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Symposium

Learning and Control in Motor Cortex across Cell Types and Scales

Michael N. Economo,[1,2,3] **Takaki Komiyama,**[4,5,6]* **Yoshiyuki Kubota,**[7,8,9,10]* **and Jackie Schiller**[11]*

[1]Department of Biomedical Engineering, Boston University, Boston, Massachusetts 02215, [2]Center for Systems Neuroscience, Boston University, Boston, Massachusetts 02215, [3]Neurophotonics Center, Boston University, Boston, Massachusetts 02215 , [4]Department of Neurobiology, University of California San Diego, La Jolla, California 92093, [5]Center for Neural Circuits and Behavior, University of California San Diego, La Jolla, California 92093, [6]Department of Neurosciences, University of California San Diego, La Jolla, California 920937, [7]Section of Electron Microscopy, Supportive Center for Brain Research, National Institute for Physiological Sciences (NIPS), Okazaki 444-8787, Japan, [8]Department of Physiological Sciences, The Graduate University for Advanced Studies (SOKENDAI), Okazaki 444-8787, Japan, [9]Support Unit for Electron Microscopy Techniques, Research Resources Division, RIKEN Center for Brain Science, Wako 351-0198, Japan, [10]Department of Anatomy, Division of Histology and Cell Biology, Jichi Medical University, Shimotsuke 329-0498, Japan, and [11]Department of Physiology, Technion Medical School, Haifa 31096, Israel

The motor cortex is essential for controlling the flexible movements underlying complex behaviors. Behavioral flexibility involves the ability to integrate and refine new movements, thereby expanding an animal's repertoire. This review discusses recent strides in motor learning mechanisms across spatial and temporal scales, describing how neural networks are remodeled at the level of synapses, cell types, and circuits and across time as animals' learn new skills. It highlights how changes at each scale contribute to the evolving structure and function of neural circuits that accompanies the expansion and refinement of motor skills. We review new findings highlighted by advanced imaging techniques that have opened new vistas in optical physiology and neuroanatomy, revealing the complexity and adaptability of motor cortical circuits, crucial for learning and control. At the structural level, we explore the dynamic regulation of dendritic spines mediating corticocortical and thalamocortical inputs to the motor cortex. We delve into the role of perisynaptic astrocyte processes in maintaining synaptic stability during learning. We also examine the functional diversity among pyramidal neuron subtypes, their dendritic computations and unique contributions to single cell and network function. Further, we highlight how cortical activation is characterized by increased consistency and reduced strength as new movements are learned and how external inputs contribute to these changes. Finally, we consider the motor cortex's necessity as movements unfold over long time scales. These insights will continue to drive new research directions, enhancing our understanding of motor cortical circuit transformations that underpin behavioral changes expressed throughout an animal's life.

Introduction

All behavior is defined by movement. As a result, the control of flexible, dexterous, goal-directed movements is one of the most central functions of the nervous system. The motor cortex represents one of the most well-studied motor centers in the mammalian brain, and yet despite its widely appreciated importance, when and how the motor cortex contributes to movement remain hotly debated. A major reason why "What does the motor cortex do?" is such a difficult question to answer is that it is likely involved in many processes—for example, in selecting (Cisek, 2007; Sul et al., 2011), planning (Tanji and Evarts, 1976; Shenoy et al., 2013; Svoboda and Li, 2018), and initiating (Ebbesen and Brecht, 2017; Inagaki et al., 2022) movements, in generating the dynamic motor commands that control movement execution (Evarts, 1968; Georgopoulos et al., 1986; Shenoy et al., 2013; Kaufman et al., 2014), in the feedback control that ensures movements are accurately carried out (Scott, 2004, 2012), in assembling simple movements into complex sequences (Tanji, 2001; Lu and Ashe, 2005; Zimnik and Churchland, 2021; D. Xu et al., 2022), and in predicting and processing of action outcomes (Kapogiannis et al., 2008; Ramkumar et al., 2016; Schneider et al., 2018; Levy et al., 2020). Further complicating this question, the involvement of the motor cortex in each of these processes can vary considerably across species and behavioral contexts (Lopes et al., 2023).

In addition to these fast timescale processes is another central function of the motor cortex that takes place over much longer timescales—supporting motor learning. Motor learning relies upon the motor cortex in all mammals and endows animals with the capability to generate new movements in a fast and accurate manner to expand their behavioral repertoires, to flexibly

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*T.K., Y.K., and J.S. contributed equally to this work.

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Correspondence should be addressed to Michael N. Economo at mne@bu.edu or Jackie Schiller at jackie@technion.ac.il.

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associate movements with sensory stimuli, and to adapt movements in dynamic environments (Hikosaka et al., 2002; Makino et al., 2016; Lopes et al., 2023). At the mechanistic level, these processes are supported by profound changes to neural circuits across spatial scales—molecular, cellular, and circuit level—that profoundly alter the dynamic patterns of neuronal activation associated with movement (Sanes and Donoghue, 2000; Peters et al., 2017b). Because motor learning is such a key part of complex behavior, and because of the seemingly conserved role of the motor cortex in motor learning across mammals, understanding the molecular, cellular, and circuit mechanisms of motor learning has been an active area of research for decades. Importantly, exploring mechanisms of learning within the motor system allows the precise thing being learned—the expression of a movement—to be explicitly observed externally in real time while cellular- and circuit-level changes are tracked in tandem, providing an important opportunity to study mechanisms of plasticity, that may generalize to other brain regions.

These efforts have revealed many general principles that govern motor learning—and govern plasticity in neural circuits across the brain—and have revealed even more questions that will no doubt provide much fodder for future work. Here, we discuss recent advances in motor learning across cell types and spatial and temporal scales. We also describe the opportunities for new discovery motivated by these exciting advances.

Structural Plasticity at the Synapse Level

Dendritic spine plasticity is thought to be a key component of learning and memory at the structural level and involves the dynamic regulation of new spine formation, stabilization, and elimination. Motor learning is correlated with a significant increase in the formation of new spines on the apical tufts of Layer 5 pyramidal cells in the primary motor cortex (M1; T. Xu et al., 2009) indicating that spine plasticity during motor learning is necessary for motor skill acquisition. In this symposium, we will discuss new findings that reveal the presynaptic neuronal sources of synaptic inputs to new spines. In recent work, we showed that two presynaptic neural circuits supervise distinct programs of spine dynamics during the learning of a hand reach task (Sohn et al., 2022). Initially, spine dynamics in the primary motor cortex (M1) were imaged in tuft dendrites of Layer 5 pyramidal neurons during the learning process, followed by post hoc identification of the associated afferent presynaptic neurons. New spines that formed during learning initially received small synaptic contacts from corticocortical (CC) neurons, which were subsequently eliminated upon skill acquisition (Fig. 1). In contrast, spines receiving inputs from thalamocortical (TC) neurons were generated de novo, persisted, and were finally enlarged (Fig. 1). These results suggest that pyramidal cell dendrites in M1 exhibit a neural circuit-dependent division of labor during skill learning. This involves initial dynamic instructive contacts from top-down intracortical axons followed by synaptic memory formation driven by thalamic axons. This two-component process governing spine dynamics may play a crucial role in supporting diverse skill learning processes in the neocortex (Sohn et al., 2022).

At the level of synapse structure, we will also discuss new work examining the organization of perisynaptic astrocyte processes (PAPs) during the formation of new spines in motor learning. PAPs in excitatory tripartite synapses are crucial for glutamate clearance, synapse isolation, and ion homeostasis (Perea et al., 2009; Allen and Eroglu, 2017). We investigated the role of PAPs in synaptic dynamics during motor learning by analyzing PAP access to the synaptic cleft at each synapse and comparing this between newly formed and stable spines during a motor skill learning task. Serial sections of mouse M1 were collected using an automated tape-collecting ultramicrotome (ATUM) and imaged using a scanning electron microscope (Kubota et al., 2018). These serial micrographs were 3D-reconstructed to examine the spatial pattern of PAPs at newly formed and stable synapses. We developed a method to quantify the synapse-approaching pattern of PAPs, using fractional coverage volume, surface area, and mitochondria distribution. Our results revealed that the PAPs and astrocytic mitochondria were located more closely to synapses of stable than newly formed spines. The variation in the positions of PAPs and astrocytic mitochondria relative to the synaptic cleft, depending on the timing of synapse formation, maturity, and training period during motor skill learning, indicates that PAPs may actively control synaptic transmission. Together, these results demonstrate a rich set of structural changes involving presynaptic, postsynaptic, and astrocytic partners that act in concert to remodel neural circuits to support the acquisition of new motor skills.

Plasticity across Cell Types and Projection Pathways

The motor cortex is the major cortical output region of the motor system, conveying motor commands to the lower brainstem and spinal cord execution centers (Lemon, 2008). The motor cortex executes its functions via multiple pyramidal neuron types, which are divided into pyramidal tract (PT) neurons, which populate cortical layer 5b, and intratelencephalic (IT) neurons that contain subtypes spanning Laminae 2/3, 5, and 6. PT and IT neurons are broadly characterized by their unique dendritic morphologies, biophysical properties, and axonal projection patterns.

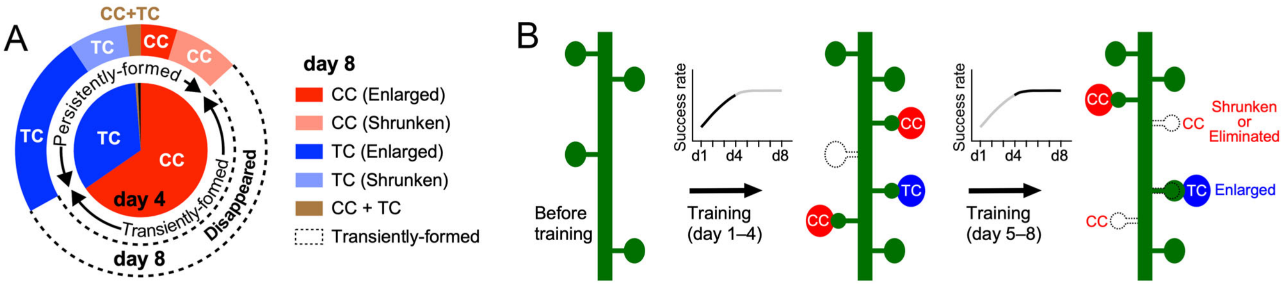

Figure 1. Elimination or shrinkage of new corticocortically-innervated (CC) spines versus sustained enlargement of new thalamocortically-innervated (TC) spines from Day 4 to Day 8. ***A***, The inner pie chart shows the proportion of inputs to new spines analyzed in the 4 d experiment. The outer pie chart represents the proportion of transiently and persistently formed spines in the 8 d training, and persistently formed spines are classified based on the presynaptic origin and spine enlargement/shrinkage between Day 4 and Day 8. ***B***, Schematic diagram of spine dynamics during motor learning. Adapted from Sohn et al. (2022).

Recent work using cutting-edge transcriptomic and imaging methods is starting to reveal an unprecedented degree of heterogeneity within each of these broad cell classes, dividing them each into multiple anatomical and molecular subtypes (Economo et al., 2018; Tasic et al., 2018; Winnubst et al., 2019; Muñoz-Castañeda et al., 2021; Yao et al., 2023).

Functionally, while many IT and PT neurons in the motor cortex show movement-related responses, recent work reveals differences in the extent and timing of their activity during movement preparation, execution, and postmovement phases and in their relationship to movement kinematics (direction, amplitude, velocity, etc.), sensory information, and outcome signals (Peters et al., 2017a; Economo et al., 2018; Levy et al., 2020; Currie et al., 2022; Park et al., 2022). How these distinct responses are generated and why they are expressed by different neuronal subtypes remains largely unknown. In this symposium, we will highlight the functional aspects of the Layer 2–3 IT and Layer 5 PT neuronal subtypes in motor learning and control.

While it is well accepted that the activity of Layer 5b PT neurons is closely related to movement (Evarts, 1968; Li et al., 2015; Peters et al., 2017a; Levy et al., 2020; Currie et al., 2022; Park et al., 2022), and that they can be divided into two classes according to their projection targets and their gene expression profiles (Fig. 2*A–C*; Tasic et al., 2016, 2018; Economo et al., 2018; Winnubst et al., 2019; Jiang et al., 2020; Muñoz-Castañeda et al., 2021; Moya et al., 2022), practically almost no information is available about the functional role of different PT subtypes in M1. A single study showed that in the anterolateral motor cortex (ALM), the thalamus-projecting PT neurons are involved in motor planning while the medulla-projecting PT neurons contain dynamics related to motor execution (Economo et al., 2018). We have recently added a dimension of cell typing of PT neurons based on their dendritic morphology and processing characteristics. We described two populations of PT neurons in M1 with morphologically distinct dendritic arbors and unique tuft integration patterns. Type 1 PT neurons are capable of sophisticated multicompartmental computation of behaviorally relevant information while the tuft of Type 2 neurons functions as a single global amplifying compartment (Fig. 2*D–F*; Otor et al., 2022). The dendritic morphologies and projection targets of Type 1 and 2 PT neurons are also distinct. Type 1 PT neurons have an early bifurcating apical tuft and a long nexus. Type 2 PT neurons have a late bifurcating apical tuft and shorter nexus (Otor et al., 2022). Our new unpublished data links Type 1 and 2 PT neurons to their projection targets. Almost all PT neurons that project to the medulla or spinal cord show Type 1 dendritic morphology, while almost all those projecting to the thalamus show Type 2 dendritic morphology. Thus, we are presenting a new facet of functional cell typing taking into consideration the structure–function dendritic subtypes of PT neurons. In this

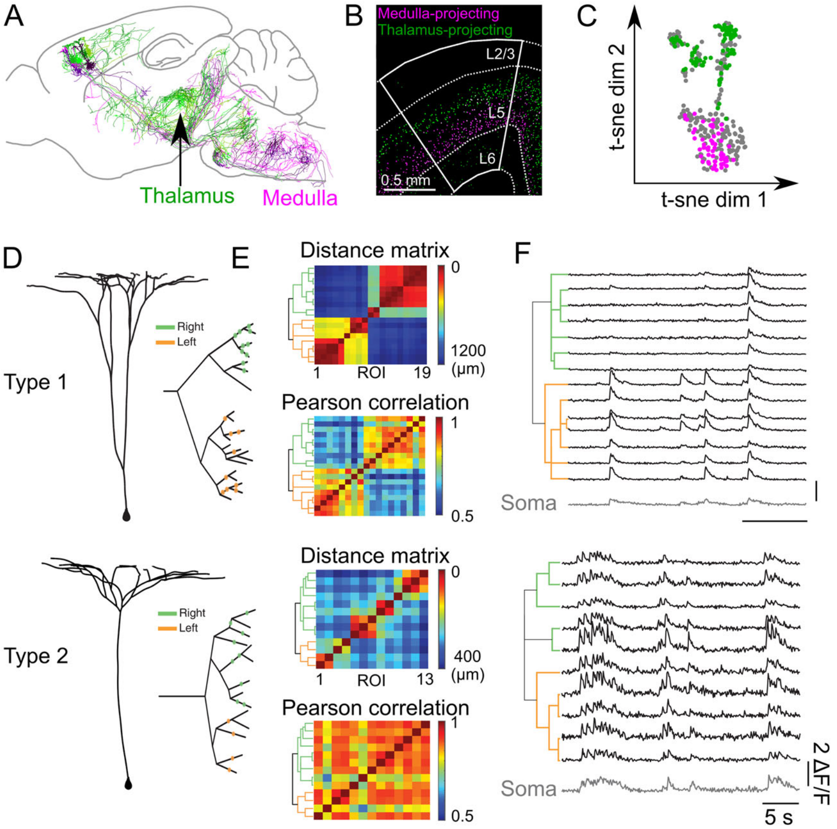

Figure 2. Cell-type and subcellular specificity in motor circuits. ***A***, The motor cortex contains two classes of pyramidal tract (PT) neurons. Single-neuron axonal reconstructions revealed that one class projects to the thalamus (green) while the other avoids the thalamus and projects to the medulla and spinal cord (magenta). ***B***, Thalamus-projecting PT neurons are located in the superficial half of cortical layer 5b, while medulla-projecting neurons populate the deep half of the layer. ***C***, Transcriptomic characterization of PT subtypes indicates that thalamus-projecting and medulla-projecting subtypes can be differentiated based on the genes that they express. ***D***, Type 1 PT neurons have apical dendrites that bifurcate in deep lamina, while Type 2 PT neurons have a single apical trunk that branches only superficial lamina. ***E***, Dendritic activation of Type 1 PT neurons may be branch-specific, with correlations in dendritic activation mirroring the distance between segments. In contrast, the dendrites of Type 2 PT neurons are globally activated. ***F***, Example calcium imaging time series from tuft dendrites and their corresponding soma illustrating branch-specific activation in Type 1 neurons and predominantly global activation of Type 2 PT dendrites. Adapted from Economo et al. (2018) (***A, B***) and Otor et al. (2022) (***D–F***).

symposium, we will discuss the possible correspondence between the Type 1 and Type 2 PT neurons of Otor et al. (2022) and the two PT populations reported by Economo et al. (2018).

Layer 2–3 neurons display activity related to motor parameters (Isomura et al., 2009; Hira et al., 2014; Peters et al., 2014; Omlor et al., 2019) but are also thought to perform "state and error estimation" (Hira et al., 2014; Heindorf et al., 2018). Indeed, in a previous study (Levy et al., 2020) we showed that a subset (~20%) of Layer 2–3 neurons report whether movements were successful in retrieving a reward ("success" and "failure" reporting neurons). In this symposium, we will present evidence from our latest study of the role of dopaminergic projections from the VTA to M1 in the development of Layer 2–3 outcome representations during learning of a hand reach motor task and in the transformation of the activity kinetics, the correlational configuration of functional connectivity, and average connectivity strength toward an expert configuration (Ghanayim et al., 2023). Furthermore, initially during learning, Layer 2–3 neurons largely encode sensory information, but with learning, the representation transforms; the relative contribution of outcome and motor components gradually increases, and the sensory component decreases (Ghanayim et al., 2023). These new findings related to the remodeling of outcome-related dynamics add a new dimension to our understanding of how the activity of motor cortical neurons changes over the course of learning in a cell-type–specific manner.

Reorganization of Motor Cortical Dynamics during Learning

It is now well established that motor learning induces a reorganization of neural activity within M1 (Peters et al., 2014, 2017a) and across cortical areas (Makino et al., 2017) that mirrors the time course of structural remodeling. In M1, initial learning of a new motor skill is associated with strong activation of large ensembles of neurons with a high degree of trial-to-trial variability. As animals practice motor skills over the course of days and weeks, the motor cortical activation associated with the same movement becomes weaker, with fewer cells activated less strongly, but in a more consistent manner across trials (Fig. 3; Costa et al., 2004; Kargo and Nitz, 2004; Komiyama et al., 2010; Peters et al., 2014).

Mirroring changes in neural dynamics, the kinematics of newly learned movements also become less variable with practice, which is a hallmark of motor learning. Does the relationship between neural activity and movement kinematics then remain invariant? Close examination of both motor cortical dynamics and movement kinematics suggests that this is not the case. The neural dynamics associated with movements become more sparse and less variable, even when comparing movements early and late in learning that are kinematically indistinguishable (Peters et al., 2014). Thus, the decrease in across-trial variability that accompanies learning may relate to an algorithmic strategy for learning new movements, rather than simply reflecting kinematic changes in movements. In this conceptual model, an initial increase in neuronal variability might allow animals to test variations of a particular movement. A particularly effective variant of the movement may then be selected and reinforced to further hone the consistency of its neural representation as well as its expression. The same might be said about neural representations—there is likely considerable degeneracy between M1 activity and movement kinematics such that multiple M1 activity patterns can drive the same movement. Of multiple activity patterns that can drive the learned movement, one is selected and reinforced to become the "engram" of the learned movement—the neural ensemble whose activation is causally related to its expression.

Research has begun to unravel some of the myriad circuit-level mechanisms that support the changes in neural dynamics that accompany motor learning. Mounting evidence suggests that local inhibitory interneurons gate changes in synaptic plasticity. A reduction of dendrite-targeting inhibitory input occurs early in learning, permitting the formation of spines (Chen et al., 2015), which are clustered spatially to facilitate the cooperative activation of postsynaptic neurons (Fu et al., 2012; Hedrick et al., 2022, 2024). This process likely evolves under the control of extrinsic neuromodulators. Disruption of neuromodulatory inputs to the motor cortex, such as acetylcholine (Conner et al., 2003, 2005) and dopamine (Molina-Luna et al.,

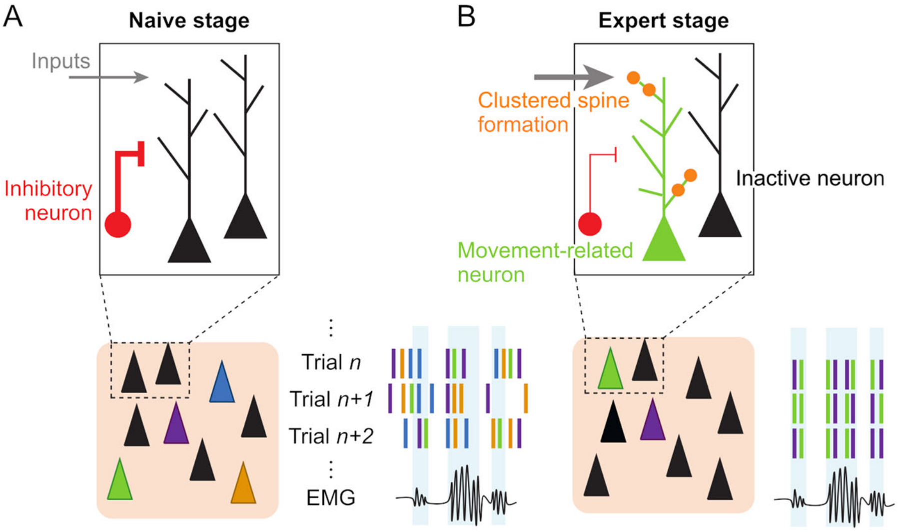

Figure 3. Evolution of motor cortical dynamics during motor learning mediated by structural remodeling. ***A***, Early stages of motor learning are characterized by strong activation of large neural ensembles during movement, with a high degree of trial-to-trial variability (black triangles, inactive neurons; colored triangles, active neurons). ***B***, The formation of new spines that are clustered spatially (orange) on movement-related neurons (green) is thought to be mediated by a downregulation of dendrite-targeted inhibition (red). These changes lead to more consistent activation of sparser neural ensembles when learned movements are executed.

2009), profoundly impair motor learning. Acetylcholine interacts with specific subtypes of inhibitory neurons in M1 to coordinate dendritic disinhibition during early phases of learning (Ren et al., 2022). Adding further complexity, structural and dynamical changes in cortical circuits associated with motor learning likely occur in a cell-type–specific manner. Layer 2/3 pyramidal neurons display shifting dynamics with respect to movement over time (Peters et al., 2014). The PT neurons that convey motor commands to low-level motor circuits in the brainstem and spinal cord relate to movement in a less mutable manner (Peters et al., 2017a). Together, this dynamic reorganization generates a neural circuit that is dedicated to producing reproducible spatiotemporal neural activity that reliably drives the learned movement (Peters et al., 2017b).

How is this learned circuit organized? One likely possibility is that this involves a precise interaction between external inputs from upstream regions and local circuits within M1. For example, the local M1 network might reorganize to generate a dynamical system that reliably generates reproducible transient dynamics in response to external inputs. For example, inputs from the motor thalamus nuclei are considered to be critical for motor cortex dynamics in mice (Sauerbrei et al., 2019) and songbirds (Moll et al., 2023). There are a few predictions that emerge from this model. First, during motor learning, external inputs may “learn” to activate a group of M1 neurons that act as “starter cells” to initiate the learned dynamics within M1. Second, activation of these starter cells may trigger a cascade of activation that reliably generates the learned activity pattern. These predictions will be explored in a presentation during the symposium.

Dynamic Engagement of Motor Cortex across Learning

In addition to structural plasticity within the motor cortex (Yu and Zuo, 2011) and the commensurate change in neural dynamics that they engender (Peters et al., 2017b), the degree to which the motor cortex is involved in the control of movement is, in itself, plastic. It is long been thought that separate neural circuits support flexible movements and those that are highly practiced or “habitual” (Yin and Knowlton, 2006; Makino et al., 2016). For example, the dorsomedial striatum is thought to mediate the generation of flexible actions designed to maximize the value of outcomes given a particular environmental context (Yin and Knowlton, 2006). In contrast, the dorsolateral striatum is more closely related to habitual movements (Joel and Weiner, 2000; Yin and Knowlton, 2006). However, before habitual movements have become habitual, they must first take the form of flexible movements, which become habitual through a learning process that accompanies repetitive practice. This observation implies a learning-related switch in the striatal circuitry supporting the same movement that follows from repetitive practice.

In a similar manner, there is a great deal of evidence suggesting an analogous switch in the necessity of the motor cortex that follows from learning and practice in rodents (Lopes et al., 2023). For example, in an interval timing task in which rats learn to produce idiosyncratic movement sequences, motor cortical lesions selectively impair animals’ ability to learn appropriate sequences but do not impair their ability to execute the same movements once they have been learned and practiced (Kawai et al., 2015). A similar result was observed in mice trained on a joystick pressing task; only after repetitive practice was the execution of these movements found to be insensitive to transient optogenetic inactivation of the motor cortex (Hwang et al., 2019).

Importantly, in both studies, movements become insensitive to motor cortex perturbation not just only after movements were learned but also after a long period of practice—typically after animals had performed tens of thousands of repetitions of the movement over the course of 1 or more months. At earlier points in training, after animals had learned to perform correct movements, but before this extensive period of overtraining, optogenetic perturbation partially impaired movement execution (Hwang et al., 2019). Together, these observations suggest that the necessity of the motor cortex in controlling movements wanes slowly over a timescale of weeks to months. Hwang et al. observed that movements were associated with strong motor cortical activation with a high degree of trial-to-trial variability early in learning, which quickly gave way to weaker, more consistent dynamics following skill acquisition (Fig. 4*A*), as has been observed in other studies (Peters et al., 2014, 2017b; Hwang et al., 2019). Interestingly, in the late stages of training, as movements became insensitive to motor cortex perturbation, a second shift in cortical dynamics was observed—again to more variable patterns of activation (Hwang et al., 2019). When animals were trained to perform two motor actions, the less variable of the two movements was found to be both less sensitive to cortical perturbation and to be associated with weaker, more variable cortical activation—perhaps a neural signature of the control of movement shifting from the motor cortex to other subcortical motor centers (Fig. 4*B*).

While these studies clearly demonstrate that the involvement of the motor cortex in generating highly practiced movements

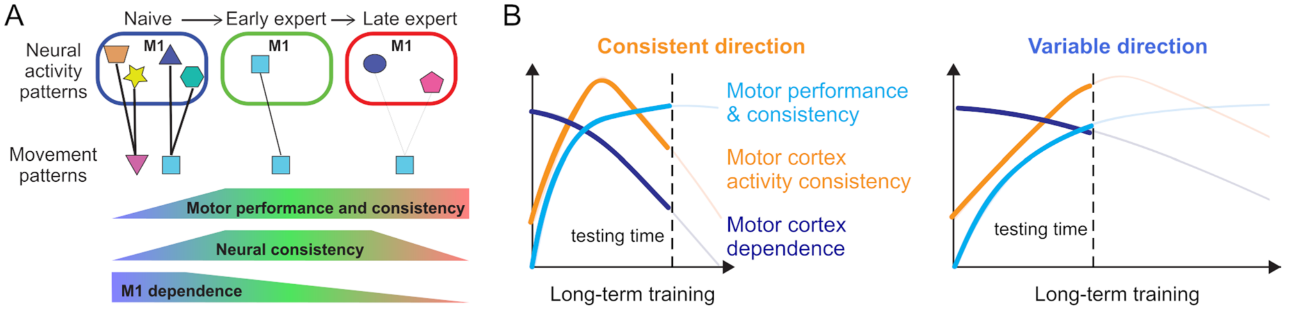

Figure 4. Long timescale shifts in the engagement of the motor cortex in learned movements. ***A***, Schematic diagram illustrating the relationship between neural activity in the motor cortex, the necessity of the motor cortex, and the expression of movement during stages of motor learning. ***B***, When animals learn two movements simultaneously, the more consistent movement is less cortically dependent and associated with more neural variability in the late stages of learning compared with the more variable movement. This suggests a similar relationship between motor performance, cortical dependence, and cortical dynamics for both movements but different rates of progression through the stages of learning.

evolves over long time scales, when and why the motor cortex is engaged in the control of movement remain a complex topic (Lopes et al., 2023). Highly dexterous movements appear to remain cortically dependent, even after long periods of training (Guo et al., 2015; Lopes et al., 2023). Further, mounting evidence suggests that subtle details of behavioral tasks can have a profound impact on the neural circuits supporting movements. The same movement might engage the motor cortex when its execution is linked to an external cue, but not when it is performed in a spontaneous, self-initiated manner (Mizes et al., 2023a). Further, movements that do not require the motor cortex for their execution per se might become cortically dependent when trained alongside movements that do (Mizes et al., 2023b).

In addition to slow changes in the cortical involvement in movements over days, weeks, and months, cortical circuits may also be engaged and disengaged in the control of movement on fast timescales, waxing and waning on a moment-to-moment basis according to behavioral demands. For example, locomotion appears to selectively engage motor cortical control when animals encounter obstacles (Drew et al., 2002). Building upon these observations, this symposium will also discuss how animals learn to engage the motor cortex dynamically on sub-second timescales based on their expectation of and uncertainty of future events.

Concluding Remarks

This review underscores the critical role of the motor cortex in both the control of movement and the processes of motor learning. By integrating a disparate set of recent findings, we have highlighted the reorganization that takes place in neural circuits during motor learning—both structurally and in terms of the neural dynamics observed to accompany movement. We touch on recent results examining changes in input and output pathways of the motor cortex and new insights into a critical role for astrocytes in spine formation and stabilization and explore differential effects of plasticity across the heterogeneous cell types that compose cortical circuits. The adaptive reorganization of motor cortical dynamics results in more consistent and efficient neural activity patterns as movements are refined, a circuit-level reflection of the sophisticated plasticity mechanisms that endow the motor cortex with the ability to support an ever-changing and expanding set of motor actions. Moving forward, it will be essential to further embrace the complexity inherent to the mechanisms of motor learning—examining how changes from the molecular to circuit level facilitate motor learning.

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