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Motoring ahead with rodents

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How neural circuits underlie the acquisition and control of learned motor behaviors has traditionally been explored in monkeys and, more recently, songbirds. The development of genetic tools for functional circuit analysis in rodents, the availability of transgenic animals with well characterized phenotypes, and the relative ease with which rats and mice can be trained to perform various motor tasks, make rodents attractive models for exploring the neural circuit mechanisms underlying the acquisition and production of learned motor skills. Here we discuss the advantages and drawbacks of this approach, review recent trends and results, and outline possible strategies for wider adoption of rodents as a model system for complex motor learning.

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Introduction

We interact with the world through movements. While innate movements are generated by specialized hard-wired circuits, learned behaviors require neural substrates with the capacity to generate new and adaptive motor programs. Despite the ubiquity and importance of learned motor patterns for our daily lives, the identity and function of the circuits involved in their acquisition are not well understood. Though much can be learned from sophisticated behavioral experiments on humans [1–3], addressing the mechanistic underpinnings of motor learning requires animal models suitable for invasive studies.

For many years, these questions have been explored by recording and manipulating neural activity in monkeys trained to interact with manipulanda. Since a major advantage of using monkeys is the similarity of their cortical organization to that of humans, research on complex motor learning has largely focused on how highly trained and consolidated movement patterns are represented by neurons in different motor cortical areas [4,5]. Details of how learning shapes the structure and function of the motor networks, and how these circuits implement the computations required for various forms of motor learning [1], have also started to emerge [6–9]. Yet a comprehensive account of how procedural memories are formed, evoked, and translated into neural activity that drives learned behaviors is still lacking.

An increasingly detailed circuit level understanding of how a brain can acquire and generate complex motor sequences comes from work on songbirds [10]. Zebra finches learn their vocalizations by first memorizing the song of a tutor, then engaging in vocal exploration, using auditory feedback to evaluate their performance relative to the stored template. Over a few weeks of vocal practice, birds gradually converge onto a copy of the tutor's song, a process accompanied by a dramatic increase in song stereotypy. The neural circuit mechanisms underlying this process are now being understood and principles of how circuits underlie complex sensorimotor learning are emerging [11•,12–14]. The extent to which these functional principles, instantiated in a specialized 'song circuit', generalize to more flexible learning systems, such as those implemented by the mammalian brain, remains to be investigated.

Progress in exploring neural mechanisms underlying motor learning in mammalian nervous systems is promised by work on rodents. Sophisticated molecular tools for measuring and manipulating the structure and function of neural circuits now exist [15•,16], enabling the functional dissection of brain networks underlying a variety of complex behaviors, including motor learning. Transgenic mice with well characterized deficits of neural function, and rodent models of human disease affecting motor learning and performance, are also available for study [17,18]. Importantly, rodents can acquire new motor programs that in complexity and precision rival ones that humans struggle to learn (Figure 1). Training such behaviors in rodents can be fully automated using operant techniques, enabling high throughput behavioral assays [19].

While rodents lack some of the cortical specializations that support high manual dexterity and visuomotor skills in primates, they share the basic mammalian neural architecture for motor control: a descending motor pathway from cortex to brainstem and spinal cord, as well as feedback pathways through the basal ganglia and

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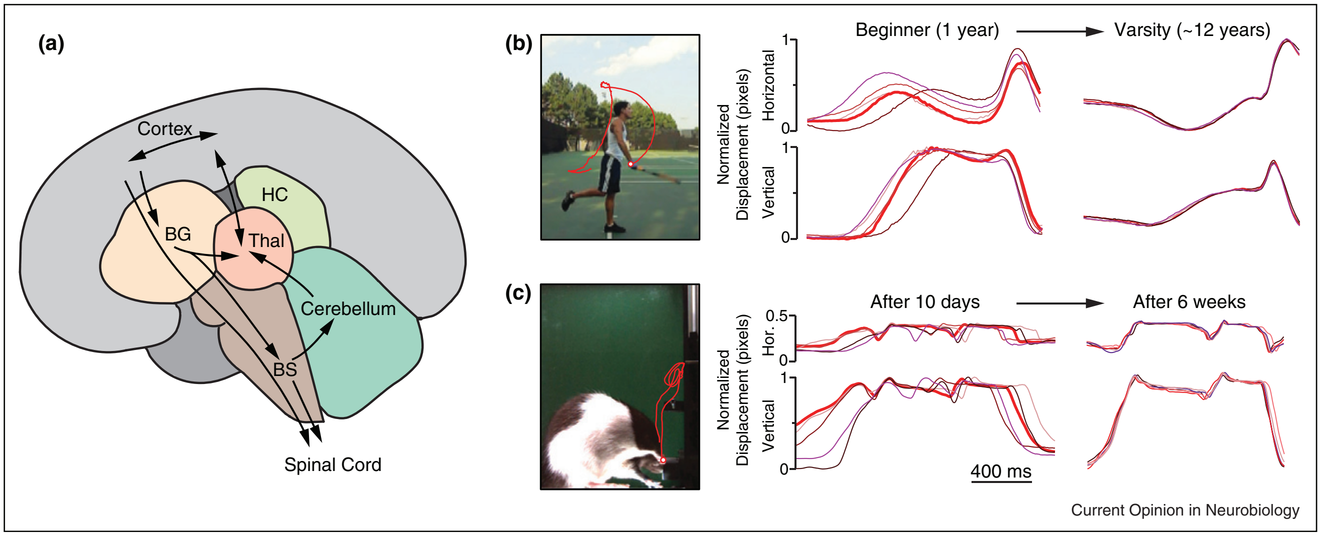
Figure 1



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Motor learning. **(a)** Schematic representation of the mammalian motor circuits supporting the acquisition and production of learned motor behaviors (BG — basal ganglia; Th — thalamus; BS — brain stem). **(b)** and **(c)** (Left) Examples of learned motor sequences in humans (tennis serve, b) and rats (joystick manipulation, c). Hand or paw positions (red lines in still images) were extracted from high speed movies (200 Hz) using color-based image processing, facilitated by subjects wearing a purple glove (humans) or having a red forepaw tattoo (rat). (Right) Movement stereotypy increases with practice. Five representative trajectories for a beginner and a varsity tennis player hitting a serve (top), and a rat early and late in the process of learning to displace a joystick below a threshold twice with a 650 ms delay. Trajectories normalized to maximum displacement in each condition. Thick red lines denote the sample trajectories on the left. Time scale is the same for all graphs. Traces aligned with respect to when the ball is hit or when the paw first touches the joystick. Adapted from [33].

cerebellum [20]. In addition to a primary motor cortex, rodents have at least one secondary motor cortical area, the rostral forelimb area (RFA) [21,22]. Elucidating the functional role of the RFA and its relation to higher order motor areas in primates will enhance the utility of rats and mice as models for higher level cortical processing. As it is, rodents represent a promising and largely untapped opportunity for addressing the role of primary motor cortex, its interaction with subcortical circuits, and the function of the basal ganglia, cerebellum, and brainstem in motor learning. Below, we highlight recent studies using rodents to address these questions, starting with a background section on established approaches and experimental paradigms, followed by a discussion of the insights they have produced.

Experimental approaches for studying motor learning in rodents

Historically, the rodent of choice for behavioral studies has been the laboratory rat (*Rattus Norvegicus*), but advances in mouse genetics, spurring the development of genetic tools for functional and anatomical circuit analyses, have recently motivated a shift to mice [15•]. Yet rats have the advantage of being bigger and stronger, allowing weightier devices to be used for neural recordings and circuit manipulations in behaving animals. In comparative studies, rats have also shown superior learning abilities [23] which together with the promise of rat transgenics [24,25] should ensure a continuing niche for rats in the study complex motor learning. Currently, the choice of rodent is dictated by the specific needs and aims of a given study, and rats and mice are often used interchangeably in similar paradigms.

Complicating the study of 'motor learning', defined here as the acquisition or improvement of motor sequences or skills, is that it is not a uniform process, but rather the result of many different interacting ones [26] (e.g. cognitive, motivational, sensory, and motor), each of which can be involved to different extents during different stages of learning [27] and rely on distinct sets of neural circuits and mechanisms. Differences in experimental design add further complexity and heterogeneity. Some paradigms rely on trial-and-error learning, while others use sensory cues to instruct behavioral sequences [28]; some tap into innate predispositions [29,30], while others are far less ethological [28,31]; some reach asymptotic performance in a matter of days [32], while others take months [33]. While these approaches all produce increasingly reliable and stereotyped motor behaviors, it is often unclear how insights from different studies inform each other and consequently how they contribute to our overall understanding of how procedural memories in mammalian brains are formed. The multitude of paradigms and the lack of constraints in designing new ones stand in stark contrast to the songbird field, which owes much of

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its success to the cumulative benefits of an entire community working on exactly the same, genetically constrained, behavior [34]. Thus while comparing results across studies differing in specific ways can help identify neural circuits and mechanisms specialized for certain aspects of motor learning, there may be, going forward, virtue in consolidating the experimental approaches into a few well-motivated paradigms.

Current paradigms

All behavioral studies on rodents that require animals to repeatedly produce a particular response will involve an aspect of motor learning. Sensory discrimination tasks, for example, in which the animal reports its decision with a movement (e.g. lever press or nose poke), often result in faster and more stereotyped responses [35,36]. These changes can be attributed to learning new associations between a stimulus and a response, but they also involve, through repeating the same action many times, changes in the motor output constituting the response. More careful monitoring of the animal's behavior in these studies will help to disambiguate the different learning processes [35].

Paradigms developed to explicitly study motor learning come in two main flavors: ones that improve naturally expressed *motor behaviors and skills* and those that use reward-based learning to train *motor sequences de novo*. A popular test of motor skill learning is the rotarod, in which animals are placed on a rotating cylinder and improve their ability to stay on [32]. Learning is fast, with most performance gains occurring on the first day of training. Used extensively to assess motor function in rodent models of disease, the test is easy to administer and score, and has been successfully used to demonstrate general correlates of motor skill learning [37•,38–40]. The rotarod may be less well suited for fine-grained analyses of how motor circuits encode acquired skills and behaviors, as precise measures of motor output are difficult to obtain.

Another type of assay involves rodents learning to reach for and manipulate uncooked pasta or food pellets positioned in difficult to reach places [29,41]. Given the role of motor cortex in forepaw dexterity, these tests have mainly been used to assess recovery and relearning of fine motor skills after cortical lesions and manipulations [29,42].

While the above paradigms assay improvement and refinement of, at least partially, innate motor skills, a different type of motor learning task involves ordering simple actions (e.g. lever presses or nose pokes) into sequences [28,43••,31,44]. Complexity of the behavior can be calibrated by varying the number of movements sequenced and the degree of temporal precision enforced. The behavior can be trained operantly, by trial-and-error [31,43••], or implicitly, by using sequences of sensory cues [28,45]. The task is similar to those used for studying motor sequence learning in primates [28] and has intriguing parallels also to birdsong, allowing for meaningful comparisons across different model systems. Thus this experimentally tractable, flexible, and easily automatable paradigm [19] has the potential to address a wide range of fundamental questions relating to the neural mechanisms underlying motor sequence learning.

Insights from recent rodent studies

Role of motor cortex

Despite decades of lesion studies in rats and mice, questions about the role of cortex in the acquisition and generation of learned motor skills remain. While decorticated rodents have a variety of documented deficits in motor performance, they are surprisingly subtle when compared to cortical injuries in humans [46]. Most notable is a decrease in forepaw dexterity, which compromises the animals' ability to learn and execute fine motor skills. Rats without a motor cortex, however, can recover performance on skilled reaching tasks to similar levels as controls, compensating for their deficits with less dexterous movements [29]. The mechanisms and circuits involved in the reorganization of the motor system following motor cortex injury remain an intense area of research [47], motivated by similar recoveries in monkeys [48] and, more importantly, in patients with motor cortex strokes [49]. But the fact that rodents can improve motor skills and learn new motor sequences [45,50], albeit with subtle deficits, *without* a motor cortex, raises important questions about the aspects of motor learning for which cortex is necessary. Addressing this will be helped by observing animals with specific cortical deficits in increasingly more complex learning paradigms, and by performing detailed behavioral analysis to identify differences in learning strategies.

Learning-related changes in cortical dynamics

How motor learning is expressed in cortex has been examined by observing changes in cortical activity that correlate with improved performance. Laubach *et al.* [36], recording from motor cortex neurons in rats during the acquisition of a stimulus–response association, found that learning significantly increases the reliability with which correlated firing in groups of neurons can predict trial outcome. Additional evidence that sensorimotor associations are encoded in the dynamics of neural ensembles is provided by Komiyama *et al.* [51••], who trained head-fixed mice to associate odors with a lick or no-lick response while measuring activity of Layer 2/3 neurons in motor cortex using 2-photon Ca^{2+} imaging. The authors found that the temporal correlation among neuron pairs belonging to the same functional type (i.e. cells responding during the same aspect of the behavior) increased with learning. Interestingly, the number of task-relevant neurons decreased slightly after a few days of practice, suggesting that consolidation of a

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learned motor behavior leads to a sparsening of its cortical representation.

To examine correlates of learning-related changes in movement patterns, Cohen and Nicolelis [35] recorded from primary motor cortex in rats during early stages of a two-choice conditional task, characterized by increased motor stereotypy without manifest associative learning. Comparing the activity of neuronal populations at the beginning and end of this training phase revealed an increase in the firing rate modulation of single neurons around the time of movement initiation, but without a reduction in the firing rate variance to explain increased motor stereotypy. While information about performance available from single neurons did not increase, there was, after practice, a marked improvement in how populations of simultaneously recorded neurons predicted movements, again suggesting that learning-related changes are expressed at the level of neuronal ensembles. Removing the associative learning component altogether, Costa *et al.* [38] analyzed cortical activity during rotarod learning in mice and observed a substantial increase in the number of task-related neurons during the first training session, followed by more subtle changes to the cortical activity patterns as learning progressed. Interestingly, the mean firing rate of the neurons did not change with learning in either of these studies, suggesting a well balanced network that, despite significant functional reorganization, is able to maintain constant levels of activity.

Synaptic correlates of motor learning

The synaptic basis of learning-related plasticity in motor cortex has been explored in rats trained on skilled reaching tasks [52,53]. Using evoked potentials in brain slices as a readout of synaptic strength, these studies found that the strength of inputs to Layer 1 [52] and Layer 2/3 [53] neurons increased with learning. Training animals after plateau performance was reached resulted in no further synaptic potentiation [52], but the initial gains were retained even after months without practice. Moreover, the range over which synapse strength could be modified shifted upward during this time, allowing for new experience-dependent changes to be expressed in the circuit [53].

Structural correlates of motor learning were recently demonstrated by imaging the spine dynamics of cortical pyramidal neurons in mice acquiring new motor skills [54•,39]. Formation of spines was observed already an hour after the first training session [54•] and these new spines were preferentially stabilized during subsequent practice. The degree of spine formation correlated well with behavioral improvement. These learning-induced morphological changes were recently shown to be restricted to neurons directly relevant to the learned task [55••]. Taken together, these studies show that motor skill learning is associated with rapid, but long-lasting, synaptic reorganization in subsets of neurons actively engaged by the learning experience.

The collective picture emerging from studies of motor cortex at the synaptic and circuit levels is one in which motor learning is accompanied by a functional reorganization of cortical networks that establish task-relevant circuits whose dynamics encode aspects of the learned motor behavior.

Role of basal ganglia

Much work on motor learning in rodents is focused on the basal ganglia, a set of forebrain nuclei that interconnect with cortex, brainstem, and thalamus. Well conserved across mammals [56], the basal ganglia have been implicated in a variety of behavioral processes, including reward-based learning, decision making, habit formation, and motor sequence learning. A comprehensive account of studies on these various topics, many of which use rodents and relate to motor control, is beyond the scope of this review (see reviews here [57,58,59••,60]), rather we briefly summarize recent rodent studies directly assaying complex motor learning.

Striatum

Despite much interest in the basal ganglia, a consensus view of their role in motor learning has yet to emerge. Research has mostly been limited to the striatum, and especially its dorsolateral (DLS) and dorsomedial (DMS) parts, which receive inputs from sensorimotor and association cortices, respectively. Selective lesions of DMS and DLS reveal a functional heterogeneity that reflects differences in cortical inputs [57]: DMS lesions preferentially affect tasks that require the formation of sensorimotor associations (e.g. sensory guided action sequences [61]), whereas DLS lesions interfere more with improvements in motor skill and motor output (e.g. rotarod [37•] or self-initiated motor sequences [31]).

Recordings from medium spiny neurons in the striatum support the notion that DMS and DLS are part of two functionally distinct cortico-striatal pathways [62,63,37•,43••]. The extent and time course of the activity changes observed during learning differ across the two regions. Moreover, the learning-related changes in firing depends on the exact paradigm used (e.g. rotarod, conditional T-maze, simple operant task), consistent with striatum being involved in a variety of behavioral, cognitive, and learning processes that are engaged to different extents in the different tasks, and that are processed differently in the two pathways. The changes in striatal firing are likely the combination of learning-induced modifications in the inputs to striatum (e.g. from cortex [38], substantia nigra [43••]) and experience-dependent changes in striatal circuitry [37•]. Blocking plasticity in striatum has been shown, in certain paradigms, to disrupt motor learning [43••,40,64].

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Beyond striatum

Extracting principles of striatal function from these — mostly descriptive — observations has been difficult. Understanding how individual parts of the basal ganglia circuit contribute to its overall function may be helped by identifying and manipulating specific neural cell types, circuits and pathways, something that is becoming increasingly feasible in rodents [15•]. Jin and Costa [43••] used genetic and optogenetic tools to identify cell types in the substantia nigra from which they recorded during the acquisition of self-initiated motor sequences. They showed that neurons in nigrostriatal circuits evolve firing patterns that signal the start and end of learned motor sequences, consistent with the basal ganglia having a role in organizing motor elements into functional units (chunking) [63,65].

Cerebellum and other subcortical structures

When compared with motor cortex and basal ganglia, other parts of the motor system, including the cerebellum, thalamus, and motor related brainstem structures, have received considerably less attention. While the role of cerebellum in simple forms of motor learning [66,67] (e.g. classical eye-blink conditioning, and VOR adaptation) has been extensively explored in rodents, it is unclear how the insights derived from these paradigms generalize to complex sensorimotor learning. Mice should be particularly useful for addressing this issue given the availability of many transgenic lines with specific deficits in cerebellar circuitry [68]. However, interfering with LTD in the cerebellum either by genetic [69] or pharmacological [70] means does not dramatically impair the acquisition of sensorimotor associations or new motor skills, and lesions of the cerebellar–dentate nucleus result only in small learning impairments [71]. The extent to which plasticity in cerebellar circuits is involved in complex sensorimotor learning and the extent to which cerebellar function is required for plasticity in other parts of the motor circuit remain to be established.

Despite being at the intersection of information flow from cortex and cerebellum and providing output to the spinal cord, the motor learning related functions of brainstem structures (e.g. red nucleus, superior colliculus, and reticular formation) have not been explored in any depth. While the density of vital structures in the brainstem makes lesions and other crude manipulations difficult, genetic targeting of specific pathways and mechanisms in these areas holds promise for addressing their role in motor learning.

Beyond the traditional motor system, regions such as hippocampus [72] and prefrontal cortex [73] have recently been implicated in complex motor sequence learning in rodents, though their specific roles need to be further elucidated.

Conclusions

Rodents have, as this review is meant to illustrate, already contributed significantly to our understanding of mammalian motor learning. There are powerful arguments for why these efforts should continue and expand. The most compelling ones are perhaps not specific to motor learning, but relate to the substantial resources and initiatives devoted to understanding mammalian nervous system function through work on mice (e.g. Connectome, Blue Brain Project, Allen brain atlas). This accumulation of knowledge and technology is dramatically increasing the power of rodents as model organisms for linking neural circuits and behavior. Studies relating more directly to the rodent motor system are also being pursued in variety of contexts, contributing to an increasingly more detailed understanding of the anatomy and physiology of the circuits involved in motor learning [74,75].

Methodological innovation and better adoption of existing techniques can also dramatically increase the utility of rodents. Fully automated training systems for reward-based learning will facilitate a systematic functional dissection of neural circuits and mechanism involved in the acquisition of new motor skills and sequences [19]. Improved behavioral monitoring will be similarly crucial. Most motor learning studies in rodents collapse the animal's behavior into a simple binary or scalar metric of performance that does not adequately reflect the complexity of motor output. Continuous tracking of the animals' movements at high resolution will be crucial for correlations with neural data and to evaluate aspects of motor output affected by targeted circuit manipulations. Incorporating movement and force sensors into manipulanda or using inertial sensors on behaving animals [76] is readily available solutions that could quickly penetrate the field. High speed video (Figure 1), combined with sophisticated image processing further increases the resolution of behavioral tracking [77]. Continuous and sensitive measures of motor output have enabled the success of the songbird as a model system, and should have a similar impact on the study of mammalian motor learning.

Much of what we know about the function of the motor system comes from pharmacology and lesion studies. Increasing the temporal and spatial specificities of such circuit manipulations through wider adoption of genetic and optogenetic techniques should also dramatically advance our understanding.

These methodological improvements combined with existing experimental infrastructure and behavioral paradigms position the rodent as a powerful model system with the promise of illuminating mechanistic principles underlying motor learning in mammalian brains.

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