MI plasticity is N-methyl-D-aspartate receptor dependent, which suggests first that common mechanisms regulating synaptic efficacy prevail across at least these two cortical structures and second that plasticity mechanisms of development persist in adult neocortex.

In contrast to other sites or developmental periods, however, LTP induction in the mature MI appears to be more constrained. LTP of the horizontal pathways alone fails unless inhibition is transiently reduced during, but not after, stimulation (Hess et al 1996). Tetanization of vertical pathways along with simultaneous horizontal activation is an additional condition that permits LTP (Hess et al 1996). This vertical activation presumably includes thalamocortical fibers and a mixture of other inputs and output fibers with recurrent collaterals. These results suggest that modification in adult MI representations due to increases in synaptic efficacy requires a specific context: Alterations in the level of inhibition or concomitant activity of extrinsic pathways appear to open a window of opportunity for functional restructuring of intracortical connections that then leads to a change in the MI output map. These results further raise the intriguing possibility that the cerebello-thalamocortical pathway, which forms one important vertical input to motor cortex, provides one of these gating signals. Unlike LTP, LTD is readily induced in horizontal pathways by repetitive low-frequency stimulation, without the need for additional manipulations (Hess & Donoghue 1996a). It is significant that synaptic modification is not limited to horizontal pathways; other connections can modify as well (Donoghue et al 1996), but these connections are not strategically situated in a way to link populations of cells distributed across MI.

Through activity-sensitive mechanisms, the synaptic efficacy of the interconnections among MI neurons can be continuously adjusted up and down, presumably throughout life, as a consequence of their exposure to appropriate activity patterns. The extent of these adjustments is likely strongly regulated by context. These findings seem to place MI at the center of an arena where functional reorganization of motor representations occurs, because MI contains both the substrate (the horizontal connection system) and the mechanisms (LTP/LTD) for reorganization. Nevertheless, one cannot rule out subcortical sites as participants in lesion-induced reorganization of MI because the potential for synaptic modification is widespread in the nervous system (Randic et al 1993).

LEARNING

Although the definition of motor learning is complex and controversial (Donoghue et al 1996), for current purposes we consider two types motor learning. First, motor-skill learning can be considered the acquisition of new spatiotemporal

muscle-activation patterns, occurring, for example, when a pianist learns a novel set of hand motions for a musical score or when individually known movements combine to form a novel movement sequence. Second, we consider two types of motor adaptation: sensory-motor adaptation and conditional sensory-motor associations. Examples of sensory-motor adaptation include practice of known motor skills, such as repeating a sequential action like an already learned musical score, or learning to move in an altered physical environment, such as in microgravity. A common example of conditional sensory motor associations is learning for the first time to associate the changing of a traffic light from green to red with the need to move the right foot from a car's accelerator pedal to the brake pedal. After learning the association, continued application of this rule would then fall under the category of sensory-motor adaptation. No widely accepted definitions distinctly separate either the two forms of experience-dependent learning or the two forms of motor adaptation. Instead, our descriptions of the forms of motor-skill learning can only be considered as working definitions of types of modifications in motor behavior that may invoke similar or different cortical mechanisms. It is also worth noting that separation of these forms of learning may be artificial, and the definitions could prove to be unwarranted. Nevertheless, they provide a framework for building a meaningful understanding of motor learning and the neural operations that are responsible for its impressive range and diversity.

MI and Learning: Experimental Animals

Changes in MI maps in experimental animals have been observed in relation to acquisition of new skilled motor actions. Electrical stimulation maps changes in monkeys after learning a new visually guided step tracking movement (Suner et al 1993, Sanes & Donoghue 1997) or a precision grasping task (Nudo et al 1996), and in rats that have acquired a skilled reaching movement (Kleim et al 1998). These tasks may be considered forms of motor-skill learning because the motor actions appear to have required the acquisition of novel spatiotemporal muscle activity patterns, but they also include forms of adaptation. It remains a challenge to evaluate whether modifications following this type of learning reflect the process of learning or altered motor actions, because by definition the action under study cannot be evaluated before it is learned. By contrast, the process of learning sensory-motor associations can be more definitively controlled because both the neural response to an initially meaningless sensory cue and an already known motor action can be tested in advance of learning a new association between them. Marked alterations in the discharge properties of some MI neurons occur during sensory-motor learning or adaptation in monkeys (Mitz et al 1991, Wise et al 1998). The latter two studies tested two different forms of what we termed motor adaptation—conditional association and sensorimotor adaptation. The former case required learning the relationship between a joystick movement and a visual cue that reported on the movement (Mitz et al 1991), whereas the latter

required establishing an association between an arbitrary visual cue and a well-learned movement (Wise et al 1998). Neurons active with the first task were readily found in premotor cortex, less so in MI, whereas those active in the second task were readily found in MI. These studies provide direct evidence that neurons within motor cortex can modify their firing properties within short time periods when sensory-motor contingencies change. They also suggest that MI neurons can be involved in various forms of motor learning; however, different aspects of learning may be relegated more or less to subdivisions of motor cortex outside of MI.

MI and Learning: Humans

Movement Repetition and Practice Motor representations in human MI appear sensitive to both short-term and long-term experience. Simple repetition of an individual movement, two movements together, or a finger movement sequence can alter MI representations rapidly. These changes in MI can sometimes occur with as little as 5–10 min of rapidly repeating movements (Classen et al 1998), although most often changes in MI hand representations required 20–30 min of repetition. More infrequent movements, although done over the course of 40 min, also can induce subtle changes in MI representation (Liepert et al 1999). In this work, combined movement of the thumb and the foot resulted in a transient medial shift toward the foot representation of the lowest-threshold thumb sites revealed by TMS. Brain imaging studies also have demonstrated that repetition of a known movement sequence can change the amount of MI activation revealed by functional MRI within a single session and across sessions (Karni et al 1995). During a single session, it appears that repetition of a previously practiced finger movement sequence or of a sequence practiced infrequently—presumably only during the brain imaging sessions—results in a diminution in the size of the movement-related MI representation of subsequently performed sequences, independently of whether practice of the sequence had occurred frequently or infrequently. Similar decreases in MI activation, revealed by PET, occur when volunteers acquire the capability of reaching within an altered local physical environment (Shadmehr & Holcomb 1997). However, a number of other studies indicates that MI activation increases with movement repetition (Grafton et al 1992, Iacoboni et al 1996, Shadmehr & Holcomb 1997, van Mier et al 1998). The discrepancy between the study of Karni et al (1995) and the other studies may relate to differences between functional MRI and PET or to changes in movement parameters observed by the second set of studies [for accuracy, see Grafton et al (1992); for reaction time, see Iacoboni et al (1996); for movement path length, see Shadmehr & Holcomb (1997); for velocity, see van Mier et al (1998)] but controlled for by Karni et al (1995). Recent work suggests that functional connectivity between MI and nearby related motor cortical regions revealed by coherence mapping with electroencephalographic recordings changes during the early phases of learning unimanual and bimanually coordinated sequences (Andres et al 1999).

In summary, substantial evidence indicates that MI representations or activation patterns exhibit flexibility because of simple movement repetition and that these changes occur quickly and can reverse equally quickly. The mechanisms by which such changes may occur have been discussed above, but it also remains unclear whether the MI flexibility adheres to rules of behavioral or neural habituation (Thompson & Spencer 1966). Future work should explore the conditions by which movement repetition may enhance or suppress MI representations and whether these changes generalize across body parts. How MI interacts with other brain areas during this type of skill acquisition requires further investigation. Additionally, because it appears that individual skill may influence the susceptibility of MI to change (see next section), an important issue to resolve concerns whether acquired or inherent skill influences the propensity of MI to exhibit modification.

Movement Sequence Learning Humans readily acquire sequential motor skills, such as riding a bicycle or typing. These motor skills commonly entail chaining together components of already known movements into new spatiotemporal sequences, but they also involve the fractionation of control of muscle groups that are ordinarily used in a concerted manner. Movement fractionation is traditionally viewed as a cardinal role of the motor cortex (Bennett & Lemon 1996). Although sensory signals can indicate what to do next in a sequential movement, especially during the initial phases of learning, many motor sequences do not depend on explicit sensory input to improve performance or to learn about the sequence. Instead, performance improvements in the sequential movement can occur by repetition alone. Although we have already considered a possible MI role regarding movement repetition, these findings mostly concerned repetition of simple movements and mostly short-term changes occurring in MI representations. Repetition of movement sequences often entails acquiring implicit and explicit knowledge about the sequence, and a role for MI in such processes beyond that of controlling movements would imply that MI takes part in forming learning-related representations. MI involvement in motor-sequence learning appears evident for two general classes of sequence learning: repetition of a sequence learned through demonstration and performed without sensory cues, and repetition of a movement sequence cued by sensory stimuli.

The amount of MI activation changes after humans practice a movement sequence independently of sensory cues, such as repeatedly tapping out a sequence. These changes can occur with minimal practice (Pascual-Leone et al 1995a, Hund-Georgiadis & von Cramon 1999), although extensive practice may be needed to reveal modifications in MI (Karni et al 1995, Pascual-Leone et al 1995b) or may yield further changes in MI representations beyond that observed initially (Pascual-Leone et al 1995b). The changes observed in MI during short-term practice of a sequence appear to differ between accomplished piano players and nonmusicians (Hund-Georgiadis & von Cramon 1999). In this case, functional MRI revealed increases in MI movement-related activation for piano play-

ers but decreases of MI activation for nonmusicians as practice continued. In general, the changes in MI representations do not seem to occur from repetition of unrelated movements but appear related to repetition of a particular sequence of motor actions (Pascual-Leone et al 1995a) for which volunteers had acquired prior knowledge about the sequential relationship of the actions. This finding suggests that MI participates in either acquisition or read-out of knowledge about movement sequences. Finally, it appears that MI reorganization in relation to movement sequences can occur independently of actual performance. Although mental rehearsal of a movement sequence does not yield equivalent performance improvements to actual practice, it does yield comparable changes in MI representations to that generated by actual performance (Pascual-Leone et al 1995a).

In addition to MI plasticity observed following repetition of already learned movement sequences performed from memory, MI representations change when humans perform and learn sequences in response to sensory cues. This body of work has mostly used a behavioral method that identifies the implicit and explicit phases of learning. This technique commonly requires participants to respond to a visual cue indicating a button press, and unbeknown to the participant, the button press sequence may have a repeating or random order. With an ordered sequence, reaction time to start the button press progressively decreases even before participants gain explicit knowledge of the movement sequence order (Nissen & Bullemer 1987). The decrement in reaction time has been interpreted as reflecting acquisition of implicit knowledge, or of knowledge similar to that occurring during improving performance of (or learning) motor skills. By contrast, declarative knowledge about the motor task becomes evident when participants can recite, or predict, the sequence order. Therefore, a relatively simple task, termed the serial reaction time task, can assess whether brain structures participate in the implicit, the explicit, or both phases of motor-sequence learning.

Using the serial reaction time task, various groups have found MI modifications during the implicit and explicit phases of the task. TMS induces larger MI representations of finger muscles during the implicit learning phase, and the change is inversely proportionate to the reaction time decrease (Pascual-Leone et al 1994). The expansion of MI representations began to retract just before explicit knowledge occurred and continued to retract, possibly below that of baseline as participants continued to practice the learned sequence. Electroencephalographic related activity, likely recorded over MI, exhibits parallel changes (Zhuang et al 1997). The alpha band within event-related desynchronization declined during implicit learning, showed a transient peak when sequence knowledge became explicit, and then declined with further practice. PET studies have also shown that MI activation increases during the course of implicit learning (Grafton et al 1995), and that such increases do not depend on whether or not the stimuli have spatial compatibility with the finger used (Hazeltine et al 1997). It does appear, however, that MI may be more involved in the effector, rather than the actual learning, aspects of visually guided motor sequences. First, changes in MI activation appear coupled to changes in reaction time (Honda et al 1998) and to the

effector used in the task (Grafton et al 1998b), which suggests a close relationship to motor actions rather than to learning. Second, extra activation in MI during sequence acquisition in comparison with random sequence performance does not occur if participants receive (a) advance information that the sequence has order (Eliassen et al 1998) or (b) the actual sequence order (Rauch et al 1995). Nevertheless, recent data suggest that MI or a border zone between MI and lateral premotor cortex may have a role in the recall from memory of internal models acquired when humans learned to move in an unusual physical environment (Shadmehr & Holcomb 1997). Despite the possibility of a MI role in recall, it appears that although MI has some involvement in learning the order of motor sequences cued by visual stimuli, current data do not provide definitive evidence of a key MI role in actual learning. Instead, MI would appear to have a greater role in the effector aspects rather than the implicit and explicit learning phases of the serial reaction time task.

Learning Sensory-Motor Associations Mammals successfully learn to operate in altered sensory environments and to associate sensory signal with movements. Adjusting movements when challenged with, for example, changed viscosity (such as in water) occurs rapidly, typically within a few repetitions, although substantial practice may be needed to compensate for complex environmental changes (Shadmehr & Mussa-Ivaldi 1994). During the learning of sensory-motor associations, neither the sensory stimuli nor the movements commonly have novelty. However, the relationship between known stimuli and movements can initially be novel. Learning to stop at a red traffic light by linking all the sensory, perceptual, and motor activities of the task represents a paradigmatic example of forming arbitrary associations between sensory events and movements. Here, we discuss first MI changes occurring during adaptation to modified sensory cues that guide or affect movement and then MI changes related to learning the association between arbitrary sensory signals and movements within the extant repertoire.

Some PET studies have revealed changes in MI activation when participants learn to move appropriately in a modified mechanical environment (Shadmehr & Holcomb 1997, 1999). In these experiments, participants learned to compensate for irregular shifts in encountered forces when making straight-line arm reaches. The learning-related PET signals in MI were not entirely related to motor performance because the change in MI activation exceeded that predicted by motor-performance changes (Shadmehr & Holcomb 1997). However, another group using similar methods did not find any changes in MI with learning (Krebs et al 1998). MI may have exhibited activation during the recall of learned performance in the altered mechanical environment, although the activation during recall may be in MI or the adjacent lateral premotor cortex (Shadmehr & Holcomb 1997).

In contrast to findings in monkey MI (Mitz et al 1991, Wise et al 1998), it appears that human MI does not have a robust relationship to the learning of conditional motor associations (Deiber et al 1997, Grafton et al 1998a, Pas-

singham et al 1998). Instead of MI activation during the formation of conditional visual motor association, structures related to MI, such as lateral premotor cortex, exhibited activation during such learning. The difference between the neuronal recording (Mitz et al 1991, Wise et al 1998) and neuroimaging work may be related to fundamental differences in the two methodologies. However, it is also possible, much like sequence learning (see above), that MI has more of a role in adjustments needed during repetition of actions and not to the formation of associations between unrelated sensory stimuli and the extant movement repertoire.

ROLE OF INTRACORTICAL CIRCUITRY IN LEARNING

In order to know whether motor cortex is a site for learning or storing motor skills, it would be essential to establish that functional reorganization occurred within motor cortical circuitry during learning. Direct evidence that skill learning leaves a trace in motor cortex after acquiring a new skill has recently been obtained in rats that learned a skilled reaching task. Increased efficacy of layer II–III horizontal connections of MI is evident in slice preparations obtained from rats that had been trained for 5 days to reach through a small hole to grasp and retrieve food pellets (Rioult-Pedotti et al 1998). The lateralization of MI provided an internal control because unimanual training mainly engages MI contralateral to that limb. Field potentials evoked across layer II–III, a measure of the efficacy of synaptic connections in this pathway, are consistently larger in the trained MI than in the untrained MI (ipsilateral to the trained limb). This result is surprising, given that complex activity patterns evoked during learning might be expected to produce both increases and decreases in synaptic efficacy that would not be revealed as any net change using nonspecific field-potential recordings, which reflect averages over large numbers of synapses. This enhancement was linked to an LTP-like mechanism (Rioult-Pedotti et al 1998). If learning-associated modification used a process like LTP, then further LTP induction should be occluded in the trained MI when applied after learning. This prediction was confirmed by showing that less LTP was obtained from the trained MI, whereas normal levels were obtained from the untrained MI in the same animals (Rioult-Pedotti et al 1998). Such evidence directly links MI horizontal connections to processes that occur with skill learning. Because MI was examined only after the skill was largely learned, it is not possible to know the relationship between field-potential changes and the time course of learning. However, this preparation makes such investigations possible. Because modifications of human motor areas can occur quickly during the process of learning (Pascual-Leone et al 1994, Toni et al 1998, Eliassen et al 1999), it should be possible to associate the relationship between the strength changes of horizontal connections and specific phases of learning.

Currently, it remains unknown whether these changes in MI properties are a result of the learning or whether they actually drive the performance changes. However, these experiments provide direct evidence that acquisition of a new

motor skill is accompanied by synaptic modification of MI circuitry. Therefore, MI cannot be considered simply a passive link in motor learning; rather, it is an active participant in changes ensuing when new actions must be learned. These processes are not likely unique to motor cortex. Similar patterns of connections are present throughout neocortex, and as described earlier, activity-driven synaptic modification is a widespread phenomenon in the adult central nervous system (Kaas 1991, Donoghue 1995, Buonomano & Merzenich 1998).

MI AND COGNITION

The MI involvement in various aspects of motor learning provides support for nonmotor roles of MI, perhaps in activities affiliated with cognition. Indeed, nearly 25 years ago, it was reported that MI neurons changed discharge rates when monkeys waited up to several seconds for an instruction to initiate movement but without actually moving (Tanji & Evarts 1976). This finding, and others that confirmed those observations (Georgopoulos et al 1989a, Kalaska et al 1992, Ashe et al 1993), indicated that MI neurons could hold premotor information for short periods, which suggests that MI neurons might exhibit the functional equivalent of elementary memory functions.

Other evidence also suggests that MI has involvement in activities beyond those strictly consistent with an upper motor neuron function. In contrast to the early emphasis of analyzing MI neuronal recordings in relation to simple motor properties, especially force (Evarts 1967), data from almost 20 years ago indicated the MI neurons could encode movement variables that have been termed higher order (Georgopoulos et al 1982). These variables include movement direction (Georgopoulos et al 1982, Kettner et al 1988), movement distance (Fu et al 1995, Taira et al 1996), target position (Fu et al 1995), or movement goal (Alexander & Crutcher 1990). In general, all these properties are encoded by some MI single neurons and by a sampled population of MI neurons. However, although various efforts have dissociated these variables from purely motoric effects (Georgopoulos 1988), sufficient data exist to suggest that neuronal correlations with higher-order movement parameters, such as direction and distance, largely, but not necessarily exclusively, reflect motoric effects. Notwithstanding this vigorous debate, the observation that MI neurons exhibit activity changes during an instructed delay period proved fruitful for two additional observations to support a MI role in cognition. First, the MI neuronal population vector changes its directional properties during the delay period in a manner consistent with visual motor mental rotation (Georgopoulos et al 1989b). These findings have received partial confirmation from functional MRI work describing changes in MI during a mental rotation task (Tagaris et al 1997, Kawamichi et al 1998). Second, MI neurons may have some relationship to the serial order within a short list of items (Pellizzer et al 1995, Carpenter et al 1999).

Mental rehearsal of movements or motor imagery appears to engage MI. An early study with PET methods suggested that only nonprimary motor cortex, and not MI, became active during mental rehearsal of movements (Roland et al 1980). Such a finding is consistent with a premotor role for nonprimary motor areas and a motor role for MI. Subsequent studies with PET or functional MRI have confirmed the original finding of no role for MI in mental rehearsal of movements (Sanes 1994, Parsons et al 1995, Stephan et al 1995, Sanes & Donoghue 1997). However, other studies have found weak signals in MI (Deiber et al 1998) or have found abundant activation signals (Sabbah et al 1995, Porro et al 1996) in relation to motor imagery. Task or methodology differences likely explain the inconsistent results, possibly with the simplest type of imagined movements yielding a MI signal, whereas more complex movement patterns fail to activate MI during mental motor imagery. Nevertheless, transcranial activation studies (Yahagi et al 1996, Rossini et al 1999) and those measuring electrical brain activity with electroencephalography or magnetoencephalography (Beisteiner et al 1995, Pfurtscheller & Neuper 1997, Schnitzler et al 1997) have provided evidence that MI circuits become active during mental motor imagery. There remains some controversy whether the effects of mental motor imagery on MI representations reflect spinal (Bonnet et al 1997) or cortical (Kasai et al 1997) excitability changes. However, it does appear that mental motor imagery, like actual movement, conforms to Sherringtonian laws of reciprocal inhibition (Hashimoto & Rothwell 1999) and induces processes that would seem to occur at a cortical level (Abbruzzese et al 1999). In their aggregate, these studies provide substantial support for a MI role in mental motor imagery, a process that verges on cognition. However, there remains some uncertainty as to whether subliminal spinal motor processes become engaged during motor mental imagery that could potentially influence understanding whether circuits in MI actually mediate the effects observed during mental motor imagery.

Most of the work discussed above about a possible MI role in cognition, naturally and conveniently, used tasks that typically required motor actions, such as repetitive movements or reaching, or assayed motor outputs following transcortical stimulation. As noted, a potential, but seemingly necessary, complication of these studies is that they depended on motor actions, either actual or imagined, or preparation for motor actions, to determine whether MI participates in cognition. A recent experiment may provide unequivocal evidence for a MI role in cognition (Acuña et al 1998). In this work, brain activation using functional MRI was examined while participants applied a previously learned logic rule about the relationship between pairs of visual stimuli. Each member of the stimulus pair had been seen before, but not together, and the items were contained within an ordered "list" of visual stimuli, for which participants had formed a mental model from prior training. The rule application involved transitive inference; a specific example would be if A is less than B and B is less than C, then the relationship between A and C becomes clear by applying a logic rule or a mental model. Although motoric responses were necessary to determine task compliance, the

application of the logic rule seemed independent of motor processing. The results indicated that although parietal and prefrontal regions exhibited specific activation during application of the transitive inference rule over application of a perceptual rule, MI also showed activation characteristics most easily interpreted by a role in applying the transitive inference rule.

In summary, current evidence suggests that MI likely has a role in cognition, although most of the clues would, not surprisingly, position such a role for MI extremely close to motor actions. Nevertheless, certain data suggest near movement independence for MI involvement in cognition. Future work will likely add interesting new information to the possibility that MI adds its processing power to cognitive calculations.

CONCLUSIONS

Changes in our understanding of the functional organization of motor cortex and its modification with learning and cognition prompt a fairly substantial shift in our view of the motor cortex. The concept that MI is largely a discretely organized, static neural keyboard upon which movements are played out seems untenable. Instead, the current data indicate that MI consists of several modules, each related to a different major system to be controlled, i.e. the head, arm, and leg. We know the organization best for the arm, which we believe to be representative of all other modules. The population of neurons within the arm module comprises a distributed neural network, in which every neuron in that network potentially contributes to every arm action. Each MI neuron controlling the arm is embedded in a network of lateral or horizontal connections with other MI arm-related neurons. Reflections of movements, muscle activity, and other aspects of motor behavior in the properties of MI are not surprising given that it appears to be a plastic network situated in the middle of a system receiving and producing signals related to diverse motor actions.

It is now apparent that adjustments in the balance of excitation and inhibition within MI change its organization and reveal a rich architecture that can support many organizational structures, if the arm area is representative. Network structure can adjust dynamically to meet the immediate needs of the system, as seen in response to postural change. In addition, synapses in MI are plastic, to allow for the organization of each module's network to be reconfigured on longer time-scales on the basis of ongoing activity. Many of the details of how this occurs and exactly how motor cortex contributes to these processes need further study. Motor cortex also appears important for learning new as well as for producing new and old motor actions. This does not diminish the long-standing implication that the cerebellum is a site of some forms of motor learning; it only expands the set of structures that participate in what is a complex set of phenomena that afford impressive behavioral flexibility in mammals. Finally, activity in motor cortex appears to be influenced by cognitive variables, which suggests that MI must be

considered as part of a larger cortical network that can be an active participant in making decisions to move on the basis of internally enacted cognitive effort.

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