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Towards Cell and Subtype Resolved Functional Organization: Mouse as a Model for the Cortical Control of Movement

Claire L. Warriner, [a†] **Samaher K. Fageiry,** [a†] **Lina M. Carmona** [a] **and Andrew Miri** [b*]

[a] *Department of Neuroscience, The Mortimer B. Zuckerman Mind, Brain, and Behavior Institute, Columbia University, New York, NY 10027, USA*

[b] *Department of Neurobiology, Northwestern University, Evanston, IL 60201, USA*

Abstract—Despite a long history of interrogation, the functional organization of motor cortex remains obscure. A major barrier has been the inability to measure and perturb activity with sufficient resolution to reveal clear functional elements within motor cortex and its associated circuits. Increasingly, the mouse has been employed as a model to facilitate application of contemporary approaches with the potential to surmount this barrier. In this brief essay, we consider these approaches and their use in the context of studies aimed at resolving the logic of motor cortical operation.

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Key words: motor control, motor cortex, cell types, corticospinal, behavioral paradigm, motor learning.

INTRODUCTION

That movement may be governed by specialized cortical regions has long been appreciated (Ferrier and Yeo, 1884; Horsley and Schafer, 1888), but how these motor cortical regions are organized to perform this role remains unresolved. Early stimulation studies that culminated in Penfield's mapping in neurosurgical patients revealed a rough somatotopy (Penfield and Boldrey, 1937), suggesting the existence of an array of descending channels that could be engaged to move particular body parts. Later attempts using more controlled stimulation and spike-triggered averaging of muscle recordings revealed a fundamental complexity, whereby the activity of individual cells is linked to direct responses in multiple muscles across multiple limb joints (Cheney and Fetz, 1985; Kalaska, 2009). The relevance of classical motor cortical somatotopy has been challenged by more recent results with longer stimulation trains that drive ethologically relevant movement components (Graziano et al., 2002; Harrison et al., 2012; Brown and Teskey, 2014). Moreover, the predominance of oligosynaptic control of muscle activity by motor cortical output has been countered by the observation of a relatively long lag between activity in cortical neurons and muscles, even for corticospinal neurons synapsing directly onto spinal motor neurons (Schieber and Rivlis, 2007).

These results highlight a fundamental ambiguity: we lack a clear view of the basic functional elements that underlie the cortical control of movement. Identifying such elements can rapidly catalyze mechanistic insight, as has been demonstrated by the discovery of subatomic particles in physics or of DNA structure in genetics. An emerging view posits that neuronal subtypes defined by features like axonal target region, target cell identity, and gene expression may reflect functional elements in neural systems (Zeng and Sanes, 2017; Arber and Costa, 2018). However, a primary barrier to testing this view and resolving functional elements within motor cortical circuits has been our inability to measure and perturb activity specifically in neuronal subtypes defined by features of cell identity that may differentiate their function.

Recognition of this barrier has led to increasing use of the mouse as a model organism for probing cortical movement control. The general power of the mouse lies in relating the organization of neural systems to their function at a fine scale where relevant mechanisms may operate and thus where relevant functional elements may lie. The comparative ease in mice of optically recording neural activity with calcium indicators, during both head-fixed (Dombeck et al., 2007, 2009) and free-behaving (Ghosh et al., 2011; Cai et al., 2016) tasks, enables experimentalists to measure neural activity in genetically-defined neuronal subpopulations at cellular resolution. The comparative ease of subcortical recording permits activity measurements from important cortical targets that historically have been harder to access. The comparative ease of optogenetic manipulations enables activity perturbation of brain areas (Arenkiel et al., 2007), neuronal subpopulations (Adamantidis et al.,

*Corresponding author.
E-mail address: andrewmiri@northwestern.edu (A. Miri).
[†] These authors contributed equally.

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2007), and single neurons (Rickgauer et al., 2014; Chen et al., 2018) on the fast timescale over which neurons communicate and movement unfolds. Efficient methods now exist for driving genetic probe expression in long-range projection neurons like corticospinals (Tervo et al., 2016) or in subsets thereof that synapse onto specific neuron types (Wickersham et al., 2007b; Kim et al., 2016; Reardon et al., 2016). In addition, single cell sequencing has now identified many new genetically distinct classes of cortical neurons (Economo et al., 2018; Tasic et al., 2018), greatly facilitating the search for distinct functional elements within neuronal populations. The precision of molecular manipulation and advances in physiological methods together create a broad range of opportunities for identifying functionally distinct cell types at a new level of granularity.

Historically, motor system studies have been carried out in mammals much larger than the humble *Mus musculus* that are anatomically and behaviorally divergent. The benefits of working with primates are clear: their anatomy and physiology are closer to that of humans, they are able to perform highly dexterous movements, and they have the cognitive capacity to master complicated tasks. However, their size, long gestational cycles, and human-like traits reduce experimental throughput and render interventional approaches costly and ethically challenging. As the mouse gains prominence as a motor system model, potential value emerges in coordinating approaches across model organisms, in comparative inquiry, and in identifying opportunities for generalizable findings from mice. In this review, we explore the study of motor cortical functional organization in the mouse. We consider a range of technical approaches that can identify manifestations of functional organization in neural circuit architecture and activity. These approaches include circuit tracing, activity measurement and perturbation, and studies across motor learning. Our goal is to help clarify the specific contribution the mouse can make to questions of general relevance.

COMPARATIVE STUDIES OF CORTICOSPINAL ORGANIZATION

Despite appreciable homology in motor system organization between rodents and primates, certain distinctions may prove functionally significant. All placental mammals have a cortical motor area rostral to somatosensory cortex, but in primates a larger portion of this region is dedicated to hand and digit control (Preuss et al., 1997; Kaas, 2012). Evidence of functional distinction and anatomical hierarchy between premotor and primary motor cortices in rodents remains limited, though recent observations (Kimura et al., 2017; Saiki et al., 2017; Yoshida et al., 2018; Fulcher et al., 2019) suggest rodent motor cortices may have something of a primate-like hierarchy. Relative to that of primates, mouse motor cortex appears more heavily interconnected with primary and secondary somatosensory cortices, and less connected with parietal and prefrontal association areas (Oh et al., 2014; Mohammed and Jain, 2016). Recent studies in rodents have shown that prolonged (hundreds of milliseconds) stimulation in different motor cortical regions evokes different classes of movements, reminiscent of previous findings in monkeys, although the diversity of movement types evoked in rodents is more limited (Harrison et al., 2012; Brown and Teskey, 2014). The relatively small scale of the mouse motor cortex (10^6 neurons, 10^4 corticospinal neurons) enables a comprehensiveness of assessment not readily achievable in larger mammals, but this scale may have constrained functional organization and motor behavioral strategies in divergent ways across evolution (Krubitzer and Seelke, 2012).

This diversity across species presents an opportunity to explore how evolutionary divergence translates into functional differences. The value of comparative approaches in the study of motor control is thus far best exemplified by considering the anatomy of the corticospinal pathway. The seminal work of Lawrence and Kuypers over 50years ago first clearly implicated this pathway as crucial for both the agility of mammalian limb movements, and the fractionation of limb joint control (Lawrence and Kuypers, 1968). Unlike spinal motor neurons whose organization is stereotyped and highly conserved across mammalian species (Jessell et al., 2011), it has long been appreciated that corticospinal neurons exhibit striking heterogeneity across mammals in the organization of their projections to the spinal cord. Kuypers spotlighted the importance of these spinal terminations, writing that:

> *'When considering the connections of the descending pathways…, it should be realized that their motor capacities are not so much determined by the location of their cells of origin…as by…the motor capacities of the interneurons and motoneurons on which these pathways terminate'* (excerpt from pg 83 Porter and Lemon, 1995, originally from Kuypers, 1973).

Kuypers observed a substantial variation in the rostrocaudal organization of corticospinal projections across species. For example, in marsupials (e.g. kangaroos), ungulates (e.g. goats), and rabbits the corticospinal tract terminates at cervical/thoracic levels and therefore does not play a direct role in lower limb control (Kuypers, 1981). This raises questions about whether descending projections from cortex play distinct roles at different segmental levels of the spinal cord. Here the mouse presents a useful model for identifying and selectively accessing caudally projecting neurons in order to address their impact on motor output.

In cats, dogs, rodents, and a subset of New World monkeys (e.g. marmosets), corticospinal projections extend into the lumbar cord but are excluded from the ventral-most region of the spinal gray matter. This is the region where motor neuron cell bodies lie, suggesting that motor output is indirectly influenced via spinal interneurons in these species. This is in contrast to the organization of projections in most primates where axons extend into the ventral gray matter of the spinal cord (Kuypers, 1981) thereby permitting corticospinal neurons to exert a direct excitatory influence on spinal motor neurons (Lemon and Griffiths, 2005). These con-

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nections are strongest onto motor neurons innervating distal hand muscles (Fritz et al., 1985) and emanate principally from primary motor cortex (Rathelot and Strick, 2006), suggesting the emergence of an evolutionarily newer mode of control within the motor cortex of most primates (Levine et al., 2012).

This raises the question: what is the functional impact of this direct access to spinal motor neurons? Comparative studies have demonstrated that the more dexterous a species is, the more anatomically developed its cortico-motoneuronal connections are (Bortoff and Strick, 1993). Although cortico-motoneuronal connections are best developed in primates, mice have proven to be an effective model for assessing their role in behavior and examining the molecular mechanisms by which they form. A recent study by Gu et al., implicated Sema6D-PlexA1 signaling in mediating the selective elimination of direct contacts onto motor neurons by corticospinal axons (Gu et al., 2017). In keeping with this, they showed that motor cortical expression of *PlexA1* is strong in wild type mice, where such connections are largely eliminated, but weak in humans where direct synapses are preserved. *PlexA1* mutant mice retain cortico-motoneuronal connectivity into adulthood and perform significantly better on tasks requiring dexterous manipulation. Collectively, these findings support the hypothesis that cortico-motoneuronal connections are particularly involved in the selective and independent movement of the digits, which underlies hand dexterity (Lemon and Griffiths, 2005).

CELL AND SUBTYPE RESOLVED CONNECTIVITY MAPPING

In the late 1800s, Ramon y Cajal meticulously reconstructed the morphology of neuronal cells in Golgi impregnated brain tissue. Despite the vagaries of this technique, he made several prescient observations about the nature of connectivity between neuronal populations (Zergeroğlu and Nalçacı, 2015). Since that era, neural tracing techniques have advanced significantly, often leveraging advances in genetics, virology, and imaging to visualize neural circuits and probe their functional significance. These techniques have enabled finer aspects of neural system organization to be charted, such as those dependent on the distinct identities of neuronal subtypes and the synaptic connectivity between them. In addition, large-scale RNA sequencing efforts are now uncovering an unprecedented diversity in cortical cell types; in two cortical regions alone over 100 transcriptionally distinct neuronal populations have been identified (Tasic et al., 2018). Arguably in no mammalian species have these emerging anatomical tools been more utilized than in the mouse.

The introduction of conventional tracers taken up by intact neurons represented a significant advance in neuroanatomical mapping that enabled observation of the input and output of a region of interest. Retrograde tracers such as Cholera toxin subunit B and Fluorogold enter neurons via receptor mediated uptake or vesicular endocytosis and are then transported to the cell body. Conversely, anterograde tracers such as biotinylated dextran amine are taken up by somata and dendrites and subsequently transported along the axon (Lanciego and Wouterlood, 2011). In motor circuits these tools have been widely adopted to map anatomical organization (VanderHorst and Ulfhake, 2006; Betley et al., 2009; Liang et al., 2011).

However, a significant drawback of conventional tracers is that bulk uptake from the injection site cannot allow for selective tracer entry into specific cell types that are spatially intermingled with other types. In the mouse, this was made possible by the emergence of genetic access to discrete cell types marked by the expression of a specific gene. Over the last 15years, elucidation of cell types in rodent cortex has progressed rapidly (Arlotta et al., 2005; Kepecs and Fishell, 2014; Tasic et al., 2016) and alongside this there have been several adaptations in neurotropic viruses that allow for delivery of genes into neuronal cells. One of the most widely used viruses for *in vivo* gene delivery are adeno-associated viruses (AAVs), largely because they mediate perduring gene expression, rarely integrate into the host genome, and exhibit no detectable pathogenicity following infection (Penaud-Budloo et al., 2008; Hammond et al., 2017).

The mapping of inputs and outputs has also been significantly facilitated by the development of a toolkit of trans-synaptic neuronal viruses. As the name suggests, these viruses have the ability to spread between synaptically coupled neurons, revealing connectivity with cell and subtype resolution. One of the most efficacious of these has been rabies, a retrograde trans-synaptic virus. Two modifications have adapted rabies for the study of neural circuitry. First, the glycoprotein (G) gene, which is critical for viral trans-synaptic spread, was deleted and is expressed only in those cells whose inputs are to be traced (Wickersham et al., 2007a,b). Second, the initial rabies infection is targeted to the cell type of interest by pseudotyping the virus with the envelope protein EnvA, which renders it unable to infect mammalian cells unless they express the cognate avian receptor TVA (Young et al., 1993; Bates et al., 1998). As with the expression of the glycoprotein, TVA expression can also be restricted to the cell type of interest.

One of the earliest applications of rabies retrograde tracing, absent these genetic modifications, was in the monkey, where it revealed surprising overlap in the motor cortical regions targeting muscles that act at different limb joints (Rathelot and Strick, 2009) and the presence of direct interactions between cerebellum and basal ganglia (Hoshi et al., 2005; Bostan et al., 2010). More recently, rabies modified as above has been used in the mouse spinal cord to map the organization of interneuron inputs to flexor and extensor motor neurons (Tripodi et al., 2011). This study revealed differences in the settling positions of premotor interneuron inputs to antagonistic muscles of the hindlimb, suggesting that they are differentially recruited by local spinal circuits. Indeed, these differences extended to the nature of the descending inputs they receive, with extensor motor neurons

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being preferentially targeted by vestibulospinal neurons (Basaldella et al., 2015).

These advances in trans-synaptic tracing have enabled experimenters to reconstruct synaptic inputs and draw conclusions that previously could only be made with electrophysiological recordings and electron microscopy, neither of which are amenable to brain-wide mapping. Combining rabies trans-synaptic technology with genetic tools in mice (e.g. the Cre/lox system for conditional gene expression) permits visualization of both the local and long-range inputs to defined neuronal cell types. In our recent work we have used this approach to demonstrate differences in the anatomical organization of corticospinal neurons that engage different target populations in the spinal cord (Fageiry et al., in preparation).

Looking to the future, there is scope to further extend the utility of these tools. For example, the lethality of rabies remains a significant limitation to its long-term use in physiological experiments. Continuing efforts to further diminish the pathogenicity of rabies (Reardon et al., 2016; Ciabatti et al., 2017) give hope for the use of this technique to deliver gene products that enable the observation and manipulation of neural activity in specific populations of presynaptic input neurons. This will enable exploration of how different neuronal subtypes inform the function of downstream populations.

THE DEVELOPMENT OF MOTOR BEHAVIORAL ASSAYS FOR CORTICAL INTERROGATION

As a new model for cortical control, appropriate behavioral paradigms in mice are still somewhat limited in number but growing quickly. Existing paradigms for use in mice differ from those typically used in primates in three primary ways. First, primate motor behavioral paradigms often involve complex behavioral sequences that separate different phases of motor behavior, like planning, initiation, execution, and sensory-guided modification, to distinct epochs so they can be separately examined. Second, primate paradigms often elicit performance of many limb movement variants, a task richness facilitated by the flexibility of primate limb movement and the ability of primates to generalize task rules (Churchland et al., 2012). This feature is particularly advantageous, as many imaginable characterizations of motor system function would benefit from observing recorded populations in a broad range of neural activity states. Yet many mouse behavioral paradigms do not emphasize the diversity of movement types needed to generate commensurate diversity in neural activity. Lastly, consistent with their lack of direct cortical projections to motor neurons, the behaviors that mice can perform exclude the most dexterous movements or tool-use seen in primates, but do include some skillful manipulation using the digits.

Inspired by previous approaches in primates, there has been recent development of behavioral paradigms in which mice perform cortically-dependent single forelimb tasks while head-fixed, facilitating stable activity recording and stereotyped behavioral trials. In one such paradigm, mice reach toward and grasp food pellets (Fig. 1A; Guo et al., 2015). In another, a vibrotactile stimulus applied to the forepaw prompts the mouse to reach towards and touch a sensor (Estebanez et al., 2017). In an elegant reprise of a classic human task, mice have also been trained to adapt to force-field perturbations while manipulating a joystick, which was found to involve sensorimotor cortex (Fig. 1B; Mathis et al., 2017). In another paradigm, a mouse learns to reach toward and grasp a water droplet, then bring the droplet to its mouth, a task which appears relatively easy to train and permits a large number of daily trials (Fig. 1C; Galiñanes et al., 2018).

Paradigms in which mice move freely allow for the expression of more ethologically relevant behavior, for which the motor system is more likely to be adapted. In one such paradigm, a mouse reaches through a narrow opening to retrieve a food pellet (Azim et al., 2014; Fink et al., 2014; Wang et al., 2017). The dexterous paw manipulations during feeding behavior are elicited in paradigms focused on pasta (Whishaw et al., 2017) and seed eating (Barrett et al., 2020). Free-moving paradigms also facilitate home cage training, which increases the number of behavioral trials. This was exploited recently for training a joystick-based center-out reach task (Bollu et al., 2019b). The continued development of methodology for neural recording in freely behaving rodents, including wireless electrophysiological recording (Gutruf and Rogers, 2018) and head-mounted microscopes (Ziv et al., 2013; Cai et al., 2016) has expanded the range of behavioral contexts amenable to physiological study.

The advent of electromyographic (EMG) recording methods for mice has improved capacity for measuring motor output as mice behave. EMG electrodes for chronic recording have been adapted and miniaturized from those used previously in larger mammals (Pearson et al., 2005; Akay et al., 2006). The use of EMG recording is essential to studies involving isometric tasks or detection of direct effects of neural perturbations on muscle activity (Miri et al., 2017; Murray et al., 2018). EMG recordings can also be used in closed-loop fashion to determine reward and guide behavioral training, a feature exploited to train mice to simultaneously contract two forelimb muscles in our recent work on voluntary cocontraction (Warriner et al., in preparation).

Realizing many of the experimental opportunities in mice will require continued development of task paradigms. Though field expertise in mouse training remains in its infancy, ultimately it may prove challenging to achieve the movement diversity seen in primate paradigms. Moreover, the behavioral repertoire of mice reflects different evolutionary pressures and mice interact with the world via movement differently from primates. These are differences that must be negotiated when using mice to discover general principles of motor system function. Fortunately, new methods are emerging for wireless recording, markerless behavior tracking (Mathis et al., 2017), and achieving statistical power for hypothesis testing in behavioral paradigms lacking an explicit trial structure (Sarup et al., 2019). This is creating new opportunities

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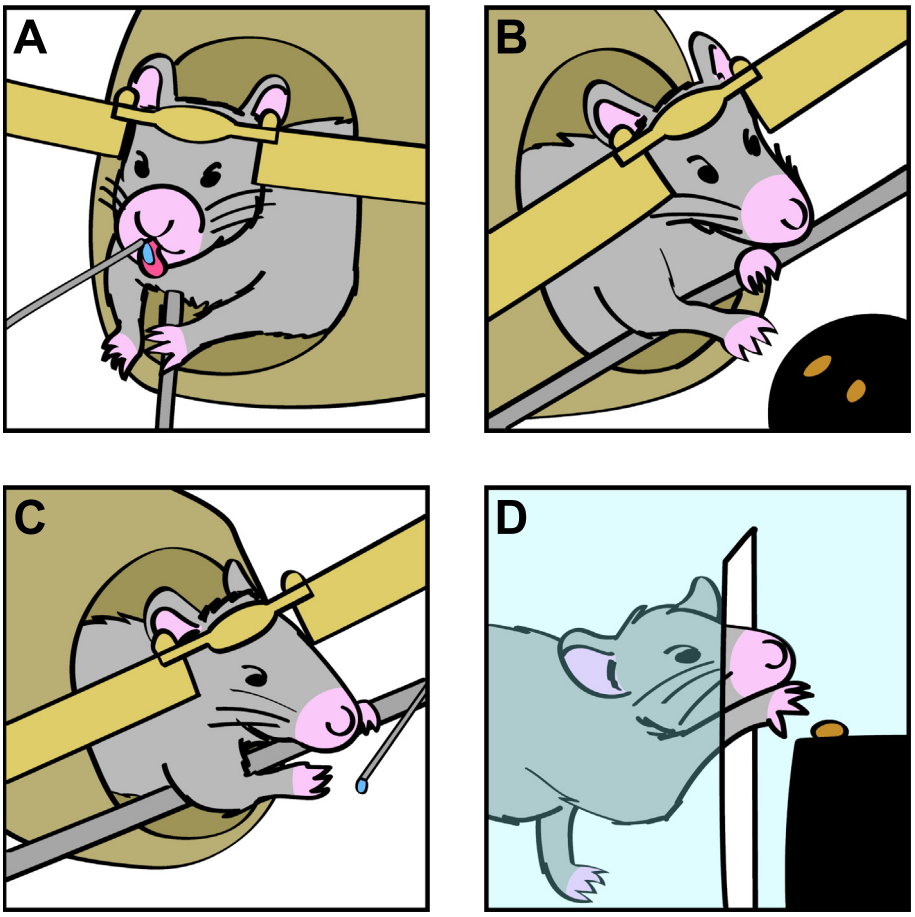

Fig. 1. Illustrations of recently developed forelimb movement paradigms for mice. **(A)** A head-fixed mouse reaches to grasp and retrieve a food pellet on a conveyor. **(B)** A head-fixed mouse moves a joystick to a reward position, potentially in the presence of a force field acting on the joystick. **(C)** A head-fixed mouse reaches to retrieve a water droplet from a spout. **(D)** A freely behaving mouse reaches to grasp and retrieve a food pellet through a narrow slot.

for physiological interrogation during diverse and ethologically relevant behaviors.

PERTURBATIVE INTERROGATION OF CORTICAL CIRCUITS

Genetic access in mouse motor circuits facilitates optogenetic perturbation, which has substantial potential for probing the function of neuronal subpopulations and informing neural system models. The building and testing of models of motor system operation benefits from the ability to probe direct interactions between neuronal populations on the fast timescale that neurons communicate (1–10ms). Reagents for optogenetic perturbation continue to progress (Kim et al., 2017), and the spatial resolution of their application continues to improve. Fast timescale perturbations can be targeted to brain areas (Arenkiel et al., 2007), subpopulations within areas (Adamantidis et al., 2007), and now to individual neurons (Rickgauer et al., 2014; Chen et al., 2018). The ability to rapidly inhibit endogenous neural activity through optogenetic perturbation enables the testing of direct functional influence. The specific influence of detectable activity features can be addressed through so-called 'closed-loop' perturbation (Grosenick et al., 2015).

The ready applicability of optogenetic approaches in mice is beginning to produce categorically new observations of motor cortical operation. Rapid inhibition in transgenic mice expressing channelrhodopsin2 in all cortical inhibitory interneurons has helped distinguish the influence of motor cortical output on trained and untrained limb movements (Guo et al., 2015), and those involving the processing of unpredictable sensory input (Heindorf et al., 2018). Coupling the temporal precision of inhibition in these transgenic mice with EMG has helped reveal that motor cortical output directly drives limb muscle activity only during certain movement types (Miri et al., 2017). This temporal precision has also enabled localization of motor cortical influence to specific behavioral phases in decision-making paradigms (Guo et al., 2013; Goard et al., 2016), and to kinematically distinct movement features that likely have a distinct dependence on sensory feedback (Bollu et al., 2019a).

These results collectively illustrate the newfound granularity of functional interrogation enabled by optogenetics, but two issues arise. First, the distinct timescale of these perturbations relative to previous approaches creates challenges for reconciling results with historical findings. This challenge arises in part because neural systems respond differently to perturbations over different timescales. Interestingly, in some instances results from fast timescale perturbation align well with predictions based on classical results with slower methods, but other recent results suggest that this similarity may diminish as task complexity increases (Pinto et al., 2019). Second, concerns have been raised about interpreting pharmacological and optogenetic perturbation results given the possibility of deficits from unintended effects downstream of the perturbation (Martin et al., 1993; Otchy et al., 2015). In general, these concerns warrant strong consideration when interpreting data. In certain cases, such concerns can be allayed though characterization of the temporal pattern (Sauerbrei et al., 2020) or latency (Miri et al., 2017) of perturbation effects on downstream targets.

CELL AND SUBTYPE RESOLVED ACTIVITY MEASUREMENT

The confluence of genetic and optical approaches has created new opportunities for resolving activity in neuronal subpopulations. Emerging methods enable the

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testing of hypotheses that impute function onto neuronal subtypes defined by features of cellular identity, as functional differences between subtypes should be reflected somehow in neural activity. One such method, referred to as 'optical tagging,' allows the identification of neurons within a recorded population according to their genetic identity through the expression of an opsin that yields light-dependent firing (Lima et al., 2009). This method has been used, for example, to show that parvalbumin-positive interneurons in motor cortex respond to sensory cues and the initiation of movement but do not seem to gate the activity of nearby pyramidal neurons (Estebanez et al., 2017). Concerns about the use of optical tagging for excitatory populations are allayed by the use of inhibitory optogenetic probes for identifying such neurons (Rowland et al., 2018). In projection neurons, such concerns can also be avoided through the use of an optical variant of the collision test, in which projecting axons of opsin-expressing neurons are stimulated with light. This has been used to distinguish the movement-related activity in intratelencephalic and pyramidal tract neurons (Li et al., 2015; Saiki et al., 2017). Optical collision was also used to parse the activity of two subtypes of pyramidal tract neurons (Economo et al., 2018) in a study that highlights the potential for functional differences among genetically distinct subtypes that share many morphological similarities.

The imaging of fluorescent calcium indicators has also spawned insights into functional organization at cellular resolution. Early *in vivo* two-photon imaging studies in forelimb motor cortex identified a clustering of neurons preferentially active during different movement types (Dombeck et al., 2009), reminiscent of functional organization on a larger spatial scale in monkeys (Graziano et al., 2002). Coupling imaging with access to genetic cell types enables a high-throughput approach for cellular resolution measurements across populations. This has been exploited recently to distinguish task-related activity in pyramidal tract neurons from that of other cortical pyramidal neurons (Heindorf et al., 2018). The relative ease of chronic activity recording with calcium indicator imaging has enabled recent studies examining changes across learning, including in movement encoding (Peters et al., 2017; Omlor et al., 2019), and activity correlations between motor cortical output and cerebellar granule cells (Wagner et al., 2019).

The ability to interrogate murine circuits with cellular and subtype resolution also enables testing long-held ideas of cell-based organization. Historical views of motor cortical organization all share a common feature: they impute distinct functions onto distinct subsets of cells (Graziano, 2006; Darling et al., 2011). Attempts to map cortical organization with electrical stimulation (Fritsch and Hitzig, 1870; Penfield and Boldrey, 1937; Graziano et al., 2002) have led to views that neurons populating distinct subregions drive particular muscle groups or movement types. These ideas have been challenged by our recent work in mice supporting a nascent alternative view that it is instead the covariation of firing patterns across an entire population that dictates motor output (Miri et al., 2017; Warriner et al., in preparation). This has added to recent results suggesting that motor cortex leverages changes in population dynamics manifest in activity covariation to flexibly control a variety of motor outputs (Kaufman et al., 2014; Pandarinath et al., 2018; Perich et al., 2018). Adjudicating between cellular and newer covariation-based views of motor cortical organization will benefit from opportunities to both map activity at cellular resolution and perturb it in real time to assess functional roles. Here the smaller scale of the mouse motor cortex is advantageous as it permits a comprehensiveness of assessment not readily achievable in larger mammals.

Thinking beyond cortex, the mouse also has particular value as a model for assessing interactions between motor cortex and other motor system regions. Functional units of cortical control may be distinguished not just by their collective firing patterns, but also by the way they respond to inputs and the changes they induce in the activity of downstream target neurons. Moreover, essentially all of our ideas about mechanism in motor control involve one neuronal population responding to input from another population. Yet historically it has been prohibitively difficult to directly observe these interactions at spike time resolution, especially when subcortical structures are involved. Fortunately, multielectrode electrode arrays newly enable the monitoring of activity in multiple connected neuronal populations (Jun et al., 2017). Methods from the rapidly evolving field of data science are radically improving our ability to find structure in the large datasets these arrays generate (Paninski and Cunningham, 2018). The relative ease of targeting subcortical structures in the mouse with such arrays makes it a particularly good system in which to characterize cortical organization based on interactions with subcortical regions.

PROBING FUNCTIONAL ORGANIZATION THROUGH MOTOR LEARNING

In addition to their role in probing cortical organization related to movement execution, rodent models have made substantial contributions to our understanding of how new movements are generated, improved, and changed over time. Early studies using corticospinal tract transection or cortical lesion implicated motor cortex in the learning of dexterous movements in rats (Castro, 1972; Whishaw et al., 1991, 1993). More recent work has disentangled this role from cortical involvement in movement execution, indicating a distinct cortical role in motor learning and stereotyping new movement sequences (Kawai et al., 2015; Hwang et al., 2019). The vital role motor cortex plays in learning suggests that its organizational logic should reflect this role. Thus, the reorganization of motor cortex that underlies learning could be useful in illuminating this logic.

The rodent has historically played a critical role in characterizing the many structural changes in cortex during motor learning. Extensive reorganization of dendritic arbors throughout motor cortex has been observed during the learning of forelimb tasks (Greenough et al., 1985; Withers and Greenough, 1989;

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Wang et al., 2011), along with both spine formation (Xu et al., 2009; Yang et al., 2009) and increased spine turnover (Fu et al., 2012; Peters et al., 2014). These structural changes highlight the reorganization of motor cortex as a consequence of learning and imply that new synapse formation is an important step in learning. In addition, increased cortico–cortico LTP (Rioult-Pedotti et al., 1998), and synaptogenesis (Kleim et al., 2002) have also been reported during learning, further supporting a functional role for these morphological changes.

Building upon this work, recent studies have aimed to identify the consequences of learning-related structural changes for cortical activity. Chronic electrical recording of motor cortical neurons across learning has helped elucidate changes in the representation of motor behavior and muscle activity by motor cortical firing patterns (Costa et al., 2004; Kargo and Nitz, 2004). Further support for such changes came from studies using calcium indicator imaging in layer 2/3 of anterior lateral motor cortex (Komiyama et al., 2010; Huber et al., 2012). More recent imaging studies have observed that while the relationship between layer 2/3 activity and movement is more variable early in learning, consistency mounts as learning progresses (Peters et al., 2014). Chronic activity recording in identified corticospinal neurons has revealed not an increased correlation between activity and movement across learning, but rather a decorrelation of corticospinal activity during dissimilar movements (Peters et al., 2017).

Moving forward, the mouse has a particular role to play in efforts to identify changes in circuit structure and activity that result from motor learning, and to interpret these changes through models of motor cortical functional organization. The relative ease of charting activity chronically across large swaths of motor cortex with optical techniques offers opportunities for testing theories of motor learning that themselves imply an underlying cortical organization (Shmuelof and Krakauer, 2011; Peters et al., 2017). The increasing ability to link structural characterizations during learning with features of cell identity could help elucidate functional distinctions across neuronal subtypes. Functional distinctions relevant to organization may also be reflected in cell and subtype resolved changes in gene expression, which are increasingly accessible with single-cell sequencing. Similar to the way changes across evolution reflect the functional utility of anatomical and behavioral features, changes in circuit structure and activity across learning could reflect critical features of cortical organization.

We note here that the precision of mechanistic inquiry depends on how our experimental paradigms capture motor learning. Motor learning involves a broad range of experience-dependent processes, with potentially diverse neural bases. It unfolds in stages that are a challenge to consistently define across different paradigms. In natural settings, motor learning transpires in complex sensory milieus and may depend on long temporal contingencies. Yet in the lab, mice are motivated with immediate rewards, and sensory cues are limited. As a consequence, much of what we explore as mechanistic underpinning of motor learning may depend critically on task design. In this respect, the relative ease of engaging freely-behaving mice in motor learning could be advantageous for capturing aspects of learning in situ.

LOOKING TO THE FUTURE

Studies in mice are increasingly leveraging technological developments in molecular biology, virology, optogenetics, imaging, and neural recording to address questions of neural system function. This has occurred in parallel with an increase in the sophistication of behavioral tasks and methods to observe and quantify task performance. This positions mouse models to exploit the growth of these diverse tools to assess neuronal function at an increasingly fine level of granularity. Such efforts may ultimately resolve basic functional elements that underlie the cortical control of movement.

Moving forward, this control will be investigated via both population activity dynamics and cell type function. Recent studies have revealed a tremendous diversity of transcriptionally defined neuronal populations, adding to the range of cell identity features the functional relevance of which can now be assessed. At the same time, machine learning approaches have demonstrated a vast computational capacity in neural network models composed of homogeneous units connected in ways not obviously illustrative of function. The capacity for interfacing large-scale physiological assessment of motor circuit function with anatomical and genetic techniques in the mouse offers a unique opportunity to explore how computational capacity emerges from biological circuits. A key challenge here is the development of behavioral paradigms best suited to this endeavor.

As we improve our understanding of motor learning, planning, and execution, comparative studies can help illuminate functional organization and identify principles conserved across species. Thus, another ongoing challenge lies in identifying questions addressable in mice that are of general interest to the motor control field. This challenge is compounded by the novelty of experimental opportunities: historical limits on the resolution of activity measurement and perturbation have impeded the development of hypotheses regarding how neuronal populations directly interact on fast timescales as movement unfolds. The challenge of establishing general relevance is also compounded by the distinct features of rodent behavioral strategy and anatomical organization. Yet the power of comparative analysis may ultimately prove such differences integral to the impact of mouse studies.

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circuits more broadly. Though this transition was at an early stage, his approach displayed the same clarity of thought and scientific rigor that was characteristic throughout his career. We would also like to thank Edera Daubert for illustrations. This work was supported by a National Institute of Health Brain Initiative U19 (C.L.W., S.K.F., L.M.C.), by a NIH-NINDS T32 Training Grant and F31 Predoctoral Award (C.L.W.), the Fulbright Science and Technology Scholars Program (S. K.F.), the Helen Hay Whitney Foundation (L.M.C.), a Searle Scholar Award, Sloan Research Fellowship, Whitehall Research Grant Award, and the Chicago Biomedical Consortium with support from the Searle Funds at the Chicago Community Trust (A.M.).

REFERENCES

Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K, de Lecea L (2007) Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature 450:420–424.

Akay T, Acharya HJ, Fouad K, Pearson KG (2006) Behavioral and electromyographic characterization of mice lacking EphA4 receptors. J Neurophysiol 96:642–651.

Arber S, Costa RM (2018) Connecting neuronal circuits for movement. Science 360:1403–1404.

Arenkiel BR, Peca J, Davison IG, Feliciano C, Deisseroth K, Augustine G, Ehlers MD, Feng G (2007) In vivo light-induced activation of neural circuitry in transgenic mice expressing channelrhodopsin-2. Neuron 54:205–218.

Arlotta P, Molyneaux BJ, Chen J, Inoue J, Kominami R, Macklis JD (2005) Neuronal Subtype-Specific Genes that Control Corticospinal Motor Neuron Development In Vivo. Neuron 45:207–221.

Azim E, Jiang J, Alstermark B, Jessell TM (2014) Skilled reaching relies on a V2a propriospinal internal copy circuit. Nature 508:357–363.

Barrett JM, Tapies MGR, Shepherd GMG (2020) Manual dexterity of mice during food-handling involves the thumb and a set of fast basic movements. Plos One 15:e0226774.

Basaldella E, Takeoka A, Sigrist M, Arber S (2015) Multisensory signaling shapes vestibulo-motor circuit specificity. Cell 163:301–312.

Bates P, Rong L, Varmus HE, Young JAT, Crittenden LB (1998) Genetic mapping of the cloned subgroup A avian sarcoma and Leukosis virus receptor gene to the TVALocus. J Virol 72:2505–2508.

Betley JN, Wright CVE, Kawaguchi Y, Erdélyi F, Szabó G, Jessell TM, Kaltschmidt JA (2009) Stringent specificity in the construction of a GABAergic Presynaptic inhibitory circuit. Cell 139:161–174.

Bollu T, Whitehead S, Kardon B, Redd J, Liu M, Goldberg J (2019a) Cortical contribution to lingual kinematics as the tongue reaches for, and misses, targets. Poster presented at: Society for Neuroscience 2019 (Chicago, IL).

Bollu T, Whitehead SC, Prasad N, Walker J, Shyamkumar N, Subramaniam R, Kardon B, Cohen I, Goldberg JH (2019b) Automated home cage training of mice in a hold-still center-out reach task. J Neurophysiol 121:500–512.

Bortoff GA, Strick PL (1993) Corticospinal terminations in two new-world primates: further evidence that corticomotoneuronal connections provide part of the neural substrate for manual dexterity. J Neurosci 13:5105–5118.

Bostan AC, Dum RP, Strick PL (2010) The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci U S A 107:8452–8456.

Brown AR, Teskey GC (2014) Motor cortex is functionally organized as a set of spatially distinct representations for complex movements. J Neurosci 34:13574–13585.

Cai DJ, Aharoni D, Shuman T, Shobe J, Biane J, Song W, Wei B, Veshkini M, La-Vu M, Lou J, Flores SE, Kim I, Sano Y, Zhou M, Baumgaertel K, Lavi A, Kamata M, Tuszynski M, Mayford M, Golshani P, Silva AJ (2016) A shared neural ensemble links distinct contextual memories encoded close in time. Nature 534:115–118.

Castro AJ (1972) The effects of cortical ablations on digital usage in the rat. Brain Res 37:173–185.

Chen I-W, Papagiakoumou E, Emiliani V (2018) Towards circuit optogenetics. Curr Opin Neurobiol 50:179–189.

Cheney PD, Fetz EE (1985) Comparable patterns of muscle facilitation evoked by individual corticomotoneuronal (CM) cells and by single intracortical microstimuli in primates: evidence for functional groups of CM cells. J Neurophysiol 53:786–804.

Churchland MM, Cunningham JP, Kaufman MT, Foster JD, Nuyujukian P, Ryu SI, Shenoy KV (2012) Neural population dynamics during reaching. Nature 487:51–56.

Ciabatti E, González-Rueda A, Mariotti L, Morgese F, Tripodi M (2017) Life-long genetic and functional access to neural circuits using self-inactivating rabies virus. Cell 170:382–392.e14.

Costa RM, Cohen D, Nicolelis MAL (2004) Differential corticostriatal plasticity during fast and slow motor skill learning in mice. Curr Biol 14:1124–1134.

Darling WG, Pizzimenti MA, Morecraft RJ (2011) Functional recovery following motor cortex lesions in non-human primates: experimental implications for human stroke patients. J Integr Neurosci 10:353–384.

Dombeck DA, Graziano MS, Tank DW (2009) Functional clustering of neurons in motor cortex determined by cellular resolution imaging in awake behaving mice. J Neurosci 29:13751–13760.

Dombeck DA, Khabbaz AN, Collman F, Adelman TL, Tank DW (2007) Imaging large-scale neural activity with cellular resolution in awake, mobile mice. Neuron 56:43–57.

Economo MN, Viswanathan S, Tasic B, Bas E, Winnubst J, Menon V, Graybuck LT, Nguyen TN, Smith KA, Yao Z, Wang L, Gerfen CR, Chandrashekar J, Zeng H, Looger LL, Svoboda K (2018) Distinct descending motor cortex pathways and their roles in movement. Nature 563:79–84.

Estebanez L, Hoffmann D, Voigt BC, Poulet JFA (2017) Parvalbumin-Expressing GABAergic Neurons in Primary Motor Cortex Signal Reaching. Cell Reports 20:308–318.

Fageiry SK, Warriner CL, Loper J, Paninski L, Reardon TR, Jessell TM, Miri A and Costa RM. Mapping corticospinal connections with spinal circuits. In preparation.

Ferrier D, Yeo G (1884) A record of experiments on the effects of lesion of different regions of the cerebral hemispheres. Philos Trans Royal Soc Lond:479–564.

Fink AJP, Croce KR, Huang ZJ, Abbott LF, Jessell TM, Azim E (2014) Presynaptic inhibition of spinal sensory feedback ensures smooth movement. Nature 509:43–48.

Fritsch G, Hitzig E (1870) Electric excitability of the excitability of the cerebrum (Uber die elektrische Erregbarkeit des Grosshirns). Epilepsy Behav 15:123–130.

Fu M, Yu X, Lu Ju, Zuo Yi (2012) Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. Nature 483:92–95.

Fulcher BD, Murray JD, Zerbi V, Wang X-J (2019) Multimodal gradients across mouse cortex. PNAS 116:4689–4695.

Galiñanes GL, Bonardi C, Huber D (2018) Directional reaching for water as a cortex-dependent behavioral framework for mice. Cell Rep 22:2767–2783.

Ghosh KK, Burns LD, Cocker ED, Nimmerjahn A, Ziv Y, Gamal AE, Schnitzer MJ (2011) Miniaturized integration of a fluorescence microscope. Nat Methods 8:871–878.

Goard MJ, Pho GN, Woodson J, Sur M (2016) Distinct roles of visual, parietal, and frontal motor cortices in memory-guided sensorimotor decisions. Elife 5 e13764.

Graziano M (2006) The organization of behavioral repertoire in motor cortex. Annu Rev Neurosci 29:105–134.

Graziano MSA, Taylor CSR, Moore T (2002) Complex movements evoked by microstimulation of precentral cortex. Neuron 34:841–851.

Greenough WT, Larson JR, Withers GS (1985) Effects of unilateral and bilateral training in a reaching task on dendritic branching of neurons in the rat motor-sensory forelimb cortex. Behav Neural Biol 44:301–314.

Grosenick L, Marshel J, Deisseroth K (2015) Closed-loop and activity-guided optogenetic control. Neuron 86:106–139.

Gu Z, Kalambogias J, Yoshioka S, Han W, Li Z, Kawasawa YI, Pochareddy S, Li Z, Liu F, Xu X, Wijeratne HRS, Ueno M, Blatz E, Salomone J, Kumanogoh A, Rasin M-R, Gebelein B, Weirauch MT, Sestan N, Martin JH, Yoshida Y (2017) Control of species-dependent cortico-motoneuronal connections underlying manual dexterity. Science 357:400–404.

Guo J-Z, Graves AR, Guo WW, Zheng J, Lee A, Rodríguez-González J, Li N, Macklin JJ, Phillips JW, Mensh BD, Branson K, Hantman AW (2015) Cortex commands the performance of skilled movement. Elife 4 e10774.

Guo Z, Li N, Huber D, Ophir E, Gutnisky D, Ting J, Feng G, Svoboda K (2013) Flow of cortical activity underlying a tactile decision in mice. Neuron 81:179–194.

Gutruf P, Rogers JA (2018) Implantable, wireless device platforms for neuroscience research. Curr Opin Neurobiol 50:42–49.

Hammond SL, Leek AN, Richman EH, Tjalkens RB (2017) Cellular selectivity of AAV serotypes for gene delivery in neurons and astrocytes by neonatal intracerebroventricular injection. Plos One 12:e0188830.

Harrison T, Ayling OS, Murphy T (2012) Distinct cortical circuit mechanisms for complex forelimb movement and motor map topography. Neuron 74:397–409.

Heindorf M, Arber S, Keller GB (2018) Mouse motor cortex coordinates the behavioral response to unpredicted sensory feedback. Neuron 101:1202. https://doi.org/10.1016/j.neuron.2019.02.042.

Horsley V, Schafer E (1888) A record of experiments upon the functions of the cerebral cortex. Philos Trans Royal Soc Lond, Ser B 179:1–45.

Hoshi E, Tremblay L, Féger J, Carras PL, Strick PL (2005) The cerebellum communicates with the basal ganglia. Nat Neurosci 8:1491–1493.

Huber D, Gutnisky DA, Peron S, O'Connor DH, Wiegert JS, Tian L, Oertner TG, Looger LL, Svoboda K (2012) Multiple dynamic representations in the motor cortex during sensorimotor learning. Nature 484:473–478.

Hwang EJ, Dahlen JE, Hu YY, Aguilar K, Yu B, Mukundan M, Mitani A, Komiyama T (2019) Disengagement of motor cortex from movement control during long-term learning. Sci Adv 5:eaay0001. https://doi.org/10.1126/sciadv.aay0001.

Jessell T, Sürmeli G, Kelly J (2011) Motor neurons and the sense of place. Neuron 72:419–424.

Jun JJ (2017) Fully integrated silicon probes for high-density recording of neural activity. Nature 551:232–236.

Kaas JH (2012) Chapter 5 The evolution of neocortex in primates. Prog Brain Res 195:91–102.

Kalaska JF (2009) Progress in motor control, a multidisciplinary perspective. 139–178.

Kargo WJ, Nitz DA (2004) Improvements in the signal-to-noise ratio of motor cortex cells distinguish early versus late phases of motor skill learning. J Neurosci 24:5560–5569.

Kaufman MT, Churchland MM, Ryu SI, Shenoy KV (2014) Cortical activity in the null space: permitting preparation without movement. Nat Neurosci 17:440–448.

Kawai R, Markman T, Poddar R, Ko R, Fantana A, Dhawale A, Kampff A, Ölveczky B (2015) Motor cortex is required for learning but not for executing a motor skill. Neuron 86:800–812.

Kepecs A, Fishell G (2014) Interneuron cell types are fit to function. Nature 505:318–326.

Kim CK, Adhikari A, Deisseroth K (2017) Integration of optogenetics with complementary methodologies in systems neuroscience. Nat Rev Neurosci 18:222–235.

Kim E, Jacobs M, Ito-Cole T, Callaway E (2016) Improved monosynaptic neural circuit tracing using engineered rabies virus glycoproteins. Cell Rep 15:692–699.

Kimura R, Saiki A, Fujiwara-Tsukamoto Y, Sakai Y, Isomura Y (2017) Large-scale analysis reveals populational contributions of cortical spike rate and synchrony to behavioural functions: Large-scale analysis of cortical spike synchrony. J Physiol 595:385–413.

Kleim JA, Barbay S, Cooper NR, Hogg TM, Reidel CN, Remple MS, Nudo RJ (2002) Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. Neurobiol Learn Mem 77:63–77.

Komiyama T, Sato TR, O'Connor DH, Zhang Y-X, Huber D, Hooks BM, Gabitto M, Svoboda K (2010) Learning-related fine-scale specificity imaged in motor cortex circuits of behaving mice. Nature 464:1182–1186.

Krubitzer LA, Seelke AMH (2012) Cortical evolution in mammals: The bane and beauty of phenotypic variability. Proc Natl Acad Sci U S A 109:10647–10654.

Kuypers H (1981) Anatomy of the descending pathways. In: Brooks V, editor. The Nervous System, Handbook of Physiology. p. 597–666.

Lanciego JL, Wouterlood FG (2011) A half century of experimental neuroanatomical tracing. J Chem Neuroanat 42:157–183.

Lawrence DG, Kuypers HGJM (1968) The functional organization of the motor system in the monkey. Brain 91:15–36.

Lemon RN, Griffiths J (2005) Comparing the function of the corticospinal system in different species: Organizational differences for motor specialization? Muscle Nerve 32:261–279.

Levine AJ, Lewallen KA, Pfaff SL (2012) Spatial organization of cortical and spinal neurons controlling motor behavior. Curr Opin Neurobiol 22:812–821.

Li N, Chen T-W, Guo ZV, Gerfen CR, Svoboda K (2015) A motor cortex circuit for motor planning and movement. Nature 519:51–56.

Liang H, Paxinos G, Watson C (2011) Projections from the brain to the spinal cord in the mouse. Brain Struct Funct 215:159–186.

Lima SQ, Hromádka T, Znamenskiy P, Zador AM (2009) PINP: A new method of tagging neuronal populations for identification during in vivo electrophysiological recording. PloS One 4:e6099.

Martin JH, Cooper SE, Ghez C (1993) Differential effects of local inactivation within motor cortex and red nucleus on performance of an elbow task in the cat. Exp Brain Res 94. https://doi.org/10.1007/BF00230200.

Mathis MW, Mathis A, Uchida N (2017) Somatosensory cortex plays an essential role in forelimb motor adaptation in mice. Neuron 93:1493–1503.e6.

Miri A, Warriner CL, Seely JS, Elsayed GF, Cunningham JP, Churchland MM, Jessell TM (2017) Behaviorally selective engagement of short-latency effector pathways by motor cortex. Neuron 95. 683-696.e11.

Mohammed H, Jain N (2016) Ipsilateral cortical inputs to the rostral and caudal motor areas in rats: Cortical inputs to rat whisker motor areas. J Comp Neurol 524:3104–3123.

Murray AJ, Croce K, Belton T, Akay T, Jessell TM (2018) Balance control mediated by vestibular circuits directing limb extension or antagonist muscle co-activation. Cell Reports 22:1325–1338.

Fritz N, I.M., Kolb FP, Lemon RN, Muir RB, van der Burg J, Wiedemann E, Yamaguchi T (1985) The cortico-motoneuronal input to hand and forearm motoneurones in the anaesthetized monkey. J Physiol, 20.

Oh SW et al. (2014) A mesoscale connectome of the mouse brain. Nature 508:207–214.

Omlor W, Wahl A-S, Sipilä P, Lütcke H, Laurenczy B, Chen I-W, Sumanovski LT, van 't Hoff M, Bethge P, Voigt FF, Schwab ME, Helmchen F (2019) Context-dependent limb movement encoding in neuronal populations of motor cortex. Nat Commun 10. https://doi.org/10.1038/s41467-019-12670-z.

Otchy TM, Wolff SBE, Rhee JY, Pehlevan C, Kawai R, Kempf A, Gobes SMH, Ölveczky BP (2015) Acute off-target effects of neural circuit manipulations. Nature 528:358–363.

Pandarinath C, Ames KC, Russo AA, Farshchian A, Miller LE, Dyer EL, Kao JC (2018) Latent factors and dynamics in motor cortex and their application to brain–machine interfaces. J Neurosci 38:9390–9401.

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.Paninski L, Cunningham JP (2018) Neural data science: accelerating the experiment-analysis-theory cycle in large-scale neuroscience. Curr Opin Neurobiol 50:232–241.

Pearson KG, Acharya H, Fouad K (2005) A new electrode configuration for recording electromyographic activity in behaving mice. J Neurosci Methods 148:36–42.

Penaud-Budloo M, Le Guiner C, Nowrouzi A, Toromanoff A, Chérel Y, Chenuaud P, Schmidt M, von Kalle C, Rolling F, Moullier P, Snyder RO (2008) Adeno-associated virus vector genomes persist as episomal chromatin in primate muscle. J Virol 82:7875–7885.

Penfield W, Boldrey E (1937) somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389–443.

Perich MG, Gallego JA, Miller LE (2018) A neural population mechanism for rapid learning. Neuron 100:964–976.e7.

Peters AJ, Chen SX, Komiyama T (2014) Emergence of reproducible spatiotemporal activity during motor learning. Nature 510:263–267.

Peters AJ, Lee J, Hedrick NG, O'Neil K, Komiyama T (2017) Reorganization of corticospinal output during motor learning. Nat Neurosci 20:1133–1141.

Pinto L, Rajan K, DePasquale B, Thiberge SY, Tank DW, Brody CD (2019) Task-dependent changes in the large-scale dynamics and necessity of cortical regions. Neuron.

Porter R, Lemon R (1995) Corticospinal function and voluntary movement.

Preuss TM, Stepniewska I, Jain N, Kaas JH (1997) Multiple divisions of macaque precentral motor cortex identified with neurofilament antibody SMI-32. Brain Res 767:148–153.

Rathelot J-A, Strick PL (2006) Muscle representation in the macaque motor cortex: An anatomical perspective. Proc Natl Acad Sci U S A 103:8257–8262.

Rathelot J-A, Strick PL (2009) Subdivisions of primary motor cortex based on cortico-motoneuronal cells. PNAS 106:918–923.

Reardon TR, Murray AJ, Turi GF, Wirblich C, Croce KR, Schnell MJ, Jessell TM, Losonczy A (2016) Rabies virus CVS-N2c G strain enhances retrograde synaptic transfer and neuronal viability. Neuron 89:711–724.

Rickgauer JP, Deisseroth K, Tank DW (2014) Simultaneous cellular-resolution optical perturbation and imaging of place cell firing fields. Nat Neurosci 17:1816–1824.

Rioult-Pedotti M-S, Friedman D, Hess G, Donoghue JP (1998) Strengthening of horizontal cortical connections following skill learning. Nat Neurosci 1:230–234.

Rowland DC, Obenhaus HA, Skytøen ER, Zhang Q, Kentros CG, Moser EI, Moser M-B (2018) Functional properties of stellate cells in medial entorhinal cortex layer II. eLife 7:e36664.

Saiki A, Sakai Y, Fukabori R, Soma S, Yoshida J, Kawabata M, Yawo H, Kobayashi K, Kimura M, Isomura Y (2017) In vivo spiking dynamics of intra- and extratelencephalic projection neurons in rat motor cortex. Cerebr Cortex 28:1024–1038.

Sarup A, Kristl A, Koh N, Young M, Bandyopadhyay S, Miri A (n.d.) A paradigm for physiological examination of naturalistic climbing behavior in mice. Poster presented at: Society for Neuroscience 2019 (Chicago, IL).

Sauerbrei BA, Guo J-Z, Cohen JD, Mischiati M, Guo W, Kabra M, Verma N, Mensh B, Branson K, Hantman AW (2020) Cortical pattern generation during dexterous movement is input-driven. Nature 577:386–391.

Schieber MH, Rivlis G (2007) Partial reconstruction of muscle activity from a pruned network of diverse motor cortex neurons. J Neurophysiol 97:70–82.

Shmuelof L, Krakauer JW (2011) Are we ready for a natural history of motor learning? Neuron 72:469–476.

Tasic B et al (2016) Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. Nat Neurosci 19:335–346.

Tasic B et al (2018) Shared and distinct transcriptomic cell types across neocortical areas. Nature 563:72–78.

Tervo DGR, Hwang B-Y, Viswanathan S, Gaj T, Lavzin M, Ritola KD, Lindo S, Michael S, Kuleshova E, Ojala D, Huang C-C, Gerfen CR, Schiller J, Dudman JT, Hantman AW, Looger LL, Schaffer DV, Karpova AY (2016) A designer AAV variant permits efficient retrograde access to projection neurons. Neuron 92:372–382.

Tripodi M, Stepien AE, Arber S (2011) Motor antagonism exposed by spatial segregation and timing of neurogenesis. Nature 479:61–66.

VanderHorst VGJM, Ulfhake B (2006) The organization of the brainstem and spinal cord of the mouse: Relationships between monoaminergic, cholinergic, and spinal projection systems. J Chem Neuroanat 31:2–36.

Wagner MJ, Kim TH, Kadmon J, Nguyen ND, Ganguli S, Schnitzer MJ, Luo L (2019) Shared cortex-cerebellum dynamics in the execution and learning of a motor task. Cell 177:669–682.e24.

Wang L, Conner JM, Rickert J, Tuszynski MH (2011) Structural plasticity within highly specific neuronal populations identifies a unique parcellation of motor learning in the adult brain. Proc National Acad Sci U S A 108:2545–2550.

Wang X, Liu Y, Li X, Zhang Z, Yang H, Zhang Y, Williams PR, Alwahab NSA, Kapur K, Yu B, Zhang Y, Chen M, Ding H, Gerfen CR, Wang KH, He Z (2017) Deconstruction of corticospinal circuits for goal-directed motor skills. Cell 171:440–455.e14.

Warriner CL, Fageiry SK, Saxena S, Paninski L, Jessell TM, Costa RM, and Miri A. Motor cortex mediates antagonist cocontraction with task-specific activity covariation. In preparation.

Whishaw IQ, Faraji J, Kuntz JR, Agha BM, Metz GAS, Mohajerani MH (2017) The syntactic organization of pasta-eating and the structure of reach movements in the head-fixed mouse. Sci Rep-UK 7:10987.

Whishaw IQ, Pellis SM, Gorny B, Kolb B, Tetzlaff W (1993) Proximal and distal impairments in rat forelimb use in reaching follow unilateral pyramidal tract lesions. Behav Brain Res 56:59–76.

Whishaw IQ, Pellis SM, Gorny BP, Pellis VC (1991) The impairments in reaching and the movements of compensation in rats with motor cortex lesions: an endpoint, videorecording, and movement notation analysis. Behav Brain Res 42:77–91.

Wickersham IR, Finke S, Conzelmann K-K, Callaway EM (2007a) Retrograde neuronal tracing with a deletion-mutant rabies virus. Nat Methods 4:47–49.

Wickersham IR, Lyon DC, Barnard RJO, Mori T, Finke S, Conzelmann K-K, Young JAT, Callaway EM (2007b) Monosynaptic restriction of transsynaptic tracing from single, genetically targeted neurons. Neuron 53:639–647.

Withers GS, Greenough WT (1989) Reach training selectively alters dendritic branching in subpopulations of layer II–III pyramids in rat motor-somatosensory forelimb cortex. Neuropsychologia 27:61–69.

Xu T, Yu X, Perlik AJ, Tobin WF, Zweig JA, Tennant K, Jones T, Zuo Y (2009) Rapid formation and selective stabilization of synapses for enduring motor memories. Nature 462:915–919.

Yang G, Pan F, Gan W-B (2009) Stably maintained dendritic spines are associated with lifelong memories. Nature 462:920–924.

Yoshida J, Saiki A, Soma S, Yamanaka K, Nonomura S, Ríos A, Kawabata M, Kimura M, Sakai Y, Isomura Y (2018) Area-specific modulation of functional cortical activity during block-based and trial-based proactive inhibition. Neuroscience 388:297–316.

Young JA, Bates P, Varmus HE (1993) Isolation of a chicken gene that confers susceptibility to infection by subgroup A avian leukosis and sarcoma viruses. J Virol 67:1811–1816.

Zeng H, Sanes JR (2017) Neuronal cell-type classification: challenges, opportunities and the path forward. Nat Rev Neurosci 18:530–546.

Zergeroğlu SA, Nalçacı E (2015) Santiago Ramon y Cajal and neuron doctrine. tnd 21:81–84.

Ziv Y, Burns LD, Cocker ED, Hamel EO, Ghosh KK, Kitch LJ, Gamal AE, Schnitzer MJ (2013) Long-term dynamics of CA1 hippocampal place codes. Nat Neurosci 16:264–266.

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