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Reorganization and plasticity in the adult brain during learning of motor skills

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On the basis of brain imaging studies, Doyon and Ungerleider recently proposed a model describing the cerebral plasticity that occurs in both cortico-striatal and cortico-cerebellar systems of the adult brain during learning of new motor skilled behaviors. This theoretical framework makes several testable predictions with regards to the contribution of these neural systems based on the phase (fast, slow, consolidation, automatization, and retention) and nature of the motor learning processes (motor sequence versus motor adaptation) acquired through repeated practice. There has been recent behavioral, lesion and additional neuroimaging studies that have addressed the assumptions made in this theory that will help in the revision of this model.

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Introduction and scope of the review

Motor skill acquisition refers to the process by which movements produced alone, or in a sequence, come to be performed effortlessly through repeated practice and interactions with the environment [1]. Such motor behaviors are used on a daily basis, and are thus important for our activities in everyday life (e.g. playing a musical instrument such as the piano, grasping small objects or practicing sports). In the laboratory, however, the cognitive processes and the neural substrates mediating our capacity to learn these behaviors have been studied using experimental paradigms that fall into two major categories: the first measures the incremental acquisition of movements into a well-executed behavior (motor sequence learning, MSL), whereas the second tests our capacity to compensate for environmental changes (motor adaptation, MA). The learning process of these remarkable abilities follows several distinct phases. First, a fast (early) learning stage in which considerable improvement

in performance occurs within a single training session; second, a slow (later) stage in which further gains can be seen across several sessions of practice; third, a consolidation stage in which spontaneous increases in performance can be experienced following a latent period of more than 6 h after the first training session without additional practice on the task, or in which no interference from a competing task can be observed provided it is administered beyond a critical time window of about 4–6 h; fourth, an automatic stage during which the skilled behavior is thought to require minimal cognitive resources and to be resistant to interference and the effects of time; and fifth, a retention stage in which the motor skill can be readily executed after long delays without further practice on the task.

During the past few years, a plethora of studies in both animals and humans have shown that several brain structures forming the cortico-striatal (CS) or the cortico-cerebellar (CC) anatomical systems are crucial for mediating the acquisition and execution of motor skills as they reach the various stages of learning described above [2,3]. Studies using functional brain imaging technology such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), in particular, have not only enabled us to identify the extent of the neural network involved in this type of non-declarative, incremental type of learning, but also to better understand the plastic changes that occur within these neural systems as performance improves with practice on a motor task. Despite such breakthroughs, however, no comprehensive theoretical framework describing the dynamic cerebral changes that occur during the different phases of learning of a sequential or adapted movement was available until recently. On the basis of results of brain imaging studies, Doyon *et al.* [4,5] have thus proposed an integrated view of the plasticity that motor memory traces can undergo across learning stages. Briefly, this model suggests that in the fast learning phase, both motor sequence and adaptation tasks recruit the CS and CC systems depending on the cognitive processes required in the task. When the skill has been learnt well, however, the neural representation of this motor behavior is then thought to be distributed in a network of structures involving only one of these two circuits; the CS and CC systems being crucial for consolidating and maintaining in long-term memory a new motor sequence or a motor adaptation skill, respectively.

Interestingly, the model proposed by Doyon and Ungerleider [4] makes several predictions with regards to the

contribution of each neural system as we acquire motor skilled behaviors. In this review, we summarize the results of recent behavioral, lesion and additional imaging work that deal with these postulates. We then offer a revised version of the model on the basis of new evidence of interactions with the limbic system, and of experience-dependent plasticity within the CS and CC neural systems during the fast learning phase.

Interactions between the cortico-striatal and the cortico-cerebellar systems during the early learning phase

In their original version of the model, Doyon and Ungerleider [4] stipulated that functional interactions between the CS and the CC systems are crucial for establishing the motor routines necessary to learn new skilled motor behaviors. Since this review, additional imaging studies supporting this prediction have been reported demonstrating that the striatum, cerebellum and other cognitive or motor related-structures contribute to this type of memory. For example, these structures have a role in both implicit and explicit sequence learning [6,7**], as well as in the acquisition of self-initiated, self-paced sequential finger movements [8]. Using motor adaptation paradigms, increasingly segregated activity in the lateral and posterior cerebellar cortex has been reported when subjects are adapting to a change in spatial rotation or velocity of a mouse in a target-reaching task [9]. Finally, activations in both the cerebellum and the basal ganglia have also been seen when volunteers are required to track a continuously changing, visually presented target by varying the force applied on a pressure sensor [10*].

Additional support for the predicted interaction between the CS and the CC networks during sequence and adaptation learning has come from behavioral and clinical studies. For example, Seidler [11**] has demonstrated that subjects not only can transfer the knowledge acquired during practice of a joystick-aiming task to three different rotation conditions but that they can also generalize this ability to another type of adaptation such as a change in gain of display of their movements, and to a sequence learning task using the same joystick apparatus. This suggests that before specificity of learning has been achieved, a similar (albeit not identical) neural network mediates these new motor skills. Using PET, Mentis *et al.* [12*] have also reported that, compared with healthy volunteers, patients with Parkinson's disease need to activate a greater volume of the cerebellum to achieve equal performance levels on a trial-and-error sequence learning task, suggesting that the CC system is capable of compensating when the nigro-striatal pathway is functionally impaired. Finally, in an elegant series of studies using a force field adaptation paradigm, Shadmehr and co-workers [13,14**] revealed that patients with Huntington's disease (HD) or at risk from HD, but not patients with cerebellar lesions, show an impairment in the use of

feedback control mechanisms to produce on-line correction of errors during an ongoing reaching movement. By contrast, cerebellar damage, but not HD, affected the individual's capacity to make use of these errors to modify the internal model necessary to compute the motor commands that initiate subsequent movements. Thus, the latter findings imply that the contribution of these two neural systems is complementary in nature.

Differential contribution of the cortico-striatal and cortico-cerebellar systems in motor consolidation

In their model, Doyon and Ungerleider [4] predicted that the cerebellum is crucial for the consolidation of a motor adaptation skill, whereas the striatum plays an equally important part in the consolidation of a motor sequence. Although findings consistent with the cerebellar-motor adaptation consolidation hypothesis have already been published [15], there is still no direct evidence that the striatum contributes to this process after learning a new sequence of movements. Substantiation of the later assumption comes, however, from recent imaging studies that focused on brain areas reactivated after practice on sequence learning. Indeed, Maquet, Peigneux and co-workers [16,17*] have shown that several brain areas, including the caudate nucleus, are activated during the acquisition of a probabilistic serial reaction time task, and that these structures are then reactivated during rapid-eye movement sleep, suggesting that the striatum participates in the consolidation of sequential skilled behaviors. These results are consistent with those of several other studies that have demonstrated that the consolidation of a finger sequence learning skill [18] is sleep dependent. For example, Walker *et al.* [19] have shown that spontaneous performance gains on this task are only observed after sleep, and not after an equivalent period awake. Furthermore, Fischer *et al.* [20] have reported complementary findings that suggest that the consolidation of motor sequence learning benefits from sleep, independently of whether subjects slept during the night or during daytime, thus precluding the hypothesis that motor consolidation on this motor task relates to circadian rhythm effects.

Importantly, however, there is increasing evidence that not every form of motor ability necessitates sleep for consolidation. Indeed, we (A Simard, J Doyon, unpublished) and others [21] have observed that the simple passage of time during daytime is sufficient to engage the process of consolidation of a motor adaptation skill. On the basis of such a behavioral dissociation, Doyon and Ungerleider's model [4] would thus propose that consolidation of a motor sequence learning after sleep should be associated with functional plasticity in the CS system, whereas consolidation of motor adaptation after the passage of time, or sleep, should be associated with cerebral changes in the CC system. At present, however, such a

working hypothesis still awaits further experimental investigations.

Dissociation between cortico-striatal and cortico-cerebellar systems in the automatic phase

When subject's performance on motor sequence or motor adaptation tasks has become automatic after extensive practice, Doyon and Ungerleider [4] proposed that the representation of the skill would be distributed within the CS and CC circuits. To investigate the neural substrates mediating this late learning phase, investigators have used one of two main experimental designs: the first uses a dual-task paradigm to determine whether or not a secondary task can be performed with minimal interference on the motor learning (primary) task of interest, whereas the second consists of comparing functional and/or anatomical plastic changes seen in individuals with over-learned skills (e.g. playing a musical instrument, knitting) with those seen in naive subjects. To date, however, studies employing these approaches have yielded inconsistent findings with respect to the prediction.

In a dual-task study designed to identify the neural substrate associated with performance during both early and automatic stages of self initiated memorized sequential finger movements, Wu *et al.* [8] reported that sequential movements activated similar brain regions in both conditions. Both before and after training, activity was observed in a distributed network of cortical and subcortical regions involved in the learning and execution of finger movements. There was less activity, however, in the cerebellum bilaterally, the left caudate nucleus and other related regions, suggesting that automatic performance was enabled by a functionally more efficient motor network. A similar conclusion was also reached on the basis of a study that compared the performance of professional pianists with that of musically naïve subjects on over-practiced tasks requiring bimanual playing scales [22]. The authors demonstrated that non-musicians elicited stronger signal increases than musicians in several cerebral structures. These included the cerebellar hemispheres bilaterally and the right basal ganglia, supporting again the notion that automatic behaviors are associated with a mere increase in efficiency of the same cortical and subcortical brain areas recruited during the early learning phase.

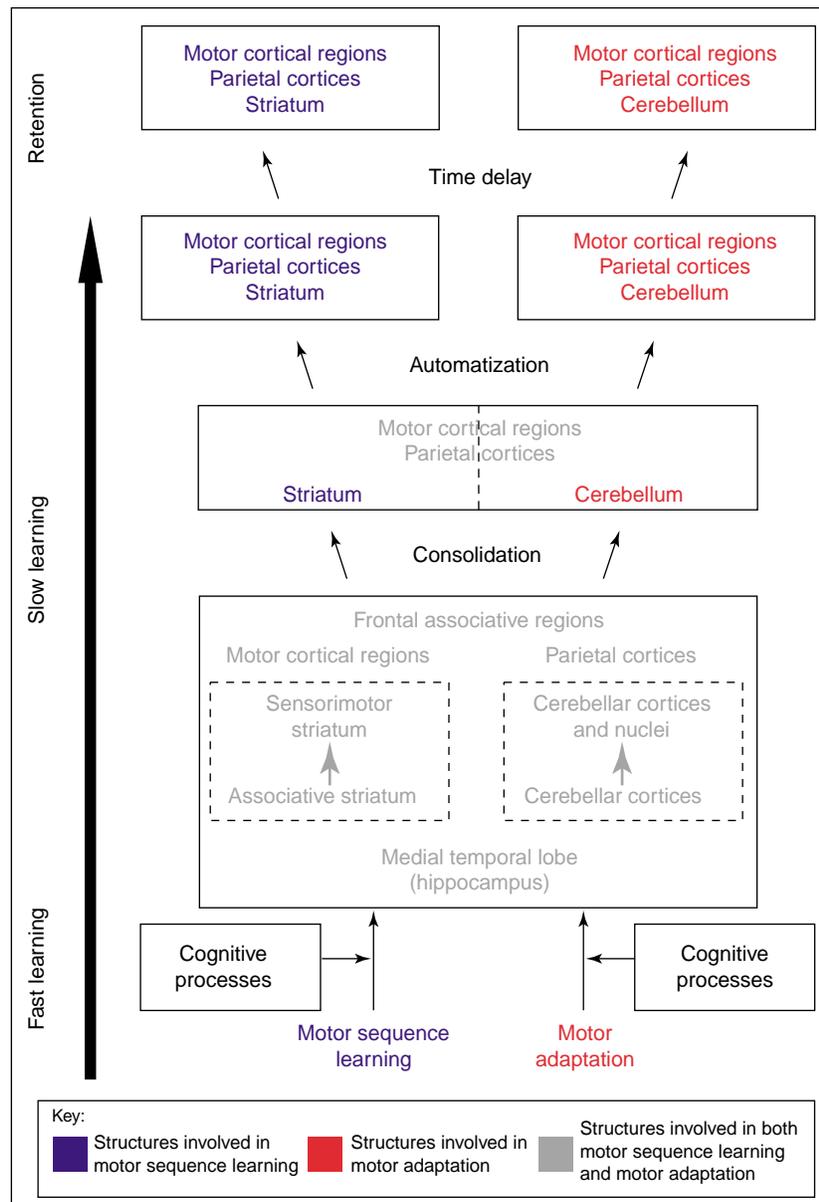
Contrary to the global efficiency hypothesis, however, recent work in our laboratory using fMRI with healthy subjects has shown that practice on sequence learning and motor adaptation tasks results in a functional dissociation of the CS and CC systems once they have become automatic. For example, Doyon and colleagues (unpublished) compared the pattern of brain regions active while highly skilled knitters performed stitches with their fully-

automatic, North American (Old) technique, or with a Continental (New) technique learned before scanning. Contrast between the NEW condition and a motor control condition requiring simple alternating crossing movements of the needles revealed an increase of activity in motor-related structures, including the putamen, globus pallidus and cerebellum (Lobules V and VI) bilaterally. By contrast, comparison of the OLD with the control conditions yielded activity in right parietal cortex, supplementary motor area (SMA) as well as bilateral putamen and globus pallidus regions, but not in the cerebellum. Interestingly, only the basal ganglia and pre-motor regions remained significantly active when the NEW condition was subtracted from the OLD, suggesting that the long-lasting representation of automatic sequential skills involves the basal ganglia and associated motor cortical regions.

More recently, we have also demonstrated that automatic execution of a motor adaptation task produces long-term plastic changes in the CC instead of the CS system (R Bouras, J Doyon, pers comm). In this study, subjects were scanned on the first day of practice (early learning) and after they reached automatic performance (i.e. after 21 days of practice on average) on a joystick, target reaching task. Automatic execution was assessed by verifying that subjects had reached complete asymptotic performance and by testing their performance in a dual-task condition. Although activations in the putamen and other motor areas were observed in the early learning phase, increased activity in the cerebellum and parietal cortex were seen after training, suggesting that the cerebellum and associated cortical regions are sufficient to mediate automatic adapted movements. Taken together, our findings are consistent with those of numerous other studies that reported a switch in the structures mediating these two motor behaviors as learning progresses [10^{*},23–26].

The inconsistent imaging findings reported above might be due, in part, to the cognitive processes involved in the tasks, the experimental designs employed in the studies and the individual differences among subjects in their cognitive, perceptual, motoric and learning abilities. Here, however, we suggest that the discrepancies reported above are probably related to the baseline control conditions used in the contrast analyses (see Doyon and Ungerleider [4] for a discussion of the methodological factors that can explain the heterogeneity among imaging studies). For example, Wu *et al.* [8] used a rest period as their control condition, whereas we and others have employed a motor control condition, enabling us to look at the experience-dependent neural plasticity involved in learning *per se*, non-contaminated by activity because of the mere motoric aspect of the task. Nevertheless, to better understand the real dynamic plasticity occurring during learning and automatization of a motor skill, however, we believe that one will need to go beyond

Figure 1



Revised model of Doyon and Ungerleider [4] describing the cerebral plasticity within the cortico-striatal and cortico-cerebellar systems during the course of learning a new sequence of movements (motor sequence learning) or to adapt to environmental perturbations (motor adaptation). This model proposes that, depending upon the nature of the cognitive processes required during learning, both motor sequence and motor adaptation tasks recruit similar cerebral structures early in the learning phase: the striatum, cerebellum, motor cortical regions, in addition to prefrontal, parietal areas and limbic areas. Dynamic interactions between these structures are likely to be crucial for establishing the motor routines necessary to learn the skilled motor behavior. Furthermore, new evidence indicates that cerebral functional plasticity within the striatum and the cerebellum can also be observed. A shift of motor representation from the associative to the sensorimotor striatal territory can be seen during sequence learning, whereas additional representation of the skill can be observed in the cerebellar nuclei after practice on a motor adaptation task. When consolidation has occurred, the subject has achieved asymptotic performance and their performance has become automatic; however, the neural representation of a new motor skill is then believed to be distributed in a network of structures that involves the CS or CC circuit depending on the type of motor learning acquired. At this stage, the model suggests that for motor adaptation, the striatum is no longer necessary for the retention and execution of the acquired skill; regions representing the skill now include the cerebellum and related cortical regions. By contrast, a reverse pattern of plasticity is thought to occur in motor sequence learning, such that with extended practice the cerebellum is no longer essential, and the long-lasting retention of the skill is now believed to involve representational changes in the striatum and associated motor cortical regions.

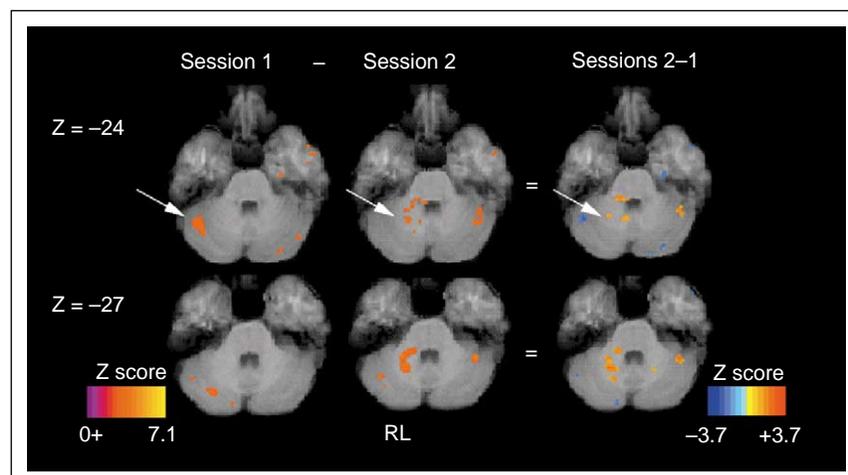
the usual activation maps obtained through peak-detection methods. This can now be achieved through the use of functional and effective connectivity analyses defined, respectively, as the temporal correlation between the time courses of activation of two regions and the influence of one neuronal population over another. One such approach using structural equation modeling (SEM), for example, has previously been employed to identify the spatio-temporal distribution of learning-related changes associated with the acquisition of an associative visuomotor task [27] or of an adapted, target-reaching movement in a disturbing force field [28]. Yet, this method is often limited by the fact that *a priori* anatomical knowledge of the cerebral network of interest is necessary for applying this statistical model. To offset this limitation, Benali and co-workers [29] have thus recently developed innovative data-driven methods to investigate the changes observed in large cerebral networks over time (i.e. dynamic connectivity). In a recent implementation of this new approach, Doyon *et al.* [30] scanned healthy volunteers over two days as they were learning to adapt to changes in the joystick movement coordinates to reach targets. While activations were observed in both the CS and the CC systems during learning, more interesting findings were obtained with the functional connectivity analyses. Our results demonstrated that experience-dependent plasticity during motor adaptation was first characterized by a transient overall increase in the amount of inter-regional connectivity within a large-scale network of cerebral structures involving the CS and CC systems. This was then followed by a gradual decrease in the number of connections within this network, and the retention of functional links within the CC system only,

again supporting the prediction that interactions between the CS and CC are necessary at the beginning of the motor adaptation process, but that specialization within the cortico-cerebellar system is sufficient for maintaining this new skilled behavior.

Doyon and Ungerleider's model of motor skill learning revisited

Since its first publication, new evidence has accumulated that calls for a revision of Doyon and Ungerleider's model [4] of motor learning. First, recent evidence from a fMRI experiment conducted at 3.0 Tesla has shown that both implicit and explicit motor sequence learning measured with the serial reaction time task does not only activate the usual cortical and subcortical motor regions in the early learning phase but also the hippocampus and related cortices [7**]. The latter findings suggest that, in addition to the CS and CC systems, the limbic structures of the medial temporal lobe contribute to the acquisition of sequential movements, regardless of the subject's awareness. These results are consistent with animal [31] and human [32] work demonstrating that these different functional networks can interact together during learning. It should be noted, however, that the limbic involvement might not be necessary for the learning to occur and to be maintained over time, because contrary to lesion studies in clinical populations with striatal or cerebellar dysfunctions, amnesic patients with damage to the limbic system can typically acquire habits and motor skills normally. Second, cerebral functional plasticity within the striatum and the cerebellum has also been observed during motor learning. Indeed, in collaboration with Lehericy and other colleagues (J Doyon, H Benali, pers comm), we have

Figure 2



Merged fMRI-MRI horizontal sections through two slices of the cerebellum illustrating the transfer in neural representations from the cerebellar cortex (session 1) to the dentate nucleus (session 2) during learning of an explicitly known sequence of finger movements. The results are shown as z score maps and reveal significant increases (orange) in BOLD signal over two scanning sessions, and the significant increases and decreases (blue) observed in the subtraction analysis (Session 2 – Session 1). They are displayed overlaid on a coplanar, high-resolution MRI scan of a single subject. The z coordinate represents the position of the sections relative to the anterior-posterior commissure line into Talairach stereotaxic system.

recently demonstrated in a fMRI study at 3.0T that there is a shift of motor representations from the associative to the sensorimotor territories of the striatum during the explicit learning of motor sequences, supporting the notion that motor skills are stored in the latter territory of the basal ganglia [3,33]. Furthermore, a transfer of activity from the cerebellar cortex to the dentate nucleus (see Figure 1) has also been observed as subjects are acquiring implicit knowledge of a declaratively known sequence of movements [23], learning to track a continuously changing force target using a pressure sensor [10[•]] or adapting to a force field in a target reaching task [28]. Taken together, these findings thus suggest that in the fast learning phase, functional and physiological changes occur at both intra- and inter-system levels, and that this plasticity is necessary to build the motor routines that will then be consolidated over time as well as after additional practice (see Figure 2).

Conclusions

In conclusion, most of the very recent behavioral, lesion and imaging work investigating the neural substrates mediating motor skill learning supports the varied predictions advocated by Doyon and Ungerleider [4]. New evidence confirms that interactions among cortico-striatal, cortico-cerebellar and limbic (hippocampal) structures are crucial for building the motor memory trace, which will then be consolidated and maintained over time within a more specialized subsystem depending on the type of motor skilled behaviors (i.e. motor sequence versus motor adaptation) acquired through repeated practice.

It should be noted, however, that the model reviewed here is specific to conditions that require the acquisition of new spatio-temporal motor sequences or the modification of an internal motor representation necessary to adapt to environmental manipulations. Indeed, one would hypothesize that forms of motor and visuomotor learning that are more cognitive and associative in nature [34] are going to recruit slightly different cerebral networks that will then undergo other patterns of cerebral plasticity with learning.

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