Learning in the Rodent Motor Cortex

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Abstract

The motor cortex is far from a stable conduit for motor commands and instead undergoes significant changes during learning. An understanding of motor cortex plasticity has been advanced greatly using rodents as experimental animals. Two major focuses of this research have been on the connectivity and activity of the motor cortex. The motor cortex exhibits structural changes in response to learning, and substantial evidence has implicated the local formation and maintenance of new synapses as crucial substrates of motor learning. This synaptic reorganization translates into changes in spiking activity, which appear to result in a modification and refinement of the relationship between motor cortical activity and movement. This review presents the progress that has been made using rodents to establish the motor cortex as an adaptive structure that supports motor learning.

Contents

INTRODUCTION

Motor learning refers to the remarkable ability of animals to tailor their movements to changing environmental demands. Although it is certainly part of an interdependent system, the motor cortex has been suggested to be a central locus for motor learning (Sanes & Donoghue 2000, Shmuelof & Krakauer 2011). After its initial discovery in dogs (Fritsch & Hitzig 1870), a prodigious amount of research was conducted on the primate motor cortex, demonstrating the fundamental properties of somatotopy (Beevor & Horsley 1890, Leyton & Sherrington 1917), deficits following lesions (Travis & Woolsey 1956), the relationship between activity and movement (Evarts 1965), and changes during learning (Nudo et al. 1996). More recently, rodents have become a powerful system for studying the motor cortex (Ölveczky 2011). Importantly, because they can be trained to perform simple motor behaviors relatively quickly and more tools are available to study neuronal structure and circuit function across learning, rodents have become a major system for observing changes associated with motor learning.

This review aims to discuss what has been learned from studying the rodent motor cortex toward the goal of understanding how the motor cortex controls movement and supports learning. We approach this in four broad categories. First, we provide a comparative and anatomical context of the rodent motor cortex. Second, we present the morphological and connectivity dynamics that have been demonstrated in the rodent motor cortex. Third, we discuss investigations into the functional plasticity of the rodent motor cortex. Finally, we suggest several areas of interest for future study.

COMPARATIVE, ANATOMICAL, AND FUNCTIONAL FEATURES OF THE MOTOR CORTEX

The Motor Cortex Across Species

The motor cortex is defined through a composite of low-threshold microstimulation–evoked movements; projections to the motor aspects of the contralateral spinal cord, which presumably mediate this effect (Alstermark & Ohlson 2000, Asanuma & Sakata 1967); a lack of a granular layer 4 (but see Yamawaki et al. 2014); and inputs from the ventrobasal thalamic nuclei. Several marked changes have occurred within the motor cortex across phylogeny, correlating with both an increase in dexterity and a changing demand for sensory-guided movement. The somatosensory and motor cortex overlap to varying degrees across species, with an increasing degree of segregation observed from marsupials to rodents to primates (Donoghue et al. 1979, Nudo & Frost 2007). The number of discrete cortical motor areas is increased greatly from two in rodents (Neafsey & Sievert 1982, Tennant et al. 2011) to at least seven in primates (Dum & Strick 2002), potentially reflecting an increased capacity for coupling vision to movement (Georgopoulos & Grillner 1989). Connectivity of corticospinal neurons with the ventral spinal cord is more extensive in dexterous animals and can include direct contact to spinal motoneurons in primates (Armand 1982, Heffner & Masterton 1975, Lemon 2008). In rodents, by contrast, monosynaptic connections from the motor cortex to spinal motoneurons are either extremely sparse or completely absent in adults (Alstermark et al. 2004, Maeda et al. 2016). The corticospinal tract also projects through different routes in the spinal cord in different species (Noback & Shriver 1969, Nudo & Frost 2007); however, the topographic location of corticospinal neurons in the cortex is conserved (Nudo & Masterton 1990). The common somatic location but different axonal pathways of corticospinal neurons have led to the hypothesis that the corticospinal system may represent a mixture of homologous and convergent evolution. Specifically, corticospinal neurons may have arisen from a common ancestral corticofugal neuron that did not project past the brainstem, and the axonal extension to the spinal cord may then have emerged separately multiple times across evolution (Noback & Shriver 1969, Nudo & Masterton 1990).

Connectivity of the Rodent Motor Cortex

The ability to perform acute slice recordings coupled with a broader set of histological methods has put rodents at the forefront of determining motor cortex connectivity (**Figure 1**). One emerging principle from these experiments is lamina-specific connectivity, which has great functional implications. On the input side, for example, it has been found that basal ganglia–recipient and cerebellum-recipient nuclei of the thalamus project asymmetrically to the motor cortex, with the former projecting predominantly to layer 1 apical dendrites of layer 2/3 and layer 5 neurons, whereas the latter projects directly to layer 2/3 and, to a lesser extent, to layer 5 (Hooks et al. 2013; Kuramoto et al. 2009, 2013). The differential projection patterns of these two thalamic recipient zones suggest that information from the basal ganglia and cerebellum may take different routes through the motor cortex and partake in different types of computation. The motor cortex is therefore in a prime position to integrate motor signals corresponding to particular functional roles, for example, using basal ganglia information to guide movement selection and cerebellar information to initiate or shape ongoing movements (Kaneko 2013). Inputs from other cortical areas also arrive with characteristic laminar profiles. For example, somatosensory areas primarily drive layers 2/3 and 5a (Mao et al. 2011), whereas frontal areas are biased toward contacting layers 5 and 6 (Hira et al. 2013b, Hooks et al. 2013, Rouiller et al. 1993). Within the motor cortex, the predominant flow of information travels from superficial to deep layers (Weiler et al.

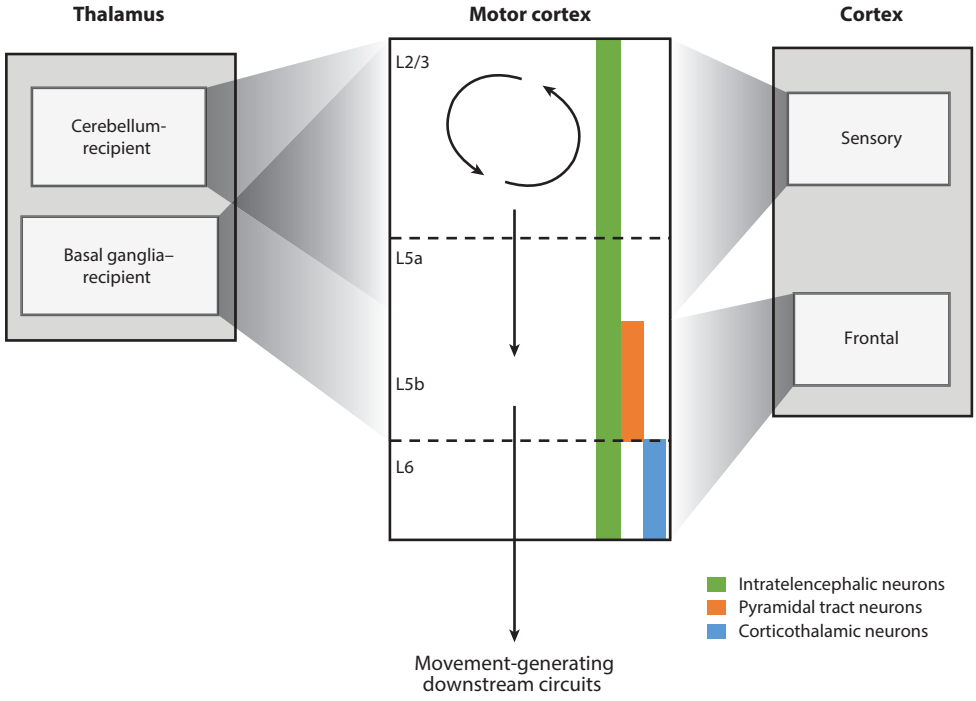

Figure 1

Simplified schematic of the connectivity of the rodent motor cortex. Arrows represent major pathways. Activity from basal ganglia–recipient thalamus and frontal cortex can reach deep corticofugal cells directly, whereas motor-related thalamic nuclei and sensory cortical activity arrive indirectly through highly recurrent layer 2/3 networks. Color boxes indicate the soma locations of different types of output cells. Adapted with permission from Hooks et al. (2013) and Macmillan Publishers Ltd.: Nature Neuroscience, Weiler et al. (2008).

2008). These patterns of connectivity may represent parallel pathways to drive motor cortex output neurons in deep layers. One route originates from the thalamus and posterior cortical areas and arrives via the highly recurrent superficial layers of the motor cortex, whereas the other arrives directly from frontal cortical areas and the thalamus, bypassing the superficial layers (Hooks et al. 2013, Kaneko 2013). The deep corticofugal neurons are themselves laminarly organized, with intratelencephalic-type neurons distributed from layers 5a to layer 6, pyramidal tract–type neurons restricted to layer 5b, and corticothalamic-type neurons restricted to layer 6 (Harris & Shepherd 2015). These classes of output cells are also connected in characteristic ways with other cells in the motor cortex (Anderson et al. 2010, Kiritani et al. 2012, Yamawaki & Shepherd 2015), and, importantly, individual output neurons can project to multiple cortical and subcortical areas through extensive axonal collaterals (Kita & Kita 2012).

Functions of the Motor Cortex

The role of the motor cortex in subserving certain types of movements has been causally supported by a century of manipulation studies, in which disruption of the motor cortex produces motor deficits. Acute pharmacological or optogenetic inactivation of the motor cortex is highly effective

in reducing motor aptitude (J.-Z. Guo et al. 2015, Otchy et al. 2015, Peters et al. 2014). Even the earliest lesion experiments have made clear, however, that the motor cortex is not necessary for the production of all movements (Fritsch & Hitzig 1870). In fact, even though complete primary motor cortex lesions induced temporary paralysis in primates, animals regained substantial motor ability as long as other motor cortical areas were still present (Fulton 1935, Murata et al. 2015). Certain forms of movement, including walking, can be spared even if the entire cortex is removed (Travis & Woolsey 1956). Instead, damage to corticospinal pathways in both primates and rodents produces a permanent deficit in the production of dexterous movements, particularly in the arm and digits (Alaverdashvili & Whishaw 2008, Castro 1972, Passingham et al. 1983, Travis & Woolsey 1956, Whishaw et al. 1993). Furthermore, lesioning the motor cortex before training abolishes the ability to learn stereotyped movements (Kawai et al. 2015, Peters et al. 2014). Notably, however, in certain types of tasks, lesions do not affect movements after they have already been learned (Kawai et al. 2015, Otchy et al. 2015). The involvement of the motor cortex in learning has been recently supported by a prodigious amount of work in rodents unveiling the plasticity of the motor cortex. These experiments typically utilize tasks that can be trained in days to weeks, including reaching tasks involving grabbing a pellet of food through a small slot (**Figure 2*a***), rotarod tasks involving running on a spinning rod, licking tasks involving licking in response to sensory cues, and lever manipulation tasks.

STRUCTURAL PLASTICITY

Morphology

One grand challenge in neuroscience is to determine the substrate of lasting memories. An advantage of rodents toward this goal is the practicality of examining changes in their neuronal architecture. Examinations of morphological plasticity of neurons in the rodent motor cortex accompanying motor learning have provided evidence that learning is supported by the formation and maintenance of new synapses (**Figure 2*b***).

Changes in neuronal morphology can be used as a proxy for changes in connectivity. Some of the first investigations of structural plasticity during motor learning yielded evidence that learning to perform a reaching task increased dendritic arborization of both superficial and deep motor cortex neurons (Greenough et al. 1985, Withers & Greenough 1989). Importantly, dendritic changes were localized to the hemisphere contralateral to the trained limb. A later study went on to demonstrate that these dendritic arborization changes are restricted to neurons that are likely involved in the learned movement—in this case, the corticospinal neurons that project to the distal forelimb–associated level of the spinal cord, presumably because of the skilled grasping required in reaching tasks (Wang et al. 2011). The increase in dendritic fields is not permanent, however, but instead returns to the prelearning level after learning has taken place, although the performance of the skilled movement is retained (Gloor et al. 2015). This transient, learning-related dendritic expansion hints at two potentially crucial features of motor learning. First, connectivity changes occur within the motor cortex, as opposed to the motor cortex simply being a relay for changes elsewhere. Second, initial dendritic expansion is balanced by later retraction, implicating a process of synaptic exploration and refinement.

Alterations of dendritic fields certainly indicate connectivity changes, but they do not provide information about the stability of individual synapses. The more targeted and subtler method of observing dendritic spines as a proxy for synaptic plasticity, by contrast, has offered a revolution in capturing learning-related connectivity dynamics. Prior to spine imaging, direct confirmation of synapse formation in the motor cortex in response to learning arose through observations of the

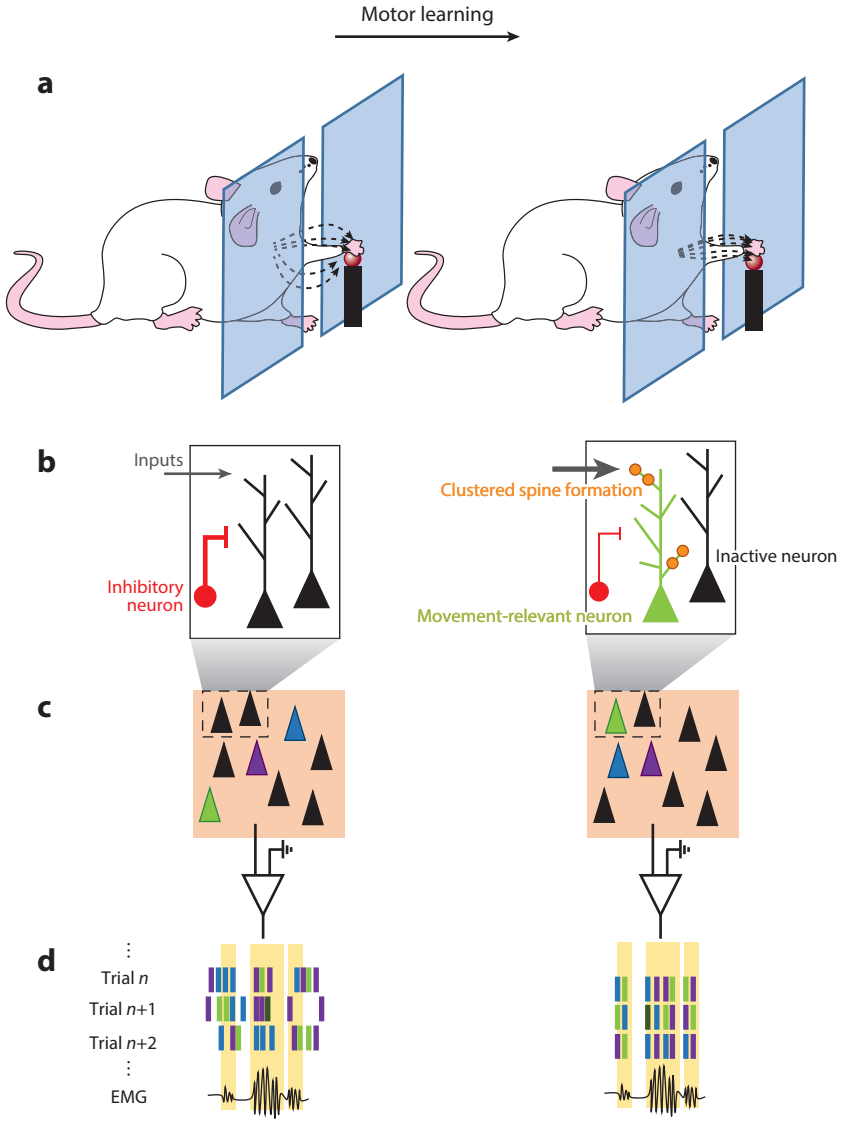

Figure 2

Schematic of the effects of learning on the motor cortex, with the naive stage on the left and the expert stage on the right. (*a*) Motor learning is characterized by increased task success and movement stereotypy, as illustrated here for a reaching task (*black dotted lines*, hand trajectories). (*b*) The motor cortex undergoes structural changes during motor learning, including a strengthening of local and long-range inputs (*gray arrows*), a decrease in inhibitory connectivity to apical dendrites (*red*, inhibitory neuron), and dendritic expansion and clustered spine formation (*orange circles*) on movement-relevant neurons (*green neuron*). (*c*) The population of neurons that exhibit movement-related activity is dynamic across learning and refines to a more consistent population (*black triangles*, inactive neurons; *colored triangles*, active neurons). (*d*) Activity of neurons becomes more correlated with movement, and the relationship between population activity and movement is dynamic but becomes more consistent, as evaluated by comparing similar movements before and after learning (*yellow regions*, periods of high muscle activity; *colored bars*, spikes of different neurons). Abbreviation: EMG, electromyograph.

ultrastructure of the motor cortex (Kleim et al. 1996). When spines were subsequently observed in slices following motor learning, it was somewhat surprising that although spine size increased, spine number did not appear to change (Harms et al. 2008). A following set of simultaneous reports, however, gave outstanding correlative evidence to support the role of synapse formation in the motor cortex during motor learning. In these studies, sparse fluorescent labeling allowed for two-photon imaging of individual dendritic branches of layer 5 neurons on multiple days during training in a reaching (Xu et al. 2009) or rotarod task (Yang et al. 2009). Learning was accompanied by new spine formation in the hemisphere contralateral to the trained limb within the first few days of training, beginning only hours after the first session. After this spine growth, a period of increased spine elimination returned the total number of spines to baseline while selectively retaining the newly formed spines. Remarkably, behavioral performance was correlated with the amount of spine growth within animals. The growth and maintenance of new spines during motor learning was then demonstrated in layer 2/3 neurons, indicating that selective synapse turnover occurs throughout the motor cortex (Peters et al. 2014). Spine formation during learning appears to be spatially organized, as newly formed spines tend to spatially cluster (Fu et al. 2012) whereas learning different motor skills invokes spine growth on separate dendritic branches (Yang et al. 2014), implying modular instead of intermixed architecture across dendrites for newly formed circuits. Together, this collection of work suggests that motor skill learning relies on the formation and selective maintenance of new synapses within the motor cortex. Indeed, it has been posited that structural changes within the motor cortex are necessary for learning, as normal protein synthesis has been shown to be required for both learning (Luft et al. 2004) and maintenance of learned skills (Kleim et al. 2003). A recent study revisited this issue with a more targeted approach. Using a novel method to label and disrupt newly potentiated spines selectively, it was found that rotarod learning–induced enlargement of spines could be reversed and performance improvements subsequently eliminated (Hayashi-Takagi et al. 2015).

Pathways

The dendritic changes described above underscore the importance of synaptic reorganization, but the identity of the presynaptic neurons remains an important and largely unanswered question. In this regard, the acute slice preparation of rodents has yielded invaluable clues as to the pathways that are modified by learning. Early work in cats suggested that inputs from the motor thalamus (Baranyi & Feher 1978) and somatosensory cortex (Sakamoto et al. 1987) to the motor cortex were putative loci of plasticity, and this work was later replicated in rodents (Iriki et al. 1989). It was only recently demonstrated that the thalamocortical pathway is in fact altered by motor learning, and importantly, potentiation of this pathway is restricted to skill-relevant neurons, paralleling the specificity of dendritic changes (Biane et al. 2016). An interesting question then arises as to whether there is a difference in plasticity of inputs from the basal ganglia– and cerebellum-recipient zones of the thalamus, which may provide clues into how the motor cortex uses subcortical information. Apart from these results, the extent to which inputs from other cortical areas or the thalamus change during learning and how they relate to spine formation and performance are avenues of future investigation.

Besides inputs from other areas, connectivity within the motor cortex itself has also been shown to be highly plastic. Long-term potentiation can be induced in the connections from superficial to deep neurons in cats (Kimura et al. 1994) and from deep to superficial layers and horizontally within superficial layers in rodents (Aroniadou & Keller 1995). The reverse was also found to be true: Synaptic depression can be induced in horizontal superficial connections (Hess & Donoghue 1996). It was then demonstrated that training in a reaching task resulted in

stronger horizontal connections within the superficial layers of the contralateral motor cortex (Rioult-Pedotti et al. 1998). This effect was paired with an occlusion of long-term potentiation in acute slices, supporting the notion that synaptic potentiation had already occurred during learning. Interestingly, potentiated connections were not seen to diminish over time, but instead the capacity for potentiation increased, presumably to allow for further learning (Rioult-Pedotti et al. 2007). Notably, large-scale potentiation from learning has been disputed, with the suggestion that learning-induced changes are balanced by synaptic depression rather than just homogeneously potentiating local connections (Cohen & Castro-Alamancos 2005). Local connectivity changes therefore provide another potential source of plasticity to sculpt circuits within the motor cortex.

Regulation of Synaptic Plasticity

During the course of experiments on synaptic plasticity, an intriguing set of requisite conditions emerged. In the pathway from somatosensory to motor cortex, tetanic stimulation alone was enough to produce potentiation (Iriki et al. 1989). In the cases of thalamocortical and local horizontal pathways, however, tetanic stimulation needed to be paired with other manipulations. In particular, inputs from the motor thalamus could be potentiated only with simultaneous stimulation of the somatosensory cortex (Iriki et al. 1989). Moreover, this associative potentiation was limited to motor cortex neurons that received input from both sources (Iriki et al. 1991). In horizontal pathways, potentiation could be induced only if inhibition was blocked pharmacologically at the recording site with bicuculline (Hess & Donoghue 1994, Hess et al. 1996). The relevance that these features had to motor learning remained speculative until recent work demonstrated a possible role of "unlocking" plasticity of motor cortical circuits during learning. The use of longitudinal two-photon imaging of neuronal structure during training of a lever press task revealed that the formation of new spines during motor learning was concurrent with a decrease in axonal boutons of local inhibitory neurons (S.X. Chen et al. 2015). Remarkably, this occurred in a dendritic domain–localized manner, where spines grew on apical and not basal dendrites, and axonal bouton elimination was restricted to somatostatin inhibitory neurons, which target apical dendrites preferentially. A causal role was then investigated by optogenetically increasing or decreasing activity of somatostatin inhibitory neurons during training, which resulted in a respective destabilization or hyperstabilization of dendritic spines. In both of these cases, learning of the task was impaired, but the same manipulations after learning had no effect on the performance of the task. This suggests that the selective nature of synapse maintenance and corresponding motor learning is critically supported by a fine-tuned system of inhibition. Changes in inhibition may likewise be controlled by changing connections onto inhibitory neurons, which is supported by motor learning–inducing increased inhibitory contacts followed by increased excitatory contacts onto inhibitory neurons in a cell type–specific manner (Donato et al. 2013).

Output Connectivity

Although most work involving motor cortex plasticity has focused on changes within the motor cortex, some research has indicated that the outputs of the motor cortex may also change as a function of learning. For example, axon fields of corticospinal neurons in the spinal cord can expand after injury (Weidner et al. 2001). Such output plasticity is possibly also engaged during learning, as connections between corticospinal neurons and spinal interneurons can be potentiated in cats (Iriki et al. 1990). Furthermore, the number of synapses in the spinal cord increases after certain types of training, potentially reflecting new corticospinal synapses (Adkins et al. 2006). There are also learning-related modifications in corticostriatal connectivity, which, interestingly,

are specific to connections with direct pathway medium spiny neurons in the striatum (Rothwell et al. 2015). The plasticity of motor cortex output is still poorly understood, and it will certainly provide an important perspective in the future to determine the output stability of the motor cortex, given the capacity for change within the motor cortex.

FUNCTIONAL PLASTICITY

Motor Maps

The past few decades have seen a tremendous progression in unveiling the role of synaptic plasticity within the motor cortex to support motor learning. The functional role of this plasticity and its relationship to movement is an advancing area of research. Functional reorganization was initially assessed through examination of microstimulation-evoked maps of movement within the motor cortex. Procedures for using electrical microstimulation to chart a map of movements in the motor cortex had been in use for a century, although it was often assumed that such maps were a fixed property (Craggs et al. 1976). When applied to a damaged system, however, these techniques provided the first demonstrations of functional reorganization (Sanes et al. 1988). A similar reorganization was then revealed during learning in squirrel monkeys (Nudo et al. 1996), which was replicated in rodents shortly thereafter (Kleim et al. 1998).

This particular class of experiments has been distributed across primates, cats, and rodents. The common trend across this work is that training effectively increased the area of the cortex that could elicit movements in the muscles involved in the novel skill. This mapping change was suggested, at least in the condition of rapid reorganization, to be served by the disinhibition of long-range latent connections within the motor cortex (Huntley 1997). Later work revealed that increases in the representational area are coincident with an area-specific increase in synapses, as determined through ultrastructure (Kleim et al. 2002). Further work capitalized on the rapid training schedule of rodents and investigated the time course of map changes as it related to synapse formation. Interestingly, this showed that synapse increases preceded map reorganizations on the order of days, both of which surprisingly lagged behind performance increases (Kleim et al. 2004). The interpretation of this result remains unclear; however, later research demonstrated that map expansions are transient phenomena, mirroring the changes observed in dendritic spines (Molina-Luna et al. 2008). Although it is not known what exactly the motor map reflects (Histed et al. 2009), it has been suggested that motor cortex maps arise from learning-sculpted circuits that support learned movements (Aflalo & Graziano 2006). Indeed, rodent motor cortex appears to be mapped as much by coordinated movements as by somatotopy (Harrison et al. 2012, Hira et al. 2015, Ramanathan et al. 2006), and manipulations of neuromodulators have linked motor maps and motor learning (see the sidebar titled Neuromodulators in the Motor Cortex).

Movement and Activity in the Motor Cortex

A more physiologically relevant way of determining functional plasticity in the motor cortex has been to eavesdrop on neuronal activity through electrophysiology or, more recently, two-photon calcium imaging. The grand challenge of this domain of research has been to determine how the relationship between activity in the motor cortex and movement is shaped by learning. Rodents again have offered unique benefits toward this goal, providing a system for observing neuronal activity throughout the duration of learning (**Figure 2*c*,*d***).

A necessary component in addressing this question is to determine how motor cortex activity relates to movement independent of learning. In this regard, the great majority of experiments

NEUROMODULATORS IN THE MOTOR CORTEX

One interesting line of results that comes from studies of rodent motor maps is related to the role of neuromodulators in learning. It was demonstrated that intact basal forebrain cholinergic neurons were required for changes in motor maps and accompanying performance increases during motor learning (Conner et al. 2003) and recovery after cortical lesions (Conner et al. 2005). Furthermore, stimulation of dopaminergic cells in the ventral tegmental area enhanced map reorganization and functional recovery following motor cortex lesions (Castro-Alaniancos & Borrell 1995), and lesions of the dopaminergic inputs to the motor cortex prevented learning (Hosp et al. 2011, Molina-Luna et al. 2009). Dopamine may control learning by regulating synaptic plasticity, as destruction of dopaminergic cells impaired long-term potentiation in acute motor cortex slice and learning-induced selective spine stabilization in the motor cortex in vivo (L. Guo et al. 2015). Motor maps can also be manipulated acutely by dopaminergic modulation, suggesting a possible fast-acting role of dopamine during learning (Hosp et al. 2009). The role of neuromodulators in motor cortex plasticity during learning remains an important area for future study.

have been carried out in primates, fueling debates from the earliest use of electrophysiology in primates (Evarts 1965) to the present (Churchland et al. 2012). As this may indicate, the translation from action potentials in the motor cortex to the flexion of muscles is a very complex problem that has so far escaped widely accepted and principled explanations. However, the fundamental findings in primates have been replicated in rodents, including, for example, the presence of preparatory activity prior to movement (Murakami et al. 2014, Storozhuk et al. 1984) and its importance in memory-guided behavior (Goard et al. 2016, Guo et al. 2014), the predominance of activity during phasic as opposed to tonic muscle contractions (Zhuravin & Bures 1989), and the temporal complexity of activity throughout movement (Hyland 1998). More recently, rodents have allowed for more targeted investigations of activity by fine-scale spatial organization, layer, and cell type, paving the way for a more circuit-oriented view of motor cortex activity (Dombeck et al. 2009, Hira et al. 2013a, Isomura et al. 2009, Li et al. 2015, Tsubo et al. 2013).

Brain-Machine Interfaces

Despite the open issue of how motor cortex activity transforms into movement, progress has been made in observing changes in activity of the motor cortex during learning. One approach has been to bypass downstream circuits altogether and instead train animals to modulate the spiking activity of specific groups of cells. These types of experiments, under the heading of brain-computer interfacing, brain-machine interfacing, or neuroprosthetics, have practical clinical implications for patients with motor disabilities, but they have also demonstrated basic features of learning in the motor cortex. Although these types of experiments have been carried out primarily in primates, including humans, many of the fundamental properties have been replicated in rodents. One important finding from this work has been to dissociate activity from movement; activity within the motor cortex does not necessarily elicit movement, and in fact, activity and movement can be decoupled by learning (Chapin et al. 1999). Although perhaps not surprising given the complexity of the circuits involved in motor production, this demonstrates a certain level of flexibility between motor cortex activity and movement that is possibly necessary for motor learning. Importantly, however, not all neurons can be modulated volitionally to equal degrees, and neurons not targeted in the task are also modified by learning, suggesting the presence of constraints possibly imposed by connectivity (Arduin et al. 2013, Clancy et al. 2014, Hira et al. 2014).

Activity Changes During Learning

Chronic recordings in rodents are beginning to shed light on the activity changes in motor cortex during motor learning. Given the complex relationship between activity in the motor cortex and movement, it is of great interest that the first such study demonstrated effects at the level of neuronal populations (Laubach et al. 2000). By recording activity in layer 5 of the motor cortex during training in a lever press task, it was shown that individual neurons did not reliably predict trial success across learning. Conversely, when the activity of the simultaneously recorded neuronal population was analyzed together, predictions of trial success increased during the first week of training, particularly if millisecond-scale resolution of activity was used. This change in information content was not due to changes in average firing rate but was instead driven by changes in fine-scale activity patterns that were coordinated across neuronal populations.

Importantly, these changes may occur independently of changes in muscle activation, indicating a shifting relationship between activity and movement. This principle was then investigated in the first day of learning by recording motor cortex activity with simultaneous forelimb muscle activity during training in a reaching task (Kargo & Nitz 2003). By quantifying synergistic patterns of muscle activity and classifying neurons according to their correlation with each synergy, they showed that movement changes during learning appeared to be directly reflected in the activity of related neurons. For example, if the activity of a neuron was correlated with a set of muscles, decreasing the use of those muscles was associated with decreased activity of that neuron. This direct reflection of movement changes in activity changes suggested that early changes in movements could occur through the selection of an activity pattern reliably associated with a given muscle output, without a change in the relationship between activity and movement. Further research, however, began to provide more evidence that the relationship between motor cortex activity and movement may not be fixed, especially over multiple days of training. Two such studies found that the fraction of cells that exhibited activity associated with movement was dynamic, and the variability of activity during movement decreased in both a reaching (Kargo & Nitz 2004) and rotarod task (Costa et al. 2004). These studies also demonstrated an increasing correlation between cortical activity and muscle activity (Kargo & Nitz 2004) and rotarod velocity (Costa et al. 2004). Another study pointed out, however, that increasingly consistent relationships between activity and movement were not necessarily expressed at the single neuron level but instead were a function of neuronal populations (Cohen & Nicolelis 2004).

Together, this line of research began to paint a picture of an evolving association between population activity in the motor cortex and movement as a function of learning. The recent advent of two-photon calcium imaging, which greatly increased the number of simultaneously recorded neurons, has been instrumental in extending this notion. The first study to utilize this technique during motor learning examined activity of layer 2/3 neurons during learning of a licking task (Komiyama et al. 2010). Although focused in a different layer, this work replicated the finding of changes in the fractions of movement-related neurons and their activity timing across learning. Interestingly, this experiment also revealed that neurons with similar relationships to behavior become increasingly correlated with each other throughout learning, suggesting the potential emergence of correlated assemblies of neurons across learning.

Longitudinal Population Changes

A greatly expanded capacity for two-photon calcium imaging came in the form of genetically encoded calcium indicators, which for the first time allowed reliable, long-term recordings of neuronal populations. This provided a means for directly investigating changing relationships between motor cortex activity and movement during learning because the same cells could be

imaged consistently across days. The first application of this approach to motor learning again utilized a licking task and extended previous work by showing dynamic fractions of movement-related neurons and changing temporal activity patterns, but importantly, it did so for the same populations of layer 2/3 neurons across days (Huber et al. 2012). Longitudinal recording from the same neurons also afforded two important new results. First, cells could become correlated or decorrelated with behavior but did not switch between different aspects of behavior. For example, licking-related cells and whisking-related cells did not switch between the two categories, indicating some degree of fixed functionality. Second, the relationship between movement and activity on one day was directly compared with later days. This revealed that the translation from activity to movement was inconsistent from day to day but became more consistent specifically for licking after learning.

This changing relationship between activity and movement possibly represents a central aspect of motor learning, such that learning may involve the motor cortex reorganizing the manner in which it drives movements. This question was addressed in another study utilizing two-photon calcium imaging in layer 2/3 with genetically encoded calcium indicators, in which animals were trained in a lever task such that lever trajectory served as a proxy for movement across learning (Peters et al. 2014). Two dynamic aspects of the relationship between activity and movement were demonstrated by this approach. First, similar movements made in early and late days of learning were accompanied by different patterns of activity, suggesting the development of a novel association between activity and movement. Second, similar movements became associated with more consistent patterns of activity across learning, indicating that a less degenerate relationship between activity and movement developed within a population of neurons. These changes during learning suggest a possible process of exploration and consolidation of movement-related neural ensembles. A complementary finding was then made by imaging the promotor activation of the immediate early gene Arc in secondary motor cortex during the learning of a rotarod task. The Arc-expressing population expanded greatly on the first day of training and then consolidated with further training. Furthermore, the cells expressing more Arc early in learning were more likely to be Arc-expressing across all training sessions (Cao et al. 2015).

Lamina-Specific Activity Changes

Together, this collection of work indicates that synaptic changes during motor learning may alter the translation of motor cortex activity into movement. A notable difference between electrophysiological and calcium imaging studies, however, has been the focus on deeper layers in the former and superficial layers in the latter, primarily for technical reasons. Given the heterogeneous connectivity across laminae within the motor cortex, it may be expected that separate forms of plasticity are exhibited in different layers. A recent study began to address this possibility by comparing the activity of layer 2/3 and layer 5a during training in a lever pull task (Masamizu et al. 2014). Somewhat surprisingly, the authors found that equal numbers of layer 2/3 cells increased or decreased their information content about movement, resulting in no change in overall information in the superficial layers. Conversely, a disproportionate number of layer 5a neurons increased their information about movement, culminating in an increase of movement information in the deep layer. This study has provided initial clues that although the relationship between activity and movement may be flexible throughout the motor cortex, this may occur in separate ways in different parts of the circuit, hinting at a new level of organization for plasticity during motor learning.

The different forms of plasticity across layers could potentially be understood in light of the specialized roles played by unique cell types. For instance, the intracortically projecting cells of layer 2/3 are likely to serve different purposes than the corticofugal cells of layer 5, and they

may be expected to be altered by learning in characteristic ways. Corticospinal cells, which are synaptically closest to actual movement, are a particularly interesting target in this regard. Hypothetically, whereas the relationship between activity and movement is malleable in most of the motor cortex, the output targeting the spinal cord may remain a stable channel through which to direct movements. Tantalizingly, previous work was able to track activity across learning in a small number of corticospinal neurons and indeed suggested that corticospinal neurons may be less dynamic than corticostriatal neurons (Masamizu et al. 2014). In preliminary work directly investigating the flexibility of larger corticospinal populations across motor learning, it appears that the relationship between corticospinal activity and movement is in fact flexible, suggesting that functional plasticity is extended throughout the motor cortex (Peters et al. 2015).

FUTURE DIRECTIONS

Dexterity and Learning

A century after its discovery, the fundamental question remains as to what exactly the motor cortex does. However, recent research has begun to home in on important principles. In particular, it is becoming increasingly clear that the motor cortex has important functions in both movement control and motor learning, and these two functions can be dissociable. For example, learning can be prevented (Conner et al. 2005, Luft et al. 2004) or reversed (Hayashi-Takagi et al. 2015) by motor cortex manipulations without interfering with ongoing motor ability. Conversely, large-scale damage to the motor cortex, which presumably impairs dexterous movement (Castro 1972), can prevent learning while leaving previously learned nondexterous movements intact (Kawai et al. 2015). These results hint intriguingly that the motor cortex may play two parallel roles. First, it is essential in the production of dexterous movements independent from learning. Second, it directs certain types of motor learning without being the final producer of the learned movements. This may represent multiple components of motor cortex function, with the intersection of these abilities being to jointly learn and produce new dexterous movements. Intriguingly, the interdependence of these functions may increase through phylogeny given that motor cortex lesions impair movements to a correspondingly more substantial degree across species (Porter & Lemon 1993, Walker & Fulton 1938).

One interesting possibility is that these functions may have a degree of cell type or laminar specificity. Information about movement can change in different ways in different layers across learning (Masamizu et al. 2014). New evidence suggests that this may be manifested by layer 2/3 specializing in learned movements, whereas layer 5b corticospinal cells represent a more general system for directing movements (Peters et al. 2015), and layer 5a presumptive corticocortical and corticostriatal cells may fall between these two levels (Masamizu et al. 2014). Given the vertically descending transfer of information in the motor cortex (Weiler et al. 2008) and the hierarchical flow of information from corticostriatal to corticospinal cells (Anderson et al. 2010, Kiritani et al. 2012), separate pathways may be used for different aspects of motor cortex function. Corticospinal cells may be the ultimate drivers of cortex-driven movement, but they can be accessed either directly by frontal cortical areas for general dexterous movements or indirectly by first going through learning-sculpted circuitry within layer 2/3 (Hooks et al. 2013).

Interactions Between the Motor Cortex and Other Regions

Another important area of neuroscience that is becoming more methodologically accessible is the functional interplay between brain regions. The motor cortex certainly does not act in motor

control and learning on its own; it is part of an interdependent, distributed system (Doya 1999, Hikosaka et al. 2002, Houk & Wise 1995, Penhune & Steele 2012). Importantly, the motor cortex receives convergent information and sends divergent outputs to many other brain areas, placing it in a position to both integrate and widely distribute motor-related signals.

Regarding afferents, investigators are greatly interested in determining how, for example, inputs from the basal ganglia– and cerebellum-recipient zones of the thalamus are routed through the motor cortex, how the motor cortex uses those inputs to guide movement, and how those connections change with learning (Kaneko 2013). Likewise, the relationship between activity of the motor thalamus and movement and how it may change with learning are largely unknown (Goldberg et al. 2013, Sommer 2003). Another generally uncharacterized manner of control comes from frontal cortical areas, which have privileged, direct access to the deep layers of motor cortex (Hooks et al. 2013) and may be important for cognitive control of movement (Siniscalchi et al. 2016).

Regarding efferents, the interaction between the motor cortex and striatum appears to be strongly involved in learning (Koralek et al. 2012, 2013; Santos et al. 2015). It will be particularly interesting to determine what kinds of information are passed from the motor cortex to the striatum across learning and how this interacts with other descending pathways (Shepherd 2013). The relationship between the motor cortex and brainstem is also likely a crucial aspect of motor control and learning, and the importance of a specific brainstem nucleus in the production of skilled movements was recently demonstrated (Esposito et al. 2014). Furthermore, the connectivity between the motor cortex and spinal cord have also been shown to change following injury (Weidner et al. 2001) and likely during learning as well (Adkins et al. 2006, Nishimura et al. 2013). Finally, in addition to descending movement commands, the motor cortex also provides efference copies of movement throughout the brain to affect global processing. The efferent signals to other motor regions establish closed loops, and determining the function and plasticity of these loops will be a major landmark in understanding the motor system. Motor cortex efferents also target nonmotor regions, and these have recently been shown to affect processing in sensory areas during movement (Schneider et al. 2014). Techniques for large-scale and targeted recording of activity transmitted from one area to another (J.L. Chen et al. 2015) and across multiple areas simultaneously (Chen et al. 2016, Lecoq et al. 2014, Xie et al. 2016) will help elucidate functional interactions at a more holistic level.

Motor Control Across Species

Finally, one ultimate goal of neuroscience is to unveil specialized features related to ethological context within species while simultaneously finding unifying principles across species. Rodents have been instrumental in developing our current understanding of motor cortex function and plasticity; however, it is of great interest to determine the mechanisms underlying motor abilities that rodents do not possess, such as the superior dexterity of primates (Shmuelof & Krakauer 2011). Alternately, songbirds represent a remarkable example of well-studied nonmammalian skilled motor learning, although it is not known whether principles such as basal ganglia regulation of variability (Woolley et al. 2014), robust patterned activity driven by recurrent connectivity (Hamaguchi et al. 2016, Long et al. 2010), or modification of previously learned movement-related activity to generate new movements (Okubo et al. 2015) exist in mammals. Recent work demonstrating a shifting relationship between activity in a motor region and song production in birds has provided an especially intriguing opportunity for drawing complements to the mammalian motor cortex (Liberti et al. 2016). As more tools are opened up to more species, greater opportunities arise for a more comprehensive understanding of the motor cortex and mechanisms of motor control.

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