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Review

Parallel contributions of cerebellar, striatal and M1 mechanisms to motor sequence learning

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ABSTRACT

When learning a new motor sequence, we must execute the correct order of movements while simultaneously optimizing sensorimotor parameters such as trajectory, timing, velocity and force. Neurophysiological studies in animals and humans have identified the major brain regions involved in sequence learning, including the motor cortex (M1), basal ganglia (BG) and cerebellum. Current models link these regions to different stages of learning (early vs. late) or different components of performance (spatial vs. sensorimotor). At the same time, research in motor control has given rise to the concept that internal models at different levels of the motor system may contribute to learning. The goal of this review is to develop a new framework for motor sequence learning that combines stage and component models within the context of internal models. To do this, we review behavioral and neuroimaging studies in humans and neurophysiological studies in animals. Based on this evidence, we present a model proposing that sequence learning is underwritten by parallel, interacting processes, including internal model formation and sequence representation, that are instantiated in specific cerebellar, BG or M1 mechanisms depending on task demands and the stage of learning. The striatal system learns predictive stimulus–response associations and is critical for motor chunking. The role of the cerebellum is to acquire the optimal internal model for sequence performance in a particular context, and to contribute to error correction and control of on-going movement. M1 acts to store the representation of a learned sequence, likely as part of a distributed network including the parietal lobe and premotor cortex.

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1. Introduction

When making a jump shot from 15 feet out, a basketball player seamlessly performs a sequence of actions – set, jump and release

– that must be perfectly coordinated to put the ball through the hoop. To execute the shot, the player must order the movements correctly, but most importantly, optimize the timing, force and trajectory of the individual components. When an athlete first learns

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the shot, the sequence of movements is disjointed, poorly controlled and requires enormous attention to execute. After many hours of practice, the individual components become smooth, efficient and can be executed on the fly, even in the heat of a game.

The kinds of complex sequences performed in professional sports or music are difficult to study in the laboratory, but over the last 15–20 years neuroscientists have used simpler tasks to examine how humans learn motor sequences, and the brain mechanisms that underlie this learning [1–7]. Behavioral studies have generally agreed that sequence learning occurs in partially separable stages: an early phase where changes are rapid, a consolidation phase where the sequence becomes resistant to interference, and a slow-learning phase where movement timing, kinematics and dynamics are optimized [8–10]. Brain imaging and other neurophysiological studies in animals and humans have identified the major brain networks involved in sequence learning, including motor and premotor regions, basal ganglia, cerebellum and parietal cortex [3,4,6,7,11]. Models attempting to link these brain mechanisms to different stages of learning have recently been developed, and propose that distinct cortico-striatal and cortico-cerebellar loops are associated with learning at different stages [3,4]. These models use a general cognitive framework, and take less account of theories of motor control. Other models of motor sequence learning have also focused on the contributions of striatal and cerebellar circuits, but have linked them to learning of different components of performance, such as spatial location and speed [2,6]. These component models have not been widely extended to neuroimaging data in humans, and do not include learning of other motor parameters such as velocity, force and timing. Finally, data from the field of motor control and motor adaptation have generated detailed information about how internal models at different levels of the motor system (i.e., cerebellum and parietal cortex) may contribute to learning by integrating motor and sensory information to update existing motor programs or create new ones [11–13]. Theories incorporating internal models are highly influential in the domain of motor control and adaptation, but have not typically been integrated into theories of motor sequence learning. Therefore, the goal of the present review is to integrate stage and component models of motor sequence learning, and to frame this in terms of the contribution of brain networks instantiating internal models. To do this, we will review behavioral and neuroimaging studies that demonstrate that sequence learning can be separated into spatial/sequential and motor control components [6,14–18], and that show that learning of these components is supported by different brain mechanisms [19–23]. Finally, we will show how learning of different components can be understood in terms of the contributions of internal models to error processing and representation of learned sequences. Based on our own data, we will give an example of how the contributions of these mechanisms change with learning in the cerebellum, striatum and M1. Finally, we present a model proposing that sequence learning is underwritten by parallel, interacting processes, such as error correction, internal model formation, stimulus–response association and sequence representation, that are instantiated in specific cerebellar, striatal or M1 mechanisms. Therefore, the ensemble of regions that are engaged at a particular phase of learning depends on task demands that call upon these specific mechanisms.

2. What is motor sequence learning?

Motor sequence learning is the acquisition and optimization of a novel series of inter-related movements. During initial acquisition the order of movements is learned and with continued practice the motor parameters are optimized, resulting in accurate and

efficient performance. A large number of studies have addressed how sequence order is acquired, focusing on implicit and explicit learning mechanisms [1,7]. However – as in the example of the jump shot – we believe that the fundamental problem for the motor learning system is not simply acquiring the order of movements, but in optimizing the entire sequence for successful performance.

Most studies of motor sequence learning examine the acquisition of novel sequences of simple movements and look for changes in accuracy of the sequential order and improvements in speed. Sequence learning is often contrasted with motor adaptation, where a known movement is adapted to a changed environment, as in learning to drive a new car or adapting to physical changes following an injury. Although this review is focused on motor sequence learning, we will integrate some relevant experimental and theoretical information from studies of motor adaptation.

The most common paradigm for studying motor sequence learning is the serial reaction time task (SRT) in which participants learn a sequence of key-press movements in response to a visual cue [7,24]. Improvements in performance on this task are measured by decreases in the number of errors and shortening of reaction time. A related task, where subjects learn to tap a series of locations on a square grid ($2 \times N$), was developed for testing sequence learning in both animals and humans [25,26]. Another commonly used task is the finger-to-thumb opposition task, in which participants practice a short sequence of finger-to-thumb movements with the goal of performing as quickly and accurately as possible [27]. Finally, other tasks have been developed to test learning of a sequence of reaching movements [15,28], force-pulses [29,30], and eye movements [31,32].

Learning in motor sequence tasks is generally assessed in terms of changes in the number of errors, changes in reaction time (RT) in response to a cue, and/or in the overall time to execute the sequence. In most tasks, improvements in error occur relatively rapidly, while RT improves more slowly. Error is usually operationalized as the wrong movement at the wrong time, but in some tasks it may represent overall deviation from a desired movement profile [28–30]. Changes in RT with learning can be absolute, as in the finger-to-thumb opposition task, where change in the speed of execution of the entire sequence is measured, or relative, as in the SRT, where changes in RT for a learned sequence are compared to performance of an equal-length sequence of randomly cued responses.

A significant theoretical issue in this domain is how to separate changes in learning of the sequence of responses *per se* from changes in implementation or performance that occur with practice [7,33,34]. A newly acquired sequence of movements is slow, inaccurate, and jerky, whereas a well-learned sequence is fast, accurate and smooth. Therefore, if performance changes with practice, it is difficult to know whether this change is related to an enhanced neural representation of the sequence or simply to more efficient implementation. A number of different methods have been used to try to control for changes in performance including: comparison with a baseline matched for speed [34]; fixed timing [21–23,27,35] and using a distractor task to prevent changes in performance during learning of the sequence [33,36]. These types of controls are critically important to assessing changes specific to the representation of the sequence. However, they do not address another basic issue, which is that in motor learning, changes in performance are changes in learning. The problem in perfecting a jump shot is not primarily whether to jump or shoot first, but in executing the sequence skillfully enough to get the job done. What the brain must encode during learning is not just a representation of the sequential order of movements, but a set of optimal movement implementation parameters. Learning of sequences and the adaptation of movement likely occur simultaneously [20,37]. In this review, we propose that acquisition and representation of sequential order and

motor optimization are partially separable, but that the learned sequence is a dynamically changing, integrated representation.

3. Implicit vs. explicit learning

Within the field of motor sequence learning, there is long tradition of research focused on separating the behavioral and neural correlates of implicit and explicit learning. This originated with the finding that amnesic patients, like HM, showed preserved motor learning [38,39]. Subsequent research has systematically examined the hypothesis that motor learning predominantly taps the implicit or procedural memory system and does not require explicit processing [1,7]. These studies use tasks where explicit awareness of the sequence is restricted such that only implicit mechanisms can operate. Explicit control of learning is minimized by using concatenated sequences [24], dual-task paradigms that distract attention [33,36], or learning of higher-order sequences that cannot be identified explicitly [40]. In these tasks, what is likely learned is the probabilistic association of a series of motor responses based on preceding responses and/or the cuing stimuli. Some brain imaging and patient studies have suggested that the BG system plays a specialized role in implicit learning; and its contribution has been hypothesized to be based on striatal mechanisms involved in associative learning [7,41–43]. Other models propose that during explicit learning anterior frontal lobe is engaged early, with motor cortical regions engaged later, and that conversely, during implicit learning, motor cortical regions are engaged early, with frontal regions implicated later [1].

This work has generated important information about purely implicit mechanisms for acquiring a sequence of responses, but in most real-world situations motor learning is not purely implicit. When we learn to tie our shoes, we learn the sequence of movements through both more explicit (teaching) and more implicit (practice) means. However, we also learn in ways that combine both, such as observation and trial and error. Practice then produces improvements in execution through relatively implicit or procedural means. Thus, the movement sequence is acquired through both implicit and explicit means, but what is acquired largely implicitly is the set of motor control parameters required for skilled performance.

Another issue not usually addressed by studies focused on separating implicit and explicit processing is that particular behavioral measures of learning may tap into more or less explicit/implicit aspects of performance. Stimulus–response associations, such as cue–response mapping or spatial location, are more open to explicit control, whereas optimization of movement parameters such as speed, timing and co-articulation are largely implicit. Finally, and most importantly, the contributions of implicit and explicit control factors may change across learning depending on task demands.

As will be described below, we and others have begun to separate different components of learning that rely on more or less explicit and implicit processes [11,15,19,20,25]. However, we will argue in this review that a comprehensive model of motor skill learning should include an integrated contribution of both explicit and implicit processes.

4. Theoretical models of motor sequence learning

Models of motor sequence learning have generally converged around the concept that there are separable stages of acquisition that can be identified from behavioral data and that are under the control of specific brain networks [6,7,11,27,35,44] (Fig. 1). First, there is an early phase where improvements in performance are rapid and explicit executive control and memory processes may be required. Then, there is a consolidation phase where performance may show incremental improvements and/or become resistant to interference. Consolidation is thought to be dependent on both sleep and the passage of time [45–48]. Third, there is a slow learning phase where performance is optimized. This phase is also described as the “automatization” phase, based on the idea that with extended practice performance becomes less attentionally demanding and/or can be performed entirely implicitly [4,35]. Delayed recall of motor sequences has been less frequently examined, but studies that have tested retention have shown that performance is often surprisingly robust over long periods of time [17,21,49,50]. These putative stages of motor sequence learning are identifiable in many behavioral studies, but how well the pattern of performance changes fits the stage model is quite variable and task-dependent.

Based on this general pattern of behavioral findings, Doyon has developed an influential model (see Fig. 1, Panel A) where changes in performance across stages of learning are framed in terms of the differential contributions of cortical–cerebellar and cortical–striatal loops [3,4,51]. In this model, early rapid changes in performance are attributed to both cortico–cerebellar and cortico–striatal mechanisms. Learning during the early stage also includes possible contributions from frontal and hippocampal executive control and memory mechanisms in tasks where learning is under explicit control. Following early learning, striatal mechanisms are proposed to contribute specifically to consolidation of learned sequences. Finally, sequence retention is hypothesized to be supported by a network including the striatum, motor and parietal cortices. This model also addresses learning in motor adaptation tasks, and its strength is that it proposes global mechanisms that contribute to specific stages in both sequence learning and adaptation tasks.

In contrast, other theories of motor sequence learning have focused on understanding the neural mechanisms required to

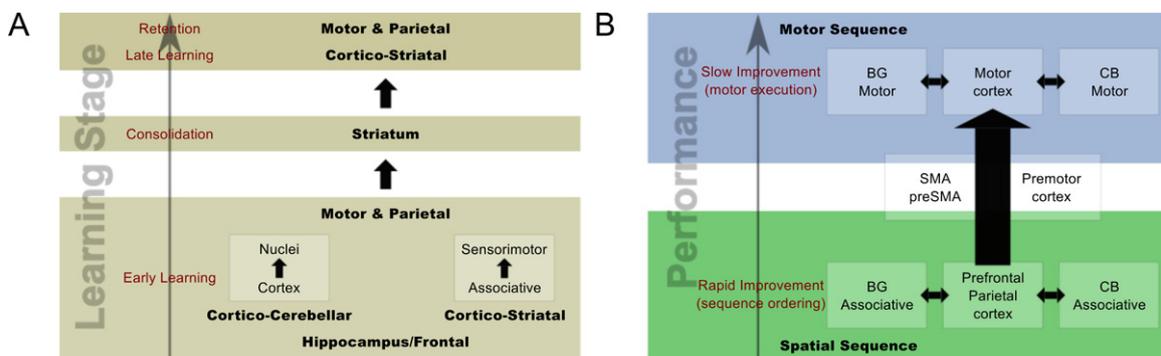


Fig. 1. This figure illustrates the stage (Panel A) and component (Panel B) models of motor sequence learning. These illustrations are adapted from similar figures from Doyon et al. [3] and Hikosaka et al. [6]. Both figures have been adapted to focus on structures relevant for motor sequence learning.

learn different task components; separating learning of the spatial/sequential/kinematic order of movements and learning of movement dynamics, such as speed, timing and sensorimotor integration [2,6]. Hikosaka and colleagues have proposed that learning of these components proceeds in parallel, but that they have different times courses and are controlled by different cortico-striatal and cortico-cerebellar loop circuits (see Fig. 1, panel B). They suggest that the spatial/sequential/kinematic component, expressed in terms of accuracy, is learned more quickly and is under more explicit control. This component is dependent on circuits linking frontal, parietal and premotor regions with caudate and lateral cerebellar association areas. On the other hand, the dynamic/motor control component, expressed in terms of changes in speed and other motor parameters, occurs more slowly and is under less explicit control. Learning of this component is controlled by circuits linking motor cortical regions with the putamen and midline cerebellar regions. In addition, they propose that reward-based learning in striatum and error-based learning in cerebellum would contribute to shaping responses. This model predicts that performance improvements during early learning are dominated by circuits mediating spatial/sequential learning (based on more explicit reward-based learning) while those of later learning are predominantly influenced by mechanisms more relevant for motor optimization (based on error-based learning). More recently, stage theories have begun to incorporate ideas from component models [17,23,34] and in this review we propose a model where stages of learning are understood in terms of the differential rate of acquisition of specific components depending on task demands.

5. Behavioral evidence for different components of motor sequence learning

Research on motor skill learning in our laboratory has focused primarily on understanding the neural mechanisms important for optimizing performance, rather than on those required to learn sequential order. In other words, we are interested in understanding how the athlete perfects the jump shot once the sequence of movements is known. To do this, we have used a variety of tasks where the sequence to be learned is more or less explicitly available, and have focused on changes in motor performance. We have drawn on both the stage and component models

of learning in our studies of younger and older adults, children, and trained musicians. Overall, our findings support the idea that there are partially separable behavioral components in learning, and that these components are controlled by distinct brain mechanisms. In the following section we review evidence that shows that the spatial/sequential vs. motor control components of learning show different time-scales of acquisition, are more or less susceptible to delay, show differential changes across development, and are differently affected by musical training. In the second section, we review brain imaging data that demonstrate that different brain networks may contribute to learning of these components. Finally, based on these data, we will try to integrate the stage and component models into a framework for motor sequence learning. This framework is centered on the idea that there are parallel interacting contributions of cerebellar, striatal, or motor cortical mechanisms depending on the stage of learning and the component of the sequence being learned.

We have used two different variants of the SRT in our laboratory. The timed motor sequence task (TMST; see Fig. 2, panel A) requires participants to tap in synchrony with a complex 10-element sequence of short and long duration visual cues [17]. Performance gains on this task are assessed by comparing the learned sequence with a simple sequence that contains the same number of short and long duration taps. This task requires only a single finger response, allowing us to assess optimization of a sequence of movements that does not include spatial processing. The multiple finger sequence task (MFST; see Fig. 2, panel B) is very similar to the SRT, where participants reproduce a 10–13 element sequence in response to a set of visual cues using four fingers of the right hand [16,52]. Performance gains on this task are assessed by comparing the learned sequence with a random baseline. Finally, we have used an auditory rhythm synchronization task to allow us to generalize beyond the visuomotor synchronization domain to musical rhythm production [53]. For both tasks performance is measured in terms of accuracy (i.e., the correct order of responses) and response synchronization (i.e., how well responses are synchronized with the stimuli). We consider the accuracy measure to represent the sequential/spatial component of the task that is more directly under explicit control, and the synchrony measure to represent the motor control component of the task that is less directly under explicit control. The duration of stimuli and interstimulus intervals remain fixed in these tasks to

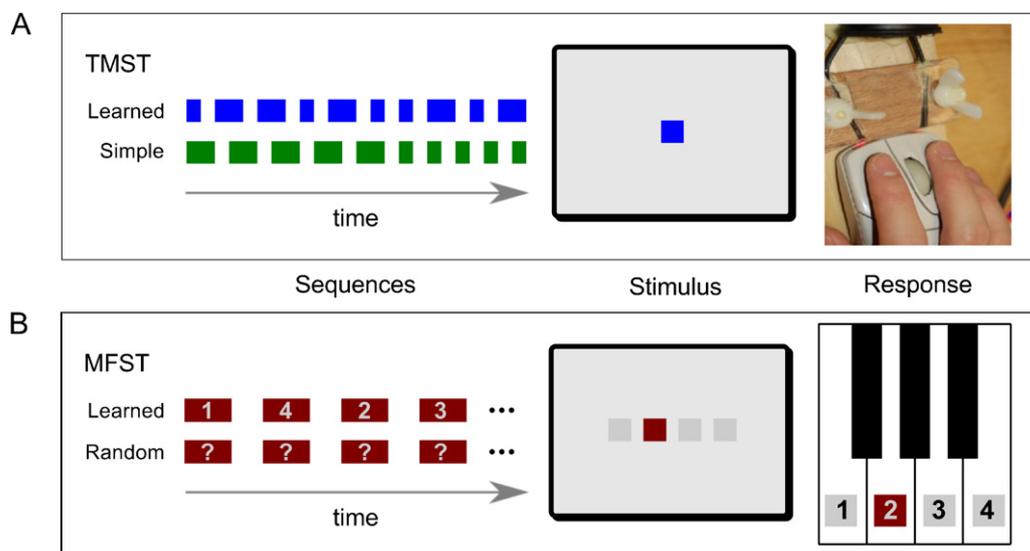


Fig. 2. This figure illustrates the TMST (Panel A) and MFST (Panel B) sequence learning paradigms developed in our laboratory. The sequence types, visually presented stimuli, and response methods are shown.

ensure that changes in synchronization performance that occur with learning are not related to overall changes in movement speed.

Based on work in both animals and humans, Hikosaka et al. [6] proposed that the sequential/spatial component of a sequence was learned more rapidly than the motor control component. Consistent with this, across different studies using both the TMST and MFST, we have found that gains in accuracy reach a plateau after 2–3 days of training whereas synchronization continues to change across additional days of practice. Why might there be differences in the time-frame of learning of these two components? First, accuracy may be easier to learn because the cue and the response in this domain have a direct one-to-one mapping, even in the TMST where the association is between a time interval (short or long) and the response. In contrast, mapping of a well-synchronized response is less direct, with many motor parameters such as timing, velocity and force contributing to performance. This is consistent with behavioral and neuroimaging studies showing that complexity of stimulus–response associations affects sequence learning [54]. Differences in the time-frame of learning may also result from the simple fact that without an accurate spatial/sequential profile, motor control components cannot be optimized [15]. Interestingly, our results show that this is true for learning a sequence with no

spatial component. This is also consistent with evidence from adaptation learning indicating that there are interacting fast and slow components of learning [55].

In long-term learning studies in animals, Hikosaka also showed that the two components of performance were retained differently [25]. Consistent with this, we varied the length of delay between learning and recall of the TMST from 1 to 6 weeks (Fig. 3, Panel A). We found that while all delays affected synchronization performance, only the longest delay affected accuracy [17]. This indicates that the spatial/sequential component is better retained, and that the motor control component requires on-going practice for maintenance. These findings make sense if we again think of the spatial/sequential component as more explicit, with a one-to-one mapping that is easier to recall. In contrast, the motor control component is less explicit and requires integration of multiple parameters for accurate performance and thus is more susceptible to degradation or interference with delay.

Further evidence for the separability of different components of learning comes from a study in which we tested three groups of children (ages 6, 8 and 10) on the MFST across two days of practice [16] (Fig. 3, Panel B). All age groups were able to learn the task, and similar to adults, accuracy improved more quickly than synchronization. For the accuracy measure, we found that after

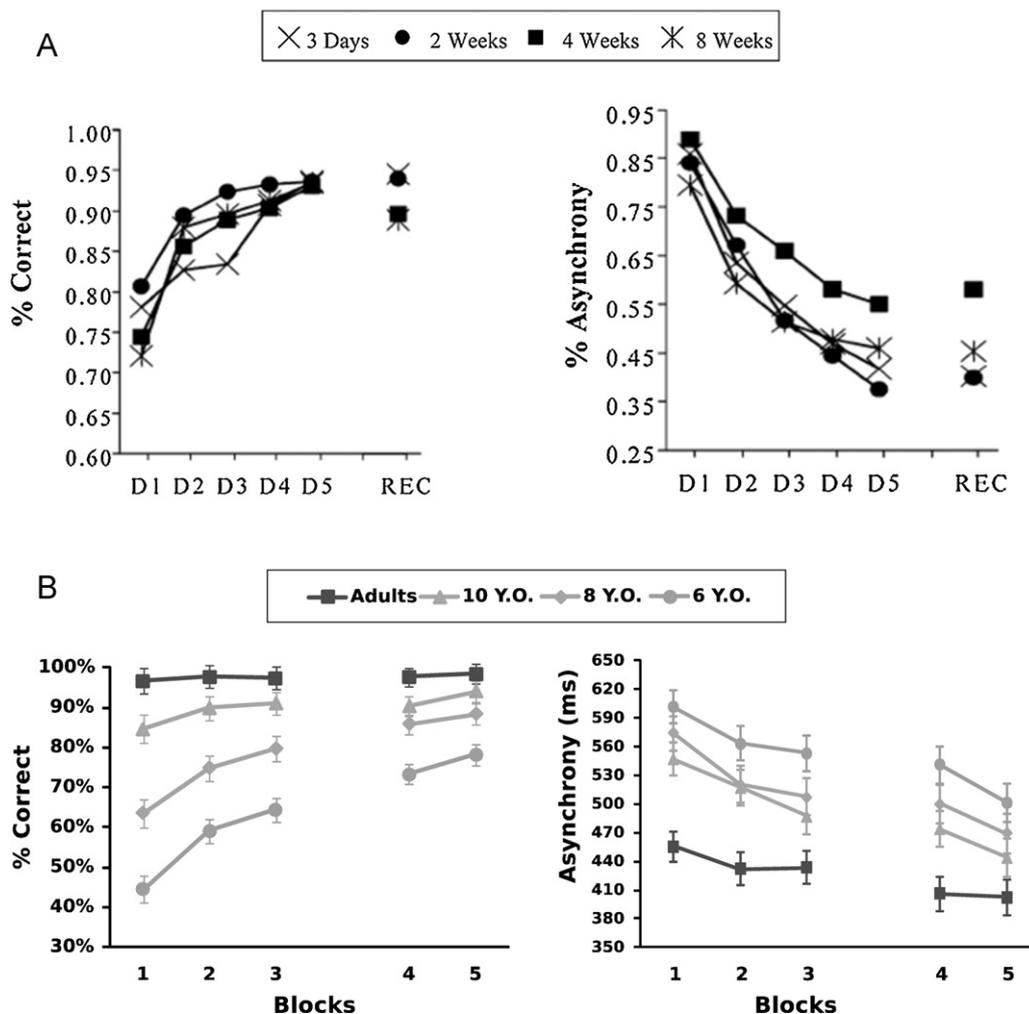


Fig. 3. TMST and MFST behavioral findings. Panel A shows the results of experiments examining the effect of variable delay on retention of the TMST in young adults [17]. Results showed that percent correct performance (left) is affected only by the longest delay, whereas response synchronization is affected by all delays (right). Panel B shows the results of an experiment examining learning of the MFST in 6, 8 and 10-year-old children compared to adults [16]. Results showed that for percent correct performance (left) only 6-year-olds performed worse than adults by the end of the second day of practice, whereas for response synchronization (right) all children still performed worse than adults at the end of the second day.

two days of practice all except the youngest group were able to perform at adult levels. In contrast, for synchronization, all children performed less well than adults throughout training. These results suggest that the brain mechanisms required for learning of the sequential/spatial component of the task develop earlier than those required for motor control and optimization.

Finally, in a series of experiments assessing the impact of musical training on sequence learning, we compared the performance of musicians and non-musicians on both the TMST and an auditory rhythm synchronization task. For auditory rhythm synchronization, the results showed that non-musicians could perform as well as musicians on the sequential component of the task, but that musicians outperformed non-musicians on the motor synchronization component of the task [56]. In addition, we showed that musicians who began training before age seven out-performed musicians who began training later for the motor, but not the sequential, component of the task [14,18]. Taken together, these results indicate that the spatial/sequential component of motor learning is less affected by the age of onset of training than the motor control component.

A final example of the dissociation between the sequential and motor components of learning comes from a study using a sequential reaching task [15]. To assess learning of the sequential order of reaches, the authors measured the number of anticipatory responses to the target location – reasoning that an anticipatory response indicated some explicit information about the location of the upcoming target. To assess the motor control component of learning they measured the accuracy of the reach trajectory, measuring smoothness and variability. Their results showed that the sequential component was acquired more quickly, and that the motor component continued to improve even after the sequence was explicitly known. Further, they showed that these measures were differentially affected by consolidation and interference.

Combined with our findings on the effects of delay [17], these results support the idea that the motor control component of sequence learning can show an almost infinite degree of optimization with practice, but that it requires continuous updating for maintenance. This explains why professional athletes and musicians practice every day, even though they know the explicit sequence of movements by heart.

6. Neuroimaging evidence for stages and different components of motor sequence learning

Over the last ten years, a large number of neuroimaging studies have examined how cortical and subcortical motor regions contribute to sequence learning. These results converge in showing the involvement of motor cortical, striatal and cerebellar networks, but do not provide consistent evidence for dissociable contributions of these systems to specific phases of learning. The most consistent finding is decreasing cerebellar activity with learning [21,22,29,30,57–59], with some studies showing increasing activity in the cerebellar nuclei as early learning progresses [29,30,57,58]. In contrast, however, studies of tool-learning have demonstrated increases in cerebellar activity as expertise is acquired [60–62]. For the striatum, the majority of studies show increases in activity with extended practice [21,22,57,58], but the time-frame of increases varies considerably across studies (from hours to days) and some studies have also shown decreases with learning [29,59]. Finally, activity in motor cortex has also not been clearly linked to specific stages of learning, with some studies showing decreasing activity with practice [36,59] and others showing increasing activity [21–23,27,35].

In order to test the contributions of these different motor networks to sequence learning in a more systematic way, a series of

neuroimaging studies from our laboratory have examined learning of the TMST both within and across multiple days of practice, as well as at delayed recall. The goal of these experiments was to identify the brain networks engaged at different stages of learning, and to attempt to separate regions engaged by the sequential and motor control components of learning. The first experiment used positron emission tomography (PET) to study learning of the TMST on the first day of training, after five days of practice and at one-month delayed recall (Fig. 4, top panel) [21]. On Day 1 of learning, greater activity was observed in bilateral cerebellar cortex for the trained sequence. When comparing Day 5 to Day 1, results showed decreased activity in the cerebellum, with increased activity in the putamen. Comparing Recall to Day 5 revealed greater activity in M1, premotor, and inferior parietal cortex. We interpreted these results as indicating that during early learning cerebellar mechanisms are involved in adjusting movement kinematics according to sensory input to produce accurate motor output. Further, we hypothesized that during late learning the BG might be involved in automatization, and that at delayed recall movement parameters appeared to be encoded in a distributed motor cortical representation.

To test the hypothesis that decreases in cerebellar activity were specific to early learning, and to assess whether these changes were related to changes in the sequencing or motor control component of the task, a second experiment examined TMST learning across three blocks of practice on a single day [22] (Fig. 4, middle panel). Similar to the previous across-day results, we found that activity in the cerebellum was greatest for the first block of practice and decreased with training. Unexpectedly, at the end of training on Day 1 we saw increases in activity in putamen and M1, similar to those observed after five days of training and delayed recall in the previous experiment. The finding that the same regions were active across very different time frames of learning suggested that different stages of learning were underwritten by similar brain mechanisms. Further, behavioral regression analyses showed that activity in the lateral cerebellar hemispheres and M1 was correlated with changes in performance for both the sequence and motor control components of the task. Most importantly, inter-regional correlation analyses showed that activity in M1 and cerebellum was correlated during learning, suggesting that interactions between these regions were directly related to learning (Fig. 4, bottom panel).

In order to test the hypothesis that similar motor networks are engaged across different stages of learning, we used fMRI to examine learning of the TMST across five days of practice [23] (Fig. 5). Consistent with our previous findings, activity on Day 1 was dominated by the cerebellum, bilateral caudate, and pre-motor regions. Across days of learning, as performance improved, activity in these regions decreased while activity in the hippocampus, frontal cortex, and putamen increased. Importantly, within the context of these global decreases, we found specific regions of left M1 and right cerebellar VIII A/VII B that were positively correlated with improvements in synchronization performance. In parallel, improvements in accuracy were correlated with increases in hippocampus, BA 9/10, and the putamen. Thus, changes in accuracy and synchronization were found to be related to two different sets of brain regions, suggesting that these networks optimize different components of learning. Specific increases in sensorimotor cerebellar cortex are a relatively novel finding for motor sequence learning, but are consistent with evidence for the development and refinement of internal models within the cerebellum [60–62]. In addition, we also found that activity in M1 on Day 1 was predictive of gains in performance between Days 1 and 2; consistent with previous findings [36,63]. Finally, we showed that correlated activity between M1 and the cerebellum was greater on Day 5 than Day 1, suggesting that M1 and the cerebellum form an integrated representation of the well-learned sequence.

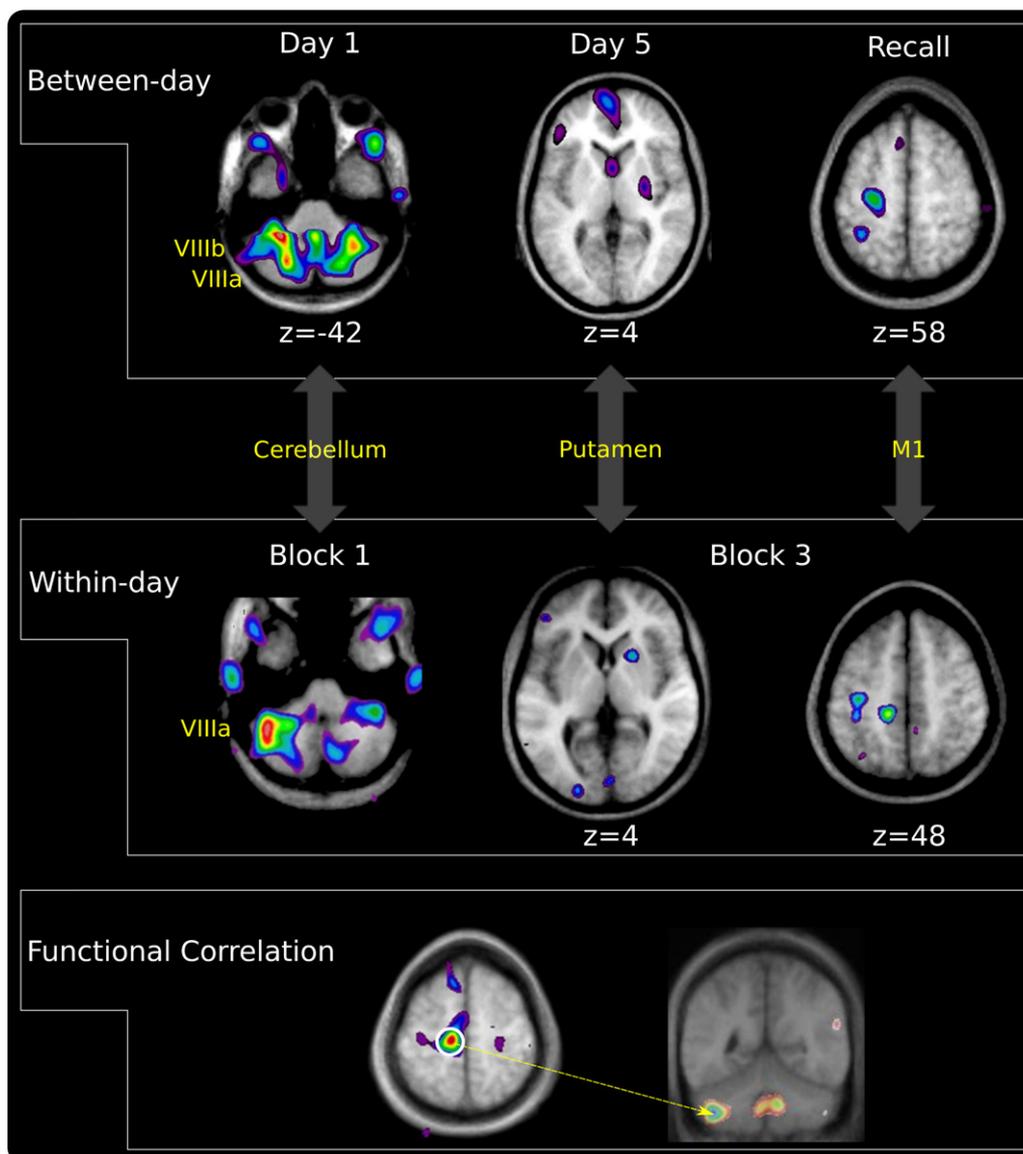


Fig. 4. Results from two PET studies examining TMST learning across days of learning and at delayed recall (top panel) [21] and within a single day of learning (middle and bottom panels) [22]. The top and middle panels demonstrate the similarity between the cerebellar, BG and motor cortical regions found to be active across and within days of learning. The bottom panel shows the functional correlations observed between activity M1 and cerebellum, where greater activity in M1 was related to decreased activity in the cerebellar cortex.

The combined results of these three experiments clearly show that the cerebellum, striatum, and motor cortical regions are all engaged in motor sequence learning, but that their contributions are likely not confined to particular stages. Further, they show that cerebellar–M1 interactions are directly related to learning, and that both M1 and the cerebellum may encode long-term representations of learned sequences. In the next section we discuss specific cerebellar, striatal, and M1 mechanisms that are involved in learning. We will then present an integrated framework describing how these mechanisms might work together to underwrite learning of different sequence components across multiple stages of acquisition.

7. What does the cerebellum do? – forward models of the sensory consequences of action

The cerebellum receives sensory and motor information from both descending cortical pathways and ascending peripheral pathways [64–66]. In addition, recent evidence has shown strong

connections to the parietal, premotor and frontal cortex [67–69]; pathways that are more prominent in humans than in other primates [70]. Based on the unique architecture of the purkinje cell – climbing fibre – parallel fibre circuit, the cerebellum has been hypothesized to participate in processes related to sensorimotor integration, error correction and the formation of internal models. The dominant current hypothesis about of the role of the cerebellum in motor control is that it instantiates internal models that facilitate optimal performance and learning (For reviews, see: Refs. [11,12,71–73]). An internal model can be defined as a set of input-output relations between motor commands and their sensory consequences. Input to the model is the efference copy of a motor command and output is the predicted sensory consequences of that action.

Internal models are hypothesized to be critical for motor learning because they allow for a comparison between the predicted and actual consequences of a movement, and thus for the assessment of movement error that is used to guide learning. Internal models in the cerebellum are thought to be instantiated in the purkinje cell

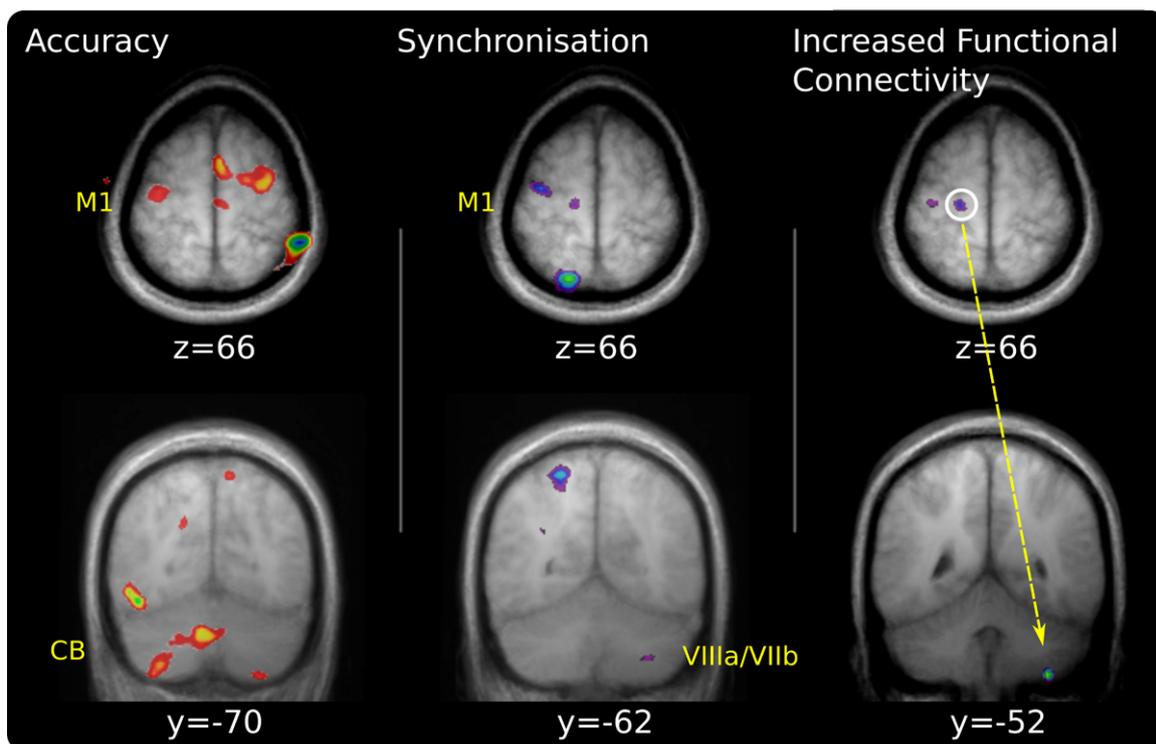


Fig. 5. Results of an fMRI study of across day learning of the TMST [23]. Panel A shows specific M1 and cerebellar regions where activity was correlated with percent correct performance. Panel B shows specific M1 and cerebellar regions where activity was correlated with response synchronization performance. Panel C shows the region of M1 where activity on Day 1 of learning predicted the degree of consolidation-related performance gain on Day 2. The regions of M1 and cerebellum that showed increasing functional connectivity between Day 1 and Day 5 are also shown here.

– parallel fibre complexes, where information about motor plans (efference copy) arrives from the cortical motor system. The climbing fibre system communicates error signals from the inferior olive that code discrepancies between planned and executed movement, and is hypothesized to “teach” or modify the existing internal model during learning. Evidence that cerebellar circuitry has the capacity to instantiate internal models comes from neurophysiological studies and computational modeling of cerebellar circuits (For review, see: Refs. [71,74]). Intriguingly, recent evidence from fMRI studies of human rule-learning suggest that cerebellar–frontal circuits may be involved in automatizing or developing internal models of cognitive behaviors, similar to the way cerebellar–motor circuits are involved in motor learning [75].

Evidence that cerebellar circuits are relevant for skill learning comes from a range of experiments in animals and humans. A study using genetically modified mice with deficiencies in cerebellar function showed that they could learn to swim to a target, but could not optimize their movement trajectories [76]. Experiments in rats learning a skilled reaching task showed expansion of the paw representation in cerebellar cortex [77–79]. Work in patients with cerebellar lesions shows that they can adapt their movements on-line to respond to a perturbation, but they cannot learn from previous errors [80,81]. Most persuasively, two recent brain stimulation experiments have demonstrated the role of the cerebellum in state estimation – a function closely related to internal models. In the first study, Miall et al. [82] showed that TMS over the cerebellar cortex impaired the accuracy of reaching movements that depended on state estimation for accuracy. In the second study, Galea et al. [83] showed that tDCS over the lateral cerebellum enhanced learning of a visuomotor rotation task by promoting a more rapid decrease in error. Finally, in a recent fMRI study Grafton [84] decomposed learning on a sequential reaching task into different components, including a specific measure of error correction. Decreases in error correction across trials were

related to decreases in activity in cerebellar cortex. This is consistent with the global decreases in cerebellar activity observed with learning in a large number of neuroimaging studies, including our own [22,23,30,36,57,84]. Taken together, these results strongly support the hypothesis that cerebellar mechanisms are important for modeling the sensory consequences of action and for using this information to compute error signals relevant for learning.

Another important hypothesized role of the cerebellum in motor learning is the storage of internal models of learned skills, such as manipulating a new tool or learning a visuospatial transformation. In an elegant series of studies, Immamizu et al. [60–62] showed specific changes in cerebellar cortex as participants learned to use a new tool. As described above, fMRI results from our lab also showed specific increases in lobule VIII after long-term training on the TMST [23]. The activation of lateral cerebellar regions that connect to the frontal lobe during performance of a well learned sequence may also be related to their contribution to the learning and representation of internal models of sequence rules [75,85]. Despite these findings indicating a role for the cerebellum in long-term representation of a motor skill, it does not appear to be required for motor memory, or storage of the motor program itself. First, cerebellar lesions do not result in the loss of specific skills, but rather cause incoordination, dysmetria and slowing (For review, see: Ref. [81]). Second, the TMS study described above [82] shows that disruption of the lateral cerebellum during reaching does not halt movement, but rather appears to disrupt the estimate of the location of the arm in space. Finally, Grafton et al. [84] showed that a measure of feedforward control, that was taken to represent the acquired internal model for the movement, was related to activity in motor cortex but not the cerebellum. Overall, current data do not support the hypothesis that the cerebellum is the site of storage of an internal model of learned skill. However, as will be discussed further below, it may be the case that the cerebellum is part of an extended network where motor cortical regions serve to store the

representation of a learned skill while associated cerebellar–cortical regions store information about the optimal motor control parameters for performance of that skill within a particular context.

The idea that the cerebellum might contribute to the long-term representation of motor skill is supported by evidence of structural changes in the cerebellum related to learning. In the rat, skill learning is associated with changes in the microstructure of cerebellar cortex [79,86]. In humans, trained musicians show greater grey matter density in cerebellar cortex than non-musicians [87]. Recent work from our lab has also shown that grey matter concentration in the cerebellum is related to the slope of learning on the TMST in regions similar to those observed in the fMRI study with the same subjects [88]. Consistent with this, Della-Maggiore et al. [89] found that white matter integrity in the cerebellum was related to learning of a visuomotor adaptation task.

8. What does the striatum do? – probabilistic learning and movement chunking

The BG are a set of subcortical nuclei with prominent connections to the motor system that send and receive information from cortical and subcortical regions. The most critical structures for motor sequence learning are in the striatum, which is comprised of the caudate nucleus, putamen, and the globus pallidus – the main output nucleus of the BG. Pathways connecting different cortical regions to the striatum are spatially segregated and hypothesized to operate as closed-loop circuits [90–93]. The striatum itself can be roughly divided into three sub-regions: the anterior–medial striatum – composed of the most anterior portions of the caudate and putamen; the dorsolateral striatum – composed of the more posterior and lateral caudate and putamen; and the ventral striatum – composed of the nucleus accumbens and the most ventral portions of the caudate and putamen [90,94]. The anterior–medial striatum is more strongly connected with frontal and pre-motor cortices. This “associative” circuit has been proposed to be involved in response selection and evaluation of outcome or reward. The dorsolateral striatum is more strongly connected to the sensorimotor and parietal cortices. It has been defined as the “sensorimotor” circuit, and has been proposed to be important for encoding motor associations, chunks or “habits” [90]. Interestingly, recent neuroanatomical studies in primates have shown that there are multi-synaptic pathways linking the cerebellum and BG [95,96]. The presence of these connections suggests that the independent contributions of the cerebellum and striatum to motor learning may be partially integrated.

Stage models of motor sequence learning propose that the associative and sensorimotor circuits of the striatum contribute differentially to the early and late phases of learning. The associative circuit has been hypothesized to be more important for early learning when executive control demands are greatest, and the sensorimotor circuit is more relevant for later learning when executive demands have decreased and motor control dominates [3,4,58,90]. There is evidence to indicate that the striatum is involved in motor memory consolidation [31,47,97], and some have proposed that it is involved in the storage of learned sequences [3,4,30,42]. However, the contribution of the striatum to long-term retention is controversial. Striatal lesions do not typically result in the inability to perform well-learned sequences, but rather impair new learning [98], or produce decrements in movement adaptation [80] or speed of response [99,100]. Importantly, a recent study in macaque monkeys [101] showed that inactivation of the output nucleus of the BG produced no deficits in retention of an over-learned sequence, although it did produce slowing and decreased movement amplitudes.

The BG have frequently been proposed to play a specific role in implicit sequence learning [36,42,102–105]. However, some studies show that there is considerable overlap in striatal contributions to both implicit and explicit learning [105–107]. Further, the results of studies of implicit learning in patients with Parkinson's disease are inconsistent, with some studies showing deficits [98] while others do not [99,108].

The possible contribution of the ventral striatum in motor sequence learning is largely unexplored. There is substantial evidence to support its involvement in probabilistic reward-based learning [109]. Some have suggested that this is a more general role of the striatum, and that its contribution to motor learning might be in learning probabilistic or predictive associations between a series of responses at least in part through reward-based mechanisms [11,90,94]. However, real experimental evidence linking reward-based mechanisms to motor learning is lacking.

A related proposal for the role of the BG in motor sequence learning is that it associates multiple movements into groups or chunks [90,110,111]. Chunks are subgroups of movements within a sequence that are usually defined by shorter RTs among members of the subgroup compared to RTs between subgroups [112]. Chunking is thought to index the development of efficient, co-articulated movements within a sequence [90,111,113,114]. It is characteristic of over-learned sequences, and is thought to be important for learning and maintaining longer and more complex sequences because it confers a memory advantage [112,115]. Depletion of dopamine in the BG of rats and monkeys results in impairments in the development and stability of movement chunks, but does not impair the expression of chunks in well-learned sequences [111,116,117]. Similarly, patients with Parkinson's disease [118] and basal ganglia stroke [119] are impaired in chunk acquisition. Consistent with this evidence, a recent fMRI study showed that activity in dorsal–lateral striatum was related to chunking in a finger sequencing task [20]. Finally, multiunit recording work in rats has shown that as T-maze learning progresses the response of striatal output neurons becomes tuned to the beginning and end of the sequence of movements – indicating that corticostriatal circuits represent the sequence as one or more chunks rather than as a series of individual movements [120].

Integrating our own work with these proposed striatal mechanisms, early learning was associated with greater activity in the anterior striatum, with a shift to more dorsal striatum later in learning [23]. This is consistent with relatively rapid changes in the accuracy or stimulus response association measure and more extended changes in the sensorimotor measure of synchronization. Overall, our data do not support a role for the striatum in retention, as we see increases in striatal activity both within and across days of learning, but no incremental engagement at delayed recall [21–23]. Taken together we propose that the striatum is important for developing probabilistic associations between individual movements (e.g., motor chunks) and that these associations evolve with practice. Further, we hypothesize that the involvement of different striatal regions in sequential learning may depend on the degree to which reward-based, explicit control and sensorimotor mechanisms are required.

9. What does M1 do? – representation and storage

Primary motor cortex, or M1, is the major cortical output to the descending motor system and generates the neural commands that result in voluntary movement. M1 is strongly interconnected with somatosensory, and spatial processing regions in the parietal lobe, the premotor cortex and SMA, as well as both the BG and cerebellum. M1 is organized as a motor map with a globally

somatotopic organization containing multiple interdigitated representations of muscle synergies or movement primitives [121,122]. These synergies can be represented by the coherent activity of weighted ensembles of connected neurons, and the encoding of a novel movement sequence in motor cortex is thought to result from changes in this weighted connectivity when sets of movements are consistently performed together [123]. The overall representational strength of the sequence is increased as movements are practiced, resulting in an expansion of the cortical representation, or “map” region, corresponding to the specific sequence of movements or skill [77,124–126]. TMS studies in humans show map expansion for practiced movements [127,128]. Map plasticity appears to occur over multiple timescales, with short-term changes that are relatively transient and long-term changes that are more permanent [129]. Supporting this idea, a recent neurophysiological study of force-field adaptation in monkeys found that different populations of neurons in M1 show fast and slow changes in coding as the animals practiced the task over five days [130]. In contrast to the population changes, they did not observe change in properties of single cells. Therefore, they interpreted their findings as showing that a new motor plan is encoded by a population of neurons, rather than changes in the properties of individual cells. Studies of motor sequence learning in animals show that neurons in M1 can encode also sequence-specific information [50,131,132], consistent with human neuroimaging studies showing long-term increases in M1 activity with extended practice [21–23,27,30,35]. Finally, recent theory suggests that motor representations are constitutively plastic, a characteristic could account for the flexibility of motor behavior and the ability to learn a large repertoire of skills [129].

The evidence reviewed above constitutes a strong body of evidence demonstrating that M1 is the likely site of storage of new motor memories, probably as part of a distributed network including premotor and parietal cortex. The specificity of M1 involvement in motor memory has been demonstrated in studies where repetitive TMS over M1 disrupts consolidation of a practiced motor task [133,134]. Complementary work with facilitative transcranial direct current stimulation (tDCS) has shown that stimulation of M1 immediately following practice enhances consolidation and long-term retention [83,135,136]. Importantly, recent studies using tDCS have also shown facilitative effects of PMC stimulation on consolidation [137,138], confirming its role in the distributed network underlying motor sequence representation.

The hypothesis that motor memories are represented in M1 is also supported by evidence of structural changes in motor cortex related to learning. In addition to plasticity in the organization of motor maps, studies in rats show microstructural changes in grey and white matter [125,139]. In humans, structural MRI studies showing changes in grey matter and white matter with learning of a new motor task, or in relation to well-learned skill. Using diffusion tensor imaging (DTI), Bengtsson et al. [140] found that musicians had greater integrity of the descending motor pathways that was related to the number of hours they practiced in childhood. In a longitudinal study of children taking one year of piano lessons, Hyde et al. [141] showed changes in grey matter structure in M1 that was related to motor performance. Finally, a DTI study showed that ten days of intensive training on a motor adaptation paradigm produced grey matter and white matter changes in the hand region of the motor cortex [142].

10. How do the cerebellum, BG and M1 work together?

Having reviewed the individual contributions of the cerebellum, striatum and M1 to motor sequence learning, the challenge is to understand how these regions work together as learning

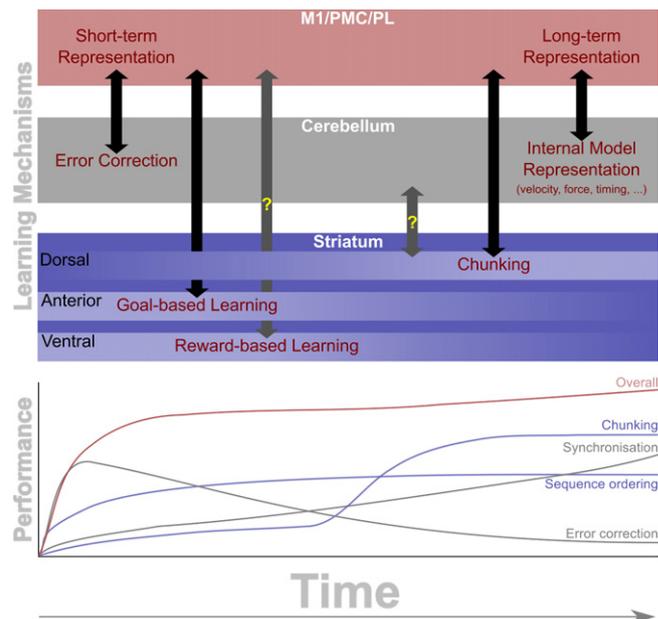


Fig. 6. Integrated model of motor sequence learning. The top panel of the figure illustrates the brain regions and associated mechanisms involved in motor sequence learning, and highlights their connectivity. Interactions between regions/mechanisms are depicted by vertical arrows, with lesser known interactions depicted by light arrows. The colour gradient within the striatum represents the relative contribution of each learning mechanism (light = greater contribution; dark = lesser contribution). The bottom panel depicts the idealized learning curve for different components of performance over time. Each component is colour-coded to its associated brain region. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

progresses. We propose that sequence learning is underwritten by parallel, interacting processes, such as error correction, internal model formation, stimulus–response association and sequence representation, that are instantiated in specific cerebellar, striatal or M1 mechanisms (Fig. 6). Therefore, the ensemble of regions that are engaged at a particular phase of learning depends on task demands that tap these specific mechanisms. This is in contrast to stage models that try to link learning at each phase to processing in unique regions. Our framework also contrasts with the component model, in that separable parameters for learning are not confined to spatial and sensorimotor, but include other parameters, such as velocity, force, timing and coarticulation – each of which may be optimized over different timecourses.

In the proposed model, the function of the striatal system is to learn probabilistic or predictive associations between stimuli and responses and/or between individual movements in a sequence. The role of the cerebellum is to acquire the optimal internal model for performing a sequence of movements in a particular context. The cerebellum also contributes to error correction and control of on-going movement. Finally, M1 stores the representation or “map” of a learned sequence, likely as part of a distributed network including parietal lobe and PMC.

As described previously, connections between these regions form separable loop systems – the cortico-striatal and cortico-cerebellar. Throughout learning these systems contribute simultaneously to sequence acquisition: the cortico-striatal system to learning of the more explicit, spatial/sequential order of movements; and the cortico-cerebellar system to correcting and optimizing motor control parameters. The degree to which each system is called into play depends on task demands and phase of learning. These different mechanisms also underlie faster and slower learning processes, where the more explicit, spatial/sequential component is learned more quickly, and the

more implicit, sensorimotor component is learned more slowly. If the sequence is learnable through explicit means or has an obvious goal state, then anterior striatal circuits and the frontal lobe would play a greater role. If, however, the sequence is largely implicit or has already been explicitly learned, then dorsal-striatal mechanisms would contribute to chunking of repeatedly performed actions. It is also possible that ventral-striatal, reward-based mechanisms are engaged in learning. Information from these striatal learning mechanisms would be integrated in M1, contributing to the reweighting of the representation of repeated or learned sequences.

Cerebellar learning mechanisms would contribute to error correction throughout the learning process and with practice new context-specific input–output models for the sequence would be formed. Interactions between the cerebellum and M1 appear to be crucial for learning, likely influencing the final representation of the sequence in M1. This joint representation is built up through an iterative process of integrating information about performance of the skill based on the predicted and actual state of the effector(s) involved. Thus, while average M1 and cerebellar activity may decrease with practice, specific increases that index encoding of the representation of the motor plan and internal model can be observed. The representations in M1 and the cerebellum may be linked to different components of learning, with the representation of the motor plan for the learned sequence of movements encoded in M1 and the motor control parameters for these movements encoded in the cerebellum. This distributed representation of a learned sequence would also likely include the PMC and parietal cortex. The cerebellum is also likely to be important for encoding the motor context of learning such as the control parameters of specific tools or manipulanda. The last leg of the triangle, the interaction between the cerebellum and striatal system, is the least well characterized. However, it follows logically that information from striatal systems about prediction and chunking of action sequences would be relayed to cerebellar systems engaged in movement optimization and vice versa.

In sum, this framework for motor learning proposes that, as with the athlete learning the jump-shot or a pianist learning a new piece, there are at least two separable components of learning – spatial/sequential order and optimal sensorimotor control – and that these components are underwritten by partially separable neural mechanisms that are optimized over different timecourses (Fig. 6, bottom panel). However, as with the athlete and the musician, learning of these components is necessarily intertwined. Making easily testable predictions from a model proposing parallel interacting systems can be more difficult. However, there are a number of directions for future research that would further specify striatal, cerebellar, and M1 mechanisms involved in learning and could better define how these systems interact.

A central direction arising from our proposal would be to identify more precisely the sensorimotor parameters thought to be represented by cerebellar internal models. This would require experiments examining cerebellar contributions to learning-related changes in movement parameters such as velocity, force, timing and coarticulation. Some such experiments have been conducted in animals, but relatively few have been done with humans. A clear prediction of our model is that activity in specific M1 sub-populations should be related to recall performance of individual sequences, with better recall resulting in greater activity. A related prediction, based on the idea that M1–cerebellar connectivity is important for learning, is that we should be able to identify specific changes in connectivity with learning. The hypothesis that dorsal-striatal mechanisms contribute to chunk formation could be tested in humans by examining the relationship between striatal activity and chunking measures during learning. An interesting question based on the recently identified anatomical

connections between the BG and cerebellum would be to test for striatal–cerebellar interactions specific to learning, possibly in the context of chunk formation. Finally, a novel direction for research would be to examine the role of ventral striatal reward-based mechanisms in sequence learning.

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