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Review

Neuroplasticity Subserving Motor Skill Learning

Eran Dayan[1] and Leonardo G. Cohen[1,*]
[1]Human Cortical Physiology and Stroke Neurorehabilitation Section, National Institute of Neurological Disorders and Stroke,
National Institutes of Health, Bethesda, MD 20892-1428, USA
*Correspondence: cohenl@ninds.nih.gov
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Recent years have seen significant progress in our understanding of the neural substrates of motor skill learning. Advances in neuroimaging provide new insight into functional reorganization associated with the acquisition, consolidation, and retention of motor skills. Plastic changes involving structural reorganization in gray and white matter architecture that occur over shorter time periods than previously thought have been documented as well. Data from experimental animals provided crucial information on plausible cellular and molecular substrates contributing to brain reorganization underlying skill acquisition in humans. Here, we review findings demonstrating functional and structural plasticity across different spatial and temporal scales that mediate motor skill learning while identifying converging areas of interest and possible avenues for future research.

Introduction

The acquisition and long-term retention of motor skills play a fundamental role in our daily lives. Skills such as writing, playing golf, or riding a bicycle are all acquired through repetitive practice. Motor skill learning refers to the process by which movements are executed more quickly and accurately with practice (Willingham, 1998). Our understanding of the neural substrates underlying the acquisition and retention of motor skills has been boosted in recent years, owing in a large part to technological and methodological advances in neuroimaging, as well as in noninvasive brain stimulation in humans, coupled with dramatic new insights emerging from animal studies both in vivo and in vitro, providing additional information about the recruitment of specific neuronal circuits during the various stages of motor skill learning. This work has overall demonstrated a strong link between acquisition of motor skills and neuronal plasticity at cortical and subcortical levels in the central nervous system that evolves over time and engages different spatially distributed interconnected brain regions. Here, we review novel findings reflecting functional and structural plasticity associated with the acquisition, consolidation, and long-term retention of motor skills in humans and experimental animals while identifying points of convergence and dispute.

A variety of tasks and experimental paradigms have been used for studying motor skill learning, including juggling, visuomotor tracking, and isometric force-production tasks, to name a few. Of particular relevance to the current review are studies of tasks that require practice of sequential movements: tapping skills like typing or playing various musical instruments. Here, our main focus is on learning sequential motor skills that show lasting improvements beyond baseline performance over lengthy periods of time. Another model for studying motor learning, which does not necessarily involve the acquisition of a new skill, has been adaptation to externally induced perturbations, such as those induced by a force field (dynamic adaptation) or by visuomotor rotations (visuomotor adaptation). These perturbations are more commonly introduced while subjects execute simple motor tasks, for instance, point-to-point ballistic reaching movements (Krakauer, 2009; Shadmehr et al., 2010; Seidler, 2010; Lalazar and Vaadia, 2008). Yet these paradigms characteristically evaluate the return to baseline levels of performance following perturbation over relatively short time periods (Krakauer and Mazzoni, 2011). However, it should be noted that repetitive practice of adaptation tasks could lead to performance improvements over time in the form of "savings," expressed as faster readaptation to external perturbations relative to the initial rate of adaptation (e.g., Landi et al., 2011). Moreover, skill learning tasks, in which lasting improvements are seen over time, for instance whole-body balancing (Taubert et al., 2010), may involve an adaptation component.

Motor skills are typically learned slowly over multiple training sessions until performance reaches nearly asymptotic levels. Across different experimental paradigms, skill acquisition develops (Figure 1A) initially relatively fast (i.e., rapid improvements measured over the course of a single training session) and later more slowly, when further gains develop incrementally over multiple sessions of practice (Doyon and Benali, 2005; Doyon and Ungerleider, 2002). Of note, the relative duration of what can be defined as fast and slow learning is highly task specific. For example, the fast stage of learning a simple four-component key-press sequence could last minutes (e.g., Karni et al., 1995), whereas the fast stage of learning to play a complex musical piece may last months (Figure 1B). Similarly, nearly asymptotic levels in end-point measures of skill can be acquired very rapidly when learning a key-press sequence but much more slowly when learning to play a complex musical piece. Skill changes can occur during training (online) but also after training ended (offline; Figure 1C). Offline processes, including skill stabilization and improvement (Fischer et al., 2005; Korman et al., 2003; Walker et al., 2002), reflect motor memory consolidation (Doyon and Benali, 2005; Muellbacher et al., 2002; Robertson et al., 2004a), an intermediate stage between fast and slow learning (Doyon and Benali, 2005; Doyon et al., 2009a). Online and offline skill gains can be maintained over time, resulting in long-term retention (Romano et al., 2010).

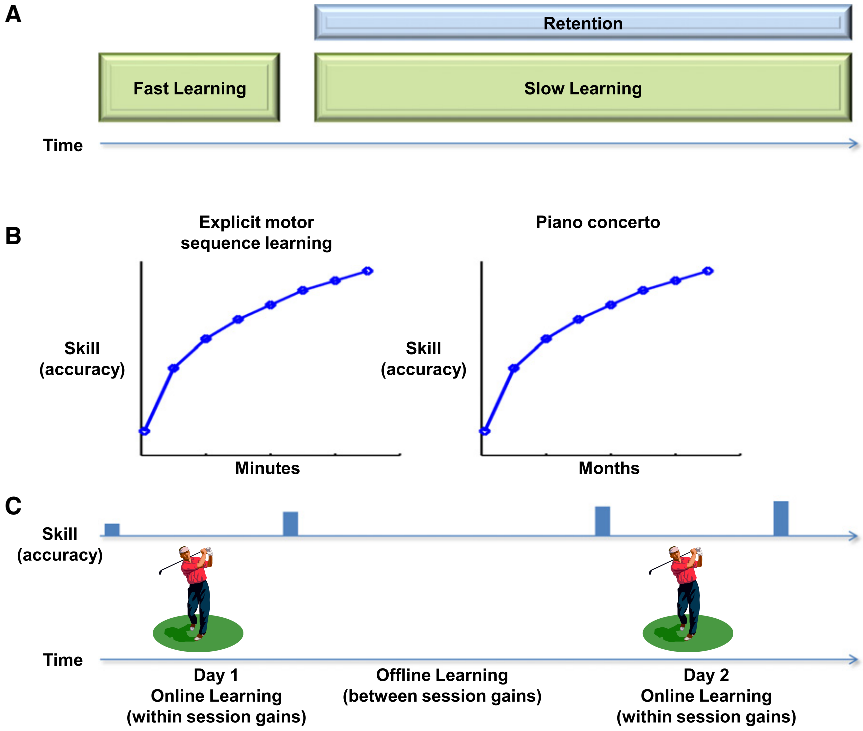

Figure 1. The Different Stages of Motor Skill Learning

(A) Motor skill learning can be divided into a fast stage, in which typically significant improvements can be seen within a single training session, and a later, slow stage, in which further gains are achieved across multiple sessions of practice. Skill can be retained after a single or multiple training sessions.

(B) The relative duration of fast and slow learning is highly task specific. For example, the fast stage of learning an explicitly known sequence of key-press movements could last minutes, whereas the fast stage of learning to play a complex musical piece may last months. Although the shape of the learning curves for these two different tasks could theoretically be the same, the time bases of the fast stages of learning may be substantially different.

(C) Performance improvements during skill acquisition can occur not only during training (online learning), but also between sessions, with no further practice (offline learning).

Identifying optimal measurements of skill learning is not trivial. Previous studies have typically defined skill acquisition in terms of reduction in the speed of movement execution or reaction times, increase in accuracy, or decrease in movement variability. Yet these measurements are often interdependent, in that faster movements can be performed at the cost of reduced accuracy and vice versa, a phenomenon which has been often referred to as speed-accuracy trade-off (Fitts, 1954). One solution to this issue is through assessment of changes in speed-accuracy trade-off functions (Figure 2; Reis et al., 2009; Krakauer and Mazzoni, 2011).

Fast Motor Skill Learning

The fast stage of motor skill learning has been studied in human and nonhuman primates (e.g., Karni et al., 1995; Lehéricy et al., 2005; Miyachi et al., 2002) and in rodents (Costa et al., 2004; Yin et al., 2009). In humans, the neural substrates of this learning stage were studied with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Fast learning of sequential motor tasks modulates regional brain activity in the dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1), and presupplementary motor area (preSMA) (Floyer-Lea and Matthews, 2005; Sakai et al., 1999), which show decreased activation as learning progresses, and in the premotor cortex, supplementary motor area (SMA), parietal regions, striatum, and the cerebellum, which show increased activation with learning (see Figure 3; Grafton et al., 2002; Honda et al., 1998; Floyer-Lea and Matthews, 2005). Thus, learning is associated with differential regional modulation of blood oxygenation level-dependent (BOLD) activity or regional cerebral blood flow (rCBF). Increasing activation is thought to reflect recruitment of additional cortical substrates with practice (Poldrack, 2000). Decreasing activation, on the other hand, suggests that the task can be carried out using fewer neuronal resources as fast learning proceeds (Poldrack, 2000).

A valuable framework for interpreting the role of this complex pattern of recruitment has been proposed by Hikosaka and colleagues (Hikosaka et al., 2002a) in a model describing the mechanisms for sequential motor skill learning. According to this model, two parallel loop circuits operate in learning spatial and motor features of sequences. Whereas learning spatial coordinates is supported by a frontoparietal-associative striatum-cerebellar circuit, learning motor coordinates is supported by an M1-sensorimotor striatum-cerebellar circuit. Transformations between the two coordinate systems rely, according to this model, on the contribution of the SMA, pre-SMA, and premotor cortices. Importantly, it was argued that learning spatial coordinates is faster, yet requires additional attentional and executive resources, putatively provided by prefrontal cortical regions (Miller and Cohen, 2001). Similarly, in another model, Doyon and Ungerleider (2002) proposed that during fast learning a cortico-striato-thalamo-cortical loop and a cortico-cerebello-thalamo-cortical loop are both recruited, operating in parallel. Further, interactions between the two systems were believed to be crucial for establishing the motor routines necessary for learning new motor skills (Doyon and Ungerleider, 2002; Doyon and Benali, 2005). Both models share the view that motor skill learning involves interactions between distinct cortical and subcortical circuits, crucial for the unique cognitive and control demands associated with this stage of skill acquisition (Hikosaka et al., 2002a; Doyon and Ungerleider, 2002).

One of the key brain regions involved in fast learning is M1. Fast motor skill learning is associated with substantial recruitment of neurons in M1 in behaving mice during the initial stages of learning an accelerating rotarod task (Costa et al., 2004) and with modulation of synaptic efficacy through long-term

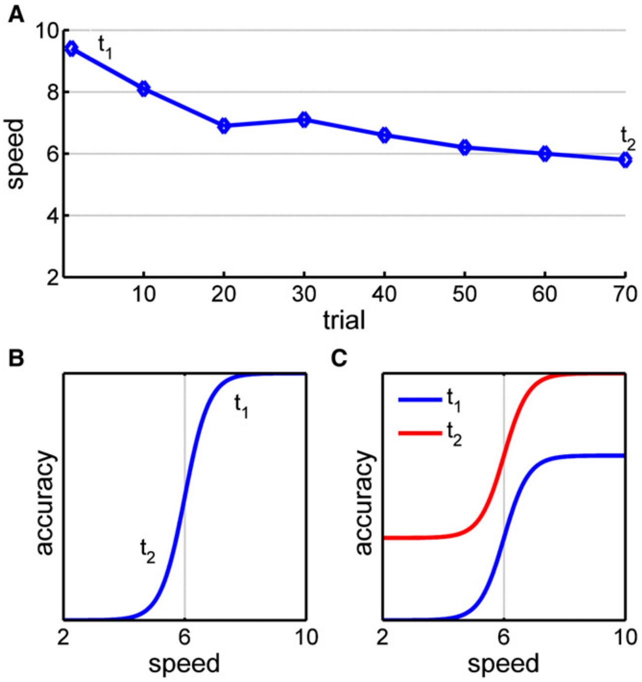

Figure 2. Shifts in Speed-Accuracy Response Functions as a Measure of Skill

(A) Simulated learning curve, in which performance improvements were defined in terms of speed. Thus, performance at time point t_2 shows clear improvements relative to performance at time point t_1.

(B) Inspecting the task's speed-accuracy response function reveals that these performance changes may reflect sampling of two points along the same function, thus simply reflecting a switch from movements that are relatively slow but accurate to movements that are relatively fast but inaccurate.

(C) A more reliable measure for skill acquisition may estimate whether learning was associated with a shift in the speed-accuracy responses, from the blue to the red function.

potentiation (LTP) and long-term depression (LTD) in rodents (Rioult-Pedotti et al., 1998, 2000). Consistently, by utilizing transcranial magnetic stimulation (TMS), it was shown in humans that learning a motor task modulates LTP-like plasticity (Ziemann et al., 2004; Stefan et al., 2006; Rosenkranz et al., 2007). BOLD activity in M1 progressively decreases as motor skill learning progresses over a single training session (Karni et al., 1995), yet it should be noted that the magnitude of engagement of M1 in fast learning is highly influenced by the specific task and by attentional demands (Hazeltine et al., 1997; Stefan et al., 2004). Consistent reorganizational changes in M1 have been described using TMS. For example, the fast stage of implicit motor skill learning, as assessed with the serial reaction time task, is accompanied by increased motor map size of the fingers engaged in the task. Interestingly, when the sequence becomes explicitly known, the M1 motor map size returns to baseline (Pascual-Leone et al., 1994). The cellular mechanisms behind learning-related plasticity in M1 appear to depend on protein synthesis within this structure and may specifically involve brain-derived neurotrophic factor (BDNF; Kleim et al., 2003). In both humans and animal models, BDNF influences synaptic plasticity (Akaneya et al., 1997; Lu, 2003). Injection of protein synthesis inhibitors targeting BDNF into the rat M1 induces a lasting loss of motor map representation (Kleim et al., 2003). Moreover, training-dependent increases in motor cortical excitability (Antal et al., 2010; Cheeran et al., 2009) and fMRI signal (McHughen et al., 2010) are reduced in healthy humans with a valine-to-methionine substitution at codon 66 (Val66Met) in the BDNF gene, when compared to subjects without this polymorphism (Kleim et al., 2006). These findings led to the hypothesis that the presence of this particular polymorphism could influence motor skill learning (Fritsch et al., 2010).

Although earlier imaging studies clearly established that the fast stage of motor skill learning is sustained by activity across a distributed set of brain regions, conventional univariate fMRI analysis, in which brain activity is analyzed in a voxel-wise manner as if each anatomically distinguishable region is independent (Marrelec et al., 2006; Tamás Kincses et al., 2008), does not provide information on interregional interactions that are required to properly test these models. The most widely used and straightforward approach for assessing interregional interactions in neuroimaging data is based on analysis of functional connectivity (Friston, 1994), which refers to the statistical dependence defined in terms of correlation or covariance between the activation in spatially remote regions. Using this approach, it was shown that M1, the premotor cortex, and the SMA have significantly greater inter- and intrahemispheric coupling during early, as compared to late, within-session explicit sequence learning (Sun et al., 2007). Interactions between M1, SMA, and premotor cortices are likely to reflect transformations between spatial and motor features of motor sequences required for fast motor skill learning (Hikosaka et al., 2002a). Additionally, fast motor skill learning is characterized by increased functional connectivity between the DLPFC and premotor cortex (Sun et al., 2007), relating to the heightened attentional demands required at this stage of skill acquisition (Hikosaka et al., 2002a; Petersen et al., 1998).

Additional information on network-level functional reorganization mediating fast learning emerged from data-driven model-free analytical approaches, such as independent component analysis (ICA), that do not assume prior knowledge of activation changes (Marrelec et al., 2006). Using this approach, a recent study characterized two networks involved in fast learning (Tamás Kincses et al., 2008): (1) an M1-premotor-parietal-cerebellar circuit that shows reduction of fMRI activity as learning progressed, consistent with a developing ability of the network to economize resources often seen during motor practice (Kelly and Garavan, 2005; Petersen et al., 1998) and (2) a posterior parietal-premotor circuit that shows increasing fMRI activity that correlates with behavioral gains, which may be consistent with the engagement of spatial processing resources required for the task (Tamás Kincses et al., 2008; Hikosaka et al., 2002a). Overall, studies employing functional connectivity analysis, both model-driven and model-free, provided clear evidence for the reorganization of cortico-cortical and cortico-cerebellar circuits in fast learning, a pattern of functional plasticity that is in agreement with previously proposed models (Hikosaka et al., 2002a; Doyon and Ungerleider, 2002; Doyon and Benali, 2005; see above). On the other hand, functional connectivity evidence for cortico-striatal interactions as proposed in these models is currently lacking. Accurate characterization of

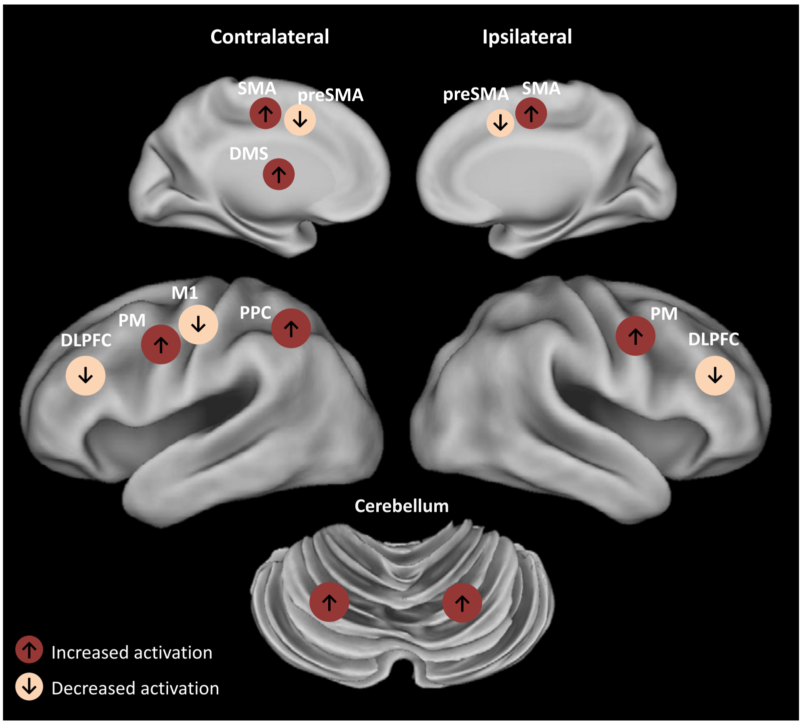

Figure 3. Neural Substrates of Fast Motor Skill Learning

Schematic depiction of the major brain regions recruited during the initial stages of motor skill learning, as identified using fMRI and PET: dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1), premotor cortex (PM), supplementary motor area (SMA), presupplementary motor area (preSMA), posterior parietal cortex (PPC), dorsomedial striatum (DMS), and posterior cerebellum. The arrows depict documented increases or decreases in activation associated with fast skill learning. Inflated cortical and cerebellar surfaces were rendered using CARET (http://brainvis.wustl.edu/wiki/index.php/Main_Page).

cortico-striatal interactions during fast learning is likely to benefit from hypothesis-driven experimental approaches that focus on these regions (e.g., Di Martino et al., 2008).

Slow Motor Skill Learning

Behavioral gains in later stages of motor skill learning are usually quantitatively smaller than those observed during fast learning and develop at a slower pace (Doyon and Benali, 2005; Karni et al., 1995; Ungerleider et al., 2002). The magnitude of changes and the time course of slow learning are task dependent. They differ substantially when learning a simple motor sequence in which performance rapidly reaches near-asymptote levels and when learning, for example, to play musical pieces on a violin, in which case performance improvements continue over many years. It has been proposed that under certain conditions, performance may become automatic, implying lesser involvement of attentional and executive resources and lesser susceptibility to interference by a secondary process or task (Schneider and Shiffrin, 1977; Ashby et al., 2010; Doyon and Benali, 2005).

Studies that examined the neuronal mechanisms involved in the slow stage of motor skill learning typically had subjects learn a motor skill over several weeks and scanned them on different occasions throughout the training period (Karni et al., 1995; Floyer-Lea and Matthews, 2005; Coynel et al., 2010; Lehéricy et al., 2005). Slow learning is associated with increased activation in M1 (Floyer-Lea and Matthews, 2005), primary somatosensory cortex (Floyer-Lea and Matthews, 2005), SMA (Lehéricy et al., 2005), and putamen (Lehéricy et al., 2005; Floyer-Lea and Matthews, 2005), as well as decreased activation in lobule VI of the cerebellum (Figure 4; Lehéricy et al., 2005). Thus, progress from early to late stages of motor skill learning is characterized by a shift in fMRI activation from anterior to more posterior regions of the brain (Floyer-Lea and Matthews, 2005), a pattern also reported when learning nonmotor tasks, which is thought to reflect a progressive decrease in reliance on attentional resources and executive function (Kelly and Garavan, 2005). Progressing from fast to slow motor skill learning is also associated with a shift in fMRI activation from associative to sensorimotor striatum (Coynel et al., 2010; Lehéricy et al., 2005), thought to contribute to slow learning of the motor component of sequences (Hikosaka et al., 2002a).

Slow learning has been linked with larger-scale functional reorganization as well. A recent study tracked functional connectivity using fMRI over a period of 4 weeks of training on an explicit motor sequence task (Coynel et al., 2010). Early learning was associated with increased integration, a metric reflecting functional interactions among several brain regions, of a premotor-associative striatum-cerebellar network. During slow learning, on the other hand, the authors reported decreased integration in this premotor-associative striatum-cerebellar network but stable connectivity within the M1-sensorimotor striatum-cerebellar network, largely consistent with data emerging from regional fMRI analysis (Floyer-Lea and Matthews, 2005; Lehéricy et al., 2005).

Engagement of neurons in the sensorimotor striatum during later stages of learning has been well documented in animal models (Miyachi et al., 2002; Yin et al., 2009) and has been proposed as a substrate for the acquisition of habitual and automatic behavior (Yin et al., 2004, 2009). For example, in vivo recordings in behaving rodents revealed that the sensorimotor striatum is engaged later in training, when performance in an accelerated rotarod task asymptoted (Yin et al., 2009). Consistently, ex vivo recordings from medium spiny neurons in sensorimotor striatum following training revealed long-lasting changes in glutamatergic neurotransmition (Yin et al., 2009). The involvement of the striatum in the stages in which motor skills become automatic has been confirmed in human neuroimaging studies (Ashby et al., 2010; Lehéricy et al., 2005; Poldrack et al., 2005). For example, using a dual-task design, in which a sequence of finger movements was learned while assessing the influence of

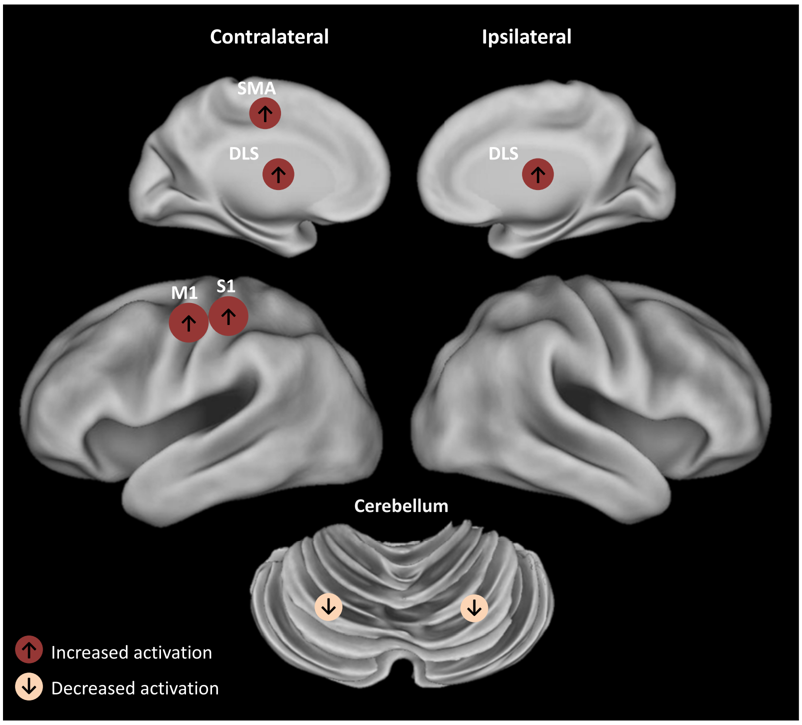

Figure 4. Neural Substrates of Slow Motor Skill Learning
Schematics of the major brain regions active in slow stages of motor skill learning, as identified using fMRI: primary motor cortex (M1), primary somatosensory cortex (S1), supplementary motor area (SMA), dorsolateral striatum (DLS), and lateral cerebellum. Arrows depict documented increases or decreases in activation. Inflated cortical and cerebellar surfaces were rendered using CARET (http://brainvis.wustl.edu/wiki/index.php/Main_Page).

a secondary interfering task, it was found that automaticity was accompanied by a decrease in activation in the associative striatum (Poldrack et al., 2005; Lehéricy et al., 2005).

Of note, the slow stage of motor skill learning in both humans and animals consistently engages M1, a key brain region in other stages of learning as well. Training to perform an explicit sequence of finger movements over several weeks showed progressively increasing BOLD activity in M1 (Karni et al., 1995, 1998; Floyer-Lea and Matthews, 2005; Lehéricy et al., 2005; but see Xiong et al., 2009; Ma et al., 2010), interpreted as reflecting recruitment of additional M1 units into the local network that represents the acquired sequence of movements (Ungerleider et al., 2002). Learning a motor sequence over several days is also accompanied by an increase in the size of motor maps and corticomotoneuronal excitability of the digits involved in the task, both measured with TMS (Pascual-Leone et al., 1995). This particular reorganization within M1 is related to learning because simple repetition of movements in the absence of a sequential order did not induce such effect. Consistently, facilitatory stimulation of M1 over 5 days with anodal transcranial direct current stimulation (tDCS) improved learning of a sequential visuomotor task. Of note, the advantage in skill of the stimulated group relative to the sham control group was still present 90 days later (Reis et al., 2009). These results support a causal link between M1 function and motor skill learning when training over multiple sessions.

Plastic changes in M1 function linked with slow motor skill learning are well established in animal models as well. For example, reorganization of movement representations in M1 has been documented in squirrel monkeys (Nudo et al., 1996) and rodents (Kleim et al., 1998, 2004). It was found that an expansion in movement representations with training, detectable only after substantial practice periods, paralleled behavioral gains (Kleim et al., 2004; Monfils et al., 2005). The extent to which changes in motor maps in humans or animals have a causal link with slow learning remains to be more carefully studied (Monfils et al., 2005), but the finding discussed above that facilitatory stimulation of M1 improves learning is suggestive of such a link (Reis et al., 2009).

Structural Plasticity Associated with Slow Learning

In addition to reorganization of functional brain networks, slow learning is associated with structural plasticity in gray matter (for review, see Draganski and May, 2008; May and Gaser, 2006). The introduction of new imaging technologies led to remarkable demonstrations of structural plasticity in the human brain. MRI-based morphometric imaging methods, mainly voxel-based morphometry (VBM; Ashburner and Friston, 2000), were used to evaluate gray matter changes linked with experience and learning. Cross-sectional studies quantified gray matter volumes in human subjects in relation to different levels of skill. For example, higher gray matter volume in auditory (Bermudez and Zatorre, 2005; Gaser and Schlaug, 2003), sensorimotor, and premotor cortex, as well as the cerebellum (Gaser and Schlaug, 2003; Han et al., 2009) has been reported in musicians relative to nonmusicians. Experts in skills that involve a strong motor component, such as typing (Cannonieri et al., 2007), playing basketball (Park et al., 2009), or playing golf (Jäncke et al., 2009), also exhibit differences in gray matter in various brain regions relative to nonexperts (see Table 1). It should be kept in mind, however, that the cross-sectional association between gray matter and skill does not necessarily imply causality. For example, gray matter features present preceding skill acquisition could make some subjects more prone to engage in practicing a specific skill (i.e., playing a specific musical instrument).

A more direct evidence for learning-induced changes in gray matter emerges from studies that utilized longitudinal designs, evaluating the same individuals learning a particular skill over relatively long time periods. In one key study (Draganski et al., 2004), subjects trained over 3 months to learn a three-ball juggling routine. Structural MRI scans were acquired at baseline (before training), at the end of training, and 3 months later in the

Table 1. Evidence for Structural Plasticity Associated with Motor Skill Learning

Study	Skill	Design	GM/WM	Main Findings
Cross-Sectional Studies				
Bermudez and Zatorre, 2005	Musicianship	Musicians, nonmusicians	GM	GM differences in the right auditory cortex
Gaser and Schlaug, 2003	Musicianship	Musicians, nonmusicians	GM	GM differences in sensorimotor cortex, premotor cortex, and cerebellum
Han et al., 2009	Musicianship	Pianists, nonmusicians	GM, WM	Higher GM density in sensorimotor cortex and cerebellum; higher FA in internal capsule
Cannonieri et al., 2007	Typing	Professional typists	GM	Positive correlation between typing experience and GM volume in the SMA, PFC, and cerebellum
Park et al., 2009	Basketball	Basketball players, controls	GM	GM volume differences in the vermian lobule VI–VII of the cerebellum
Jäncke et al., 2009	Golf	Golfers (different levels), nongolfers	GM, WM	Larger GM volumes in premotor and parietal cortices; smaller FA along the internal and external capsule and the parietal operculum and in the parietal operculum
Bengtsson et al., 2005	Musicianship	Pianists, nonmusicians	WM	Amount of practice in childhood, adolescence, and adulthood positively correlated with FA in different sets of brain regions; strong correlations between childhood practicing and FA in the internal capsule
Schmithorst and Wilke, 2002	Musicianship	Musicians, nonmusicians	WM	Greater FA in the genu of the corpus callosum; less FA in corona radiata and internal capsule
Longitudinal Studies				
Draganski et al., 2004	Juggling	3 months' practice	GM	Practice-induced GM expansion in MT/V5 and posterior intraparietal sulcus, followed by a decreased to baseline levels after 3 months with no practice
Boyke et al., 2008	Juggling	3 months' practice[1]	GM	GM increases in MT/V5, hippocampus, and nucleus accumbens
Scholz et al., 2009	Juggling	6 weeks' practice	GM, WM	FA increases in the intraparietal sulcus; colocalized increase in GM density
Driemeyer et al., 2008	Juggling	7 days' practice	GM	Increased GM density in MT/V5
Taubert et al., 2010	Balancing	6 weeks' practice	GM, WM	GM volume expansion in frontal and parietal brain areas as early as after two weekly practice sessions; parallel increases in FA

Cross-sectional and longitudinal studies demonstrating structural plasticity in gray and white matter associated with motor skill learning. In cross-sectional designs, individuals possessing different levels of skills (e.g., pianists and nonpianists) are scanned at one time point. In longitudinal designs, volunteers learn a new motor skill and are scanned along several time points, typically including a baseline scan. SMA, supplemantry motor area; PFC, prefrontal cortex; FA, fractional anisotropy; GM, gray matter; WM, white matter.

[1] Subjects were older and younger adults.

absence of additional practice. The authors documented at the end of training an expansion of gray matter in area MT/V5 and in the left posterior intraparietal sulcus, both involved in perception of motion and visuomotor processing. Yet regional gray matter decreased to near baseline 3 months following the end of training, paralleling the decrease of skill. Similar expansion in gray matter in area MT/V5 was reported in a group of elderly volunteers learning the same task, suggesting that reorganization in gray matter can also occur in the aging human brain (Boyke et al., 2008).

Later studies examined more closely the time scales of gray matter changes with slow motor skill learning (Driemeyer et al., 2008; Scholz et al., 2009; Taubert et al., 2010). Consistent with previous results, gray matter expansions were documented in the medial occipital and parietal lobes after 6 weeks of juggling practice (Scholz et al., 2009) and in bilateral occipito-temporal cortex as early as following 7 days of practice (Driemeyer et al., 2008). In another study, gray matter volume expansion was identified in parieto-frontal regions as early as following two weekly practice sessions in a whole-body balancing task

(Taubert et al., 2010). These findings are indicative of relatively rapid structural gray matter plasticity associated with motor skill learning. What mechanisms could contribute to these striking findings? Although speculative at this point, it has been proposed that processes occurring both at the synapse level and at larger scales, including rapid intracortical remodeling of dendritic spines and axonal terminals, glial hypertrophy, and synaptogenesis, might play a contributory role (Draganski and May, 2008; May and Gaser, 2006; Anderson et al., 1994). Consistently, rapid (within an hour) formation of postsynaptic dendritic spines has been detected in vivo in the pyramidal neurons of the mouse motor cortex following motor training (Xu et al., 2009), and the extent of spine remodeling has been shown to correlate with behavioral improvements after learning, suggesting that this mechanism of synaptic plasticity may contribute to motor memory formation (Yang et al., 2009). On the other hand, it should be noted that other animal studies demonstrated significant increases in synapse numbers in the rat M1 only after extensive training (Kleim et al., 1996, 2004).

Slow learning has been linked with structural plasticity in white matter architecture as well (Table 1). Diffusion MRI-based measures, such as fractional anisotropy (FA), are believed to reflect white matter integrity (Fields, 2008), providing a distinctive insight into the microstructural properties of white matter in vivo (Le Bihan et al., 2001; Mori and Zhang, 2006). Cross-sectional studies, primarily with highly trained musicians, examined white matter correlates of skilled behavior (Bengtsson et al., 2005; Han et al., 2009; Schmithorst and Wilke, 2002). Fractional anisotropy in the posterior limb of the internal capsule, which contains descending corticospinal fibers from the primary sensorimotor and premotor cortices, correlated with number of practice hours during childhood in skilled musicians (Bengtsson et al., 2005). It has been proposed that these results may reflect experience-induced plasticity during a critical developmental period (Bengtsson et al., 2005). A recent pioneering study provided more direct evidence for experience-induced changes in white matter architecture, resulting from a relatively short period of practice (Scholz et al., 2009). In this study, it was shown that 6 weeks of juggling practice resulted in increased FA in a region of white matter underlying the intraparietal sulcus. Localized increases in gray matter were detected in close proximity to these white matter regions. Yet the magnitude of changes of gray and white matter showed no correlation and developed over markedly different time courses. Interestingly, individual differences in white matter mictrostructure appear to be related to variation in learning (Johansen-Berg, 2010; Della-Maggiore et al., 2009; Tomassini et al., 2011). For example, individual differences in learning an isometric visuomotor tracking task are associated with variability in FA in the premotor cortex and the cerebellum (Tomassini et al., 2011). The cellular mechanisms underlying learning-dependent changes in white matter microstructure remain to be established, and so do the links between these changes and measures of functional plasticity. It has been proposed that changes in white matter properties, indexed by FA, could affect the velocity and synchronicity of impulse conduction between distant cortical regions and thus contribute to the optimization of information flow required for skill acquisition (see Fields, 2008, 2011), a hypothesis that requires specific testing.

Altogether, demonstrations of learning-induced gray and white matter plasticity in humans represent an exciting development in systems neuroscience. Yet the contribution of this line of research to our understanding of motor skill learning is still limited. The biological mechanisms that underlie these forms of plasticity remain to be elucidated, and its time scales need to be more clearly established. Additionally, strict comparative evaluation of structural and functional plasticity associated with motor skill learning is difficult at this point, given the different experimental paradigms used in the literature. This issue should be overcome in future investigations by evaluating both forms of plasticity in longitudinal studies in the same subjects (Thomas et al., 2009).

Offline Motor Skill Learning

Progression from fast to slow motor skill learning is thought to rely on appropriate consolidation (Doyon and Benali, 2005; Muellbacher et al., 2002; Robertson et al., 2004a), defined as the progressive stabilization of a recently acquired memory (Dudai, 2004). Through consolidation, new memories are transformed from their initial fragile states into more robust and stabile forms (Robertson et al., 2004a). In relation to motor skill learning, the term consolidation has been used in the literature to describe two different, but not mutually exclusive, phenomena: the offline behavioral skill improvements that occur after the end of a practice session (Robertson et al., 2004a) and the reduction in fragility of a motor memory trace that follows encoding (Robertson, 2009; Robertson et al., 2004a).

In humans, offline skill improvements may be affected by sleep (e.g., Diekelmann and Born, 2010; Fischer et al., 2002; Korman et al., 2003). Sleep-dependent motor memory consolidation, which correlates with the amount of stage II nonrapid eye movement sleep (Walker et al., 2002), has been mostly demonstrated for explicit motor sequence learning (Fischer et al., 2005; Korman et al., 2003; Walker et al., 2002; but see Brawn et al., 2010; Rickard et al., 2008). Other forms of procedural motor learning are not necessarily sleep dependent (Debas et al., 2010; Doyon et al., 2009b; Song et al., 2007). Notably, sleep does not benefit implicit forms of sequence learning (Robertson et al., 2004b; Song et al., 2007). In such circumstances, similar memory gains were reported after sleep and over an equivalent period of wakefulness (see also Hotermans et al., 2008).

Different brain regions are involved in consolidation of motor memories. Sleep-dependent improvements in learning a sequential finger-movement task were linked to reduced BOLD activity in M1, as measured with fMRI (Fischer et al., 2005). Furthermore, downregulating excitability of M1 by low-frequency TMS (virtual lesion) results in reduced motor memory consolidation (Muellbacher et al., 2002; Robertson et al., 2005), a time-specific effect because it was not observed when TMS was applied 6 hr posttraining (Muellbacher et al., 2002). The finding of differential effects of facilitatory anodal tDCS applied over M1 on online and offline learning of a sequential motor task, namely enhancement of offline learning, supports the existence of relatively different neuronal networks involved in the two processes (Reis et al., 2009). Another key contributor to consolidation of sequential motor skills is the striatum (Debas et al., 2010; Fischer et al., 2005; Albouy et al., 2008; Doyon and

Ungerleider, 2002). Recent work showed increased striatal activity in human subjects in whom offline consolidation was tested following a night of sleep, as compared to those in whom it was tested after an equivalent period of wakefulness (Debas et al., 2010; Fischer et al., 2005). Interestingly, BOLD activity in the ventral striatum and the hippocampus during the initial stages of oculomotor sequence learning predicted the magnitude of sleep-dependent behavioral improvements (Albouy et al., 2008). Additional evidence for the involvement of these two regions emerged from animal studies demonstrating that local injections of protein synthesis inhibitors disrupt consolidation of motor memories (Buitrago et al., 2004). This effect was present when injections were applied to M1 (Luft et al., 2004) and, to a lesser extent, the dorsal striatum (Wächter et al., 2010) but was absent after injections of control regions (Luft et al., 2004).

The neural processes leading to successful consolidation tested posttraining are likely to start operating during practice and evolve over time after training ended. Typically, evaluation of changes in BOLD signal induced by task performance assesses the consequences of these processes as tested a few hours after or the day after practice was completed. Thus, the neuronal mechanisms that operate during and early after practice and during sleep to support motor memory consolidation remain to a large extent uncertain. It was recently suggested that a possible way of closing this gap in knowledge is through measurement of intrinsic resting-state functional connectivity (Albert et al., 2009; Ma et al., 2011; Taubert et al., 2011). Spontaneous low-frequency fluctuations in the BOLD signal, in the absence of any overt input or behavior, have been widely reported in the past 15 years (for a review, see Fox and Raichle, 2007; Cole et al., 2010) and can be recorded at different times before or after training without affecting subsequent behavioral testing. Temporally coherent spontaneous fluctuations at rest have been found between spatially remote brain regions in areas known to be involved in motor, visual, and auditory processing, attention, and language (Cole et al., 2010; Fox and Raichle, 2007). Thus, resting-state functional connectivity, which may be sampled multiple times during the period leading to the behavioral measurement of consolidation, may provide a unique window for examining neural network activity along the entire course of motor skill acquisition. Available data are supportive of this contention. Learning a visuomotor tracking task over one session increased resting functional connectivity in a network that includes the prefrontal, superior, and inferior parietal cortices, as well as Crus II of the cerebellum (Albert et al., 2009). Learning a whole-body dynamic balancing task over multiple sessions showed increased resting-state connectivity between SMA/preSMA and medial parietal cortex that correlated with performance improvements (Taubert et al., 2011). Modulation of resting-state connectivity in parietal circuits was also observed along 4 weeks of daily training of an explicit sequence learning task (Ma et al., 2011). Overall, these studies suggest that functional connectivity in fronto-parietal networks supports consolidation after fast (Albert et al., 2009) and slow learning (Taubert et al., 2011; Ma et al., 2011). Comparison among these studies, however, should be done with caution, because they involved different motor skill tasks. Notwithstanding, published studies have yet to identify modulation of connectivity within striatal regions, believed to play a key role in consolidation of skills (Doyon and Benali, 2005; Doyon and Ungerleider, 2002), but preliminary findings indeed appear to support this hypothesis (K. Debas et al., 2011, Human Brain Mapping, abstract).

It should be kept in mind that previously consolidated memories are not immune to further modifications. Reactivation of a consolidated memory renders it once again labile and susceptible to interference (Nader et al., 2000; Walker et al., 2003). For example, reactivation of fear memories in rodents renders these memories susceptible to interference achieved through protein synthesis inhibition (Nader et al., 2000). Thus, reactivation of consolidated memories initiates a process of reconsolidation, whereby previously stabilized memories become labile again, requiring de novo protein synthesis in order to persist (Nader et al., 2000). In humans, evidence for reconsolidation of motor memories also exists (Walker et al., 2003; Censor et al., 2010). Learning a novel sequence of finger movements right after a previously consolidated procedural memory has been reactivated results in profoundly impaired recollection of the original procedural memory (Walker et al., 2003). As for the possible mechanisms underlying reconsolidation of human motor skill memories, it was recently shown that the application of 1-Hz repetitive TMS over M1 during the reactivation of an already-consolidated motor memory, acquired via training in an explicit sequential finger-tapping task in humans, blocks further memory modification (Censor et al., 2010). These results suggest that recurrent interactions of M1 processing with existing memory traces may be critical for further memory modification through reconsolidation (Censor et al., 2010; Censor and Cohen, 2011).

Long-Term Retention of Motor Skills

Once motor skills are acquired and consolidated, they can be retained over extended periods of time or forgotten. Under controlled laboratory settings, retention of motor skills has been demonstrated in humans (Romano et al., 2010; Savion-Lemieux and Penhune, 2005) over periods of up to a year (Romano et al., 2010) and in monkeys over similarly extensive periods (Hikosaka et al., 2002b), yet in real life, retention may occur over much longer periods. For learning of explicit motor sequences, even minimal amounts of practice spread over several days were able to induce long-term retention (Savion-Lemieux and Penhune, 2005), suggesting that long-term retention is strongly dependent on successful consolidation.

Various task attributes have a profound influence on long-term retention of skill learning. For instance, reward during practice improves long-term retention of a sequential motor skill (Abe et al., 2011). A reward-related enhancement of long-term memory has been demonstrated for other forms of memory as well (Wittmann et al., 2011) and is linked with fMRI activation in the striatum, ventral tegmental area, and hippocampus (Wittmann et al., 2005; Adcock et al., 2006). It has been proposed that dopaminergic modulation within these circuits, specifically through dopamine-dependent LTP in the hippocampus, may contribute to this effect (Calabresi et al., 2007). In the future, it will be of interest to identify the influence of reward attributes such as predictability, magnitude, and outcome uncertainty on long-term retention of motor skills. For instance, a recent study found that reward predictability and to some extent reward magnitude modulate long-term episodic memory, an effect that was absent for outcome uncertainty by itself (Wittmann et al., 2011).

Practice structure influences long-term retention of motor skills. The contextual interference (CI) effect, demonstrated in a wide variety of cognitive and motor tasks (Magill and Hall, 1990), refers to the benefits of training under interleaved or random-order conditions, as opposed to blocked practice schedules (Shea and Morgan, 1979). Recent studies have shown that training under different practice schedules implicates distinct neural substrates (Cross et al., 2007; Kantak et al., 2010; Tanaka et al., 2010; Wymbs and Grafton, 2009), including the SMA (Tanaka et al., 2010) and M1 (Kantak et al., 2010). These findings are consistent with the view that random practice may lead to more rapid memory stabilization or that motor memory encoding under random practice is associated with a more rapid shift from the SMA to other brain regions, such as the striatum or the parietal cortex (Tanaka et al., 2010). Consistent with this proposal, it was recently shown that interindividual differences in the magnitude of benefits of randomized practice schedules correlate with FA within the corticostriatal tract connecting left sensorimotor cortex to posterior putamen (Song et al., 2011). Understanding the influence of practice structure on the consolidation and retention of skilled motor behavior has potential clinical implications, because this knowledge may translate into improved training-based neurorehabilitative interventions after brain lesions.

Concluding Remarks

Technological and methodological advances in neuroimaging and in noninvasive brain stimulation in humans, together with novel findings stemming from animal-based studies, provide new insights into the neuroplastic mechanisms that underlie motor skill learning, suggesting that skill acquisition is subserved by multiple mechanisms that operate across different temporal scales. Multivariate and model-free approaches for analyzing neuroimaging data have emerged and may turn out to be a useful tool for examining the larger-scale functional reorganization associated with fast and slow motor skill learning. Another recent and intriguing development concerns the analysis of modulation of resting-state spontaneous fluctuations in BOLD activity as a possible means for studying the offline consolidation of motor skills. Noninvasive brain stimulation techniques have been used to identify a causal role for the activity in various brain regions in the acquisition of skilled motor behavior, motor memory consolidation, and long-term retention. Studies in laboratory animals identified, with fine temporal and spatial resolution, the involvement of distinct neural substrates in the various stages of motor skill learning and also helped identify the possible cellular and molecular underpinnings of learning-induced plasticity. Advances were also made in uncovering the mechanisms behind structural plasticity associated with the acquisition of motor skills. Learning-induced structural changes in both gray and white matter have been documented in humans at increasingly smaller temporal scales. Similar advances were made in the study of learning and experience-induced structural plasticity in laboratory animals, yet possible links between these findings and demonstrations of structural plasticity in humans are, to date, still speculative; however, they show clear translational value in understanding motor skill learning after brain lesions (Clarkson et al., 2010, 2011; Li et al., 2010).

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