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Review

Contributions of the basal ganglia and functionally related brain structures to motor learning

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ABSTRACT

This review discusses the cerebral plasticity, and the role of the cortico-striatal system in particular, observed as one is learning or planning to execute a newly learned motor behavior up to when the skill is consolidated or has become highly automatized. A special emphasis is given to imaging work describing the neural substrate mediating motor sequence learning and motor adaptation paradigms. These results are then put into a plausible neurobiological model of motor skill learning, which proposes an integrated view of the brain plasticity mediating this form of memory at different stages of the acquisition process.

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1. Introduction

Our capacity to plan, learn and retain new motor skills is essential for going through daily activities. Indeed, such ability is regularly elicited when, for example, one executes smooth eye-body

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coordinated actions like hitting a golf ball with a club, or when one produces multi-joint movements while reaching and grasping small objects in space. Accordingly, a great deal of research in this field has been devoted to better understand the behavioral determinants and the neural substrates that mediate this type of procedural memory. Motor learning has been experimentally studied using tasks designed to measure the incremental acquisition of sequential movements into a well-articulated behavior (motor sequence learning [MSL]), or to tests our capacity to compensate for environmental changes (motor adaptation [MA]). MSL paradigms typically require subjects to produce a sequence of movements that they either know explicitly before training (e.g., [22,24,29,56,57,83,103,114]), learn implicitly through repeated practice (e.g., [3,22,40,88,93]), discover by trial and error [53–55,89,106], or acquire through probabilistic rules [68,82]. Motor responses in those sequence learning tasks involve either finger-to-thumb opposition movements (e.g., [56,57,95]), finger presses on response boxes (e.g., [24,39]), movements of the whole arm (e.g., [22,40]), oculomotor sequential movements [3,4], or varying the isometric force applied to a pressure plate to follow a repeating waveform pattern [33,34,40]. By contrast, MA paradigms necessitate that participants adapt to changes in visual rotations (i.e., kinematic MA measure) [51,52,108] or to perturbations applied by a velocity-dependent field that pushes the hand perpendicular to its direction of motion (dynamic MA measure) (e.g., [62,96,97,99,101], see [108] and [98] for reviews). Operationally, the acquisition of such motor abilities is generally measured by a reduction in reaction time and number of errors, and/or by a change in movement synergy and kinematics (see [19,25,61,98] for reviews). Furthermore, these changes in performance are known to be incremental, implicit in nature, long lasting and dependent upon “on-line” and “off-line” triggered plastic changes in the brain.

Psychophysical studies have demonstrated that the incremental acquisition of motor skills follows several phases: First, an early, fast learning stage in which considerable improvement in performance can be seen within a single training session; and second, a later, slow stage in which further gains can be observed across several sessions of practice (e.g., [57]). Interestingly, an intermediate phase corresponding to the consolidation process of the motor routine has also been proposed, based on the demonstration that a motor memory trace can be disrupted by the administration of a competing task within a time window of 6–8 h, or when spontaneous performance gains are reported following a latent post-training period of more than 6 h without additional practice on the task. Once consolidated, the motor memory trace is believed to be resistant to interference [5], and to become readily retrievable despite long periods of time without additional training. Finally, motor skilled behaviors are regarded as fully automatized when actions are carried out effortlessly with little attentional resources needed for their successful completion.

Over the years, work ranging from electrophysiological and lesion experiments in animals to clinical population-based and imaging studies in humans has undoubtedly demonstrated that the basal ganglia, and the striatum in particular, play a critical role in the planning, learning, and execution of a new motor skill. The basal ganglia are composed of a series of subcortical nuclei that are organized into sensorimotor, associative and limbic territories based upon their anatomical connectivity and functions. The caudate nucleus, putamen and subthalamic nucleus constitute the input nuclei as they receive major afferent connections from the cerebral cortex, midbrain and thalamus, whereas the internal segment of the globus pallidus and the substantia nigra, pars reticulata form the output nuclei that send back treated information to frontal cortical areas via thalamic nuclei [1,15]. Ample evidence indicates that the processing of motor information flows through a topographically organized and segregated loop linking motor-related cortical

regions like the primary (M1), supplementary (SMA), premotor (PMC) and cingulate (CMA) motor areas with the sensorimotor divisions of the basal ganglia and thalamus [77]. Finally, a distinction between the anterior associative putamen region and the more posteroventral sensorimotor area of the putamen and globus pallidus has also been observed in humans based on diffusion imaging data [66], hence forming the anatomical basis for the functional dissociations seen between these putamen areas during the early learning and planning phase preceding the execution of learned motor sequences, for example [8,21,30,65].

Yet, the cortico-basal ganglia circuits do not constitute the only anatomical system implicated in the acquisition and planning of skilled actions. The cerebellum and its motor-associated structures, like the somatosensory motor cortex and ventral PMC forming the cortico-cerebellar loop through the dentate nucleus and ventral-posterior lateral nucleus of the thalamus [59], have also been shown to contribute to motor learning. Dynamic brain plasticity within the striatum and cerebellum, as well as functional interactions between these two cortico-subcortical systems has been reported depending on the stage of the learning process, nature (i.e., new versus learned motor behavior) of the action being planned and the type of skill being acquired (MSL, MA). Furthermore, consistent with recent electrophysiological studies in primates [13], findings from functional magnetic resonance imaging (fMRI) studies conducted at 3.0 T (e.g., [91]) and proper correlation analyses of the BOLD changes occurring during the very early stage of the learning process [4] suggest that the hippocampus contributes also to the encoding and consolidation of motor skills.

In this review, we will thus describe the brain plasticity, i.e., the reorganization over time of brain circuits, involved in motor skill learning. We will focus on the dynamic changes that are observed within the cortico-striatal system as one is learning or planning to execute a newly learned motor behavior up to when the skill is consolidated or has become highly automatized. Imaging work from Doyon's laboratory and from other research groups will be described. A special emphasis will be put on MSL paradigms, although results from imaging studies using MA tasks will also be reported to highlight the role that the cortico-striatal system plays in this other type of motor learning. Using standard contrast and correlation statistical analyses, as well as functional connectivity approaches, we will also discuss the functional interplay that exists between the cortico-striatal, cortico-cerebellar and limbic systems in this form of learning. Finally, these imaging results will be put into a plausible neurobiological model of motor skill learning [21,23,25], which proposes an integrated view of the brain plasticity mediating this form of procedural memory at different stages of the acquisition process. Due to space limitations, however, this review does not describe the work on the acquisition of arbitrary visuomotor conditional associations, normal motor prehension, object use, imitation and apraxia (see [38] for a review of the relevant literature on these related issues).

2. Motor sequence learning

From the beginning, the field of motor learning has been dominated by studies that looked only at the neural plasticity that occur in the fast learning stage where improvements in performance are most dramatic. Indeed, since early 1990s, a plethora of neuroimaging studies using positron emission tomography (PET) and fMRI have investigated the brain plasticity mediating performance changes seen during early encoding of a new motor skilled behavior. These studies have demonstrated that the striatum plays a critical role in encoding motor programs (e.g., [22,39,53,54,86,92,95]). The striatum, in concert with motor cortical regions, is activated during implicit sequence learning [22,39,86,87], when subjects are practicing a motor sequence for which they have complete explicit

knowledge [39,83,92,95], as well as during tasks [39,92,95,106] in which subjects need to utilize problem-solving strategies to find the repeating sequence of finger movements [53,55,106]. Evidence in support of the role of the basal ganglia in motor skill learning also comes from impairments found in patients with striatal dysfunction (e.g., in Parkinson's or Huntington's disease), who generally show a deficit in acquiring new motor sequences (see [20] for a more detailed discussion of the conditions under which Parkinson's disease patients have shown an impairment in MSL). In most studies referenced above, however, the cerebellum has also revealed simultaneous increased learning-dependent activity, suggesting that not only the cortico-striatal, but the cortico-cerebellar system contributes to the acquisition of motor sequences. On the few occasions in which cerebellar activations were not reported [39,41,86], this was usually due to the limited field of view of the PET cameras, which precluded full visualization of this structure [19,109]. Finally, results from early imaging studies have also revealed the gross dynamic functional interactions that occur between the striatum and cerebellum as subjects are practicing the motor skill until they reach asymptotic performance in the first training session. Indeed, while experience-dependent cerebellar activations have regularly been observed at the beginning of the acquisition process (e.g., [22,53]), several research groups using appropriate active control conditions (see [25] for a more detailed discussion of the methodological factors that can affect patterns of imaging results), have shown that this activity decreases with practice to the point of becoming undetectable when the sequential movements are well learned [24,35,42,54,94]. By contrast, investigators have reported that the striatum remains activated even when subjects have reached asymptotic performance during that session and beyond this early learning phase (e.g., [22,42,54]). Together, the latter findings suggest that the striatum and its associated motor cortical areas are critical for the long-term retention of well-learned sequences of movements.

In recent years, there has been growing interest in uncovering the learning processes that span over longer time frames, as there is evidence that changes in performance can occur over multiple sessions encompassing days, weeks or even months of practice [15,16]. Using fMRI techniques, researchers have also been able to better characterize the motor functions associated with the cortico-striatal and cortico-cerebellar systems, as well as the brain plasticity that takes place between and within each loop (e.g., [24,29,103,106] see [20,21,23,48] for reviews). For example, evidence supporting the fact that a functional interaction between the two cortico-subcortical systems can persist in the slow learning stage comes from an fMRI study carried out by Doyon and Ungerleider [25]. In this experiment, subjects were scanned during motor sequence learning using a version of the serial reaction time task, in which they were required to press as quickly as possible one of four buttons corresponding to the location of a red circle that appeared on a screen. The stimuli were either presented in an unpredictable order (random condition) or followed a repeating 10-item sequence of movements that was taught explicitly to each subject prior to scanning (explicit learning condition). Subjects were scanned over three separate sessions with intervening periods of practice of the 10-item sequence administered just prior to the second and third scan sessions. As a group, the subjects showed consistent improvement in executing the sequence of finger movements across scanning sessions, and attained the slow learning phase as their level of performance became stable in Session 3. Analysis of the functional imaging data in the early phase of learning revealed activations in the cerebellum, as well as in the right anterior cingulate, dorsal PMC and inferior parietal regions. At the end of Session 3, however, these cerebellar and cortical regions showed significant reductions in activity, while right hemispheric activations were observed in the striatum, as well as in the SMA, ventrolateral prefrontal cor-

tex, precuneus, and inferior parietal area, hence suggesting that the striatum and related motor cortical regions, but not the cerebellum, are sufficient to express and retain learned sequential behaviors.

Lehéricy et al. [65] have also investigated the neurofunctional changes observed during the entire learning process of a motor sequence: from encoding to automatization of the skill. Fourteen right-handed volunteers were scanned with a high field (3T) magnet as they were required to practice an explicitly known finger sequence of eight moves using the left hand. On Day 1, MRI scanning was carried out on three occasions to follow the dynamic cerebral changes seen during the early learning phase. Subjects were scanned again on Day 14 as well as after a month of daily practice to identify the brain structures involved during the slow and automatization phases of MSL. Automatization in the subject's performance was measured using a dual-task paradigm (i.e., reading aloud a simple text while performing the sequence task) administered before the last fMRI session. As expected, and similarly to previous pioneering fMRI work in this field by Karni et al. [56,57], the subjects' performance greatly improved with practice, reached a very stable plateau at the end of the 4-week training period, and was subject to minimal interference from the secondary task. Over the entire course of the training, learning-dependent, blood oxygenated level dependent (BOLD) signal changes revealed a significant increase in the sensorimotor region of the putamen, as well as in the pre-SMA, SMA proper, premotor and superior parietal cortices. Interestingly, this increase of activity persisted after 4 weeks of practice, and was then accompanied by a general decrease of activity in several areas within the cerebellum, including lobules V, VI, and Crus I as well as in the dentate nucleus, again confirming the distinct role of the cortico-basal ganglia loop in the retention of well-trained motor sequences. Such findings are consistent with work from Floyer-Lea and Matthews [34] who investigated both the early and late (after 3 weeks of practice) phases of MSL through the use of a sequence task demanding variable isometric force applied to a pressure plate. Early learning was associated with a decrease of activity in several cortical regions (i.e., the dorsolateral prefrontal, anterior cingulate, posterior parietal, and primary motor cortices) and the cerebellar cortex. By contrast, late learning after much improvement and some automaticity in subjects' performance elicited significant activity in the somatosensory and motor cortices as well as in the putamen.

MSL brain plasticity changes across an identical time course (1 month) of learning has been investigated by Duff et al. [29]. Similar to Lehéricy et al. [65], healthy participants were trained on an explicitly known sequence of finger movements and were scanned on three occasions; before training and after 2 and 4 weeks of daily practice. Importantly however, contrary to a conventional voxel-wise, peak-detection analysis based on simple contrasts, brain-behavior correlations or conjunctions between experimental conditions (see [19] for a discussion), Duff et al. used an innovative statistical approach designed to appreciate the full complexity of the BOLD response known to vary greatly, especially when tasks are performed over long (>30 s) periods of time in a block design. The latter approach is based on observations made by Harms and Melcher [46] who have reported that under those conditions, the BOLD signal reveals complex features: (a) brief spikes of activity at the beginning and at the end of the task, (b) changes in sustained and ramping activities during task performance, and (c) signal undershoots after completion of a block of trials. Consequently, to get a more reliable assessment of the cerebral plasticity associated with motor learning, Duff et al. [29] have conducted a systematic characterization of the BOLD response shape dynamics over the whole brain. Based on the OSORU (onset, sustained, offset, ramp and undershoot features of the BOLD signal) model proposed by Harms and Melcher [46], their analyses revealed that

motor learning alters certain characteristics of the response shape, suggesting that these features reflect different aspects of neurovascular dynamics. Among their many findings, the authors reported significant increases of the 'sustained' component in both thalamus and putamen bilaterally after 2 weeks of training, with significant concomitant decreases of the 'onset' component in several cerebral regions including the cerebellum. These results are important because they demonstrate that such transient dynamics may be a widespread phenomenon within the cortico-striatal and cortico-cerebellar systems, and thus that one needs to better quantify the spatio-temporal dynamics of BOLD signal responses that occur at different stages of the sequence learning process.

In addition to the established functional inter-relationship found between the cortico-striatal and cortico-cerebellar systems during MSL, recent work has shown that the limbic system is also implicated in this form of procedural memory. Schendan et al. [91] have demonstrated, through an fMRI experiment at 3.0T, that the hippocampus was significantly activated during MSL measured with the serial reaction time task, irrespective of whether sequential knowledge was acquired implicitly or explicitly. The latter findings suggest that, in addition to the motor-related subcortico-cortical systems, the hippocampus contributes to the acquisition of sequential movements regardless of the subject's awareness. These results are consistent with animal [73] and human [84] work providing evidence that these different functional networks can interact together during declarative and procedural learning. It should be noted, however, that the limbic involvement might not be necessary for maintaining the newly learned skilled behavior over time, as contrary to lesion studies in clinical populations with striatal or cerebellar dysfunctions (e.g., Parkinson's disease, Huntington's disease; Primary forms of Dystonia), amnesic patients with damage to the limbic system like H.M. can typically acquire habits and motor skills normally [75,98].

Finally, the studies described above have allowed us to gain valuable insights into the extent of the dynamic cerebral interactions occurring between the striatum, cerebellum, motor cortical areas and hippocampus during motor skill learning. Yet their interpretations at the network level remain limited. Indeed, none of them explores the possible functional or effective connectivity between activated regions at a large-scale neural level. A very small number of studies pertaining to the field of motor learning have been conducted using such a global approach (see [14,103,107]). Furthermore, among those few, Tamas et al. [103] are (to our knowledge) the only ones who have carried out a whole-brain connectivity analysis on MSL data. These authors have used a model-free approach based on a novel variant of the independent component analysis (ICA) technique to investigate the dynamic interactions occurring between brain activated regions. Young healthy participants were scanned in a single session while practicing a visually cued and explicitly known sequence of finger movements, or while performing a control condition in which the finger movements were randomized. The analyses yielded two task-related components; the first revealed decreased activity in a fronto-parieto-cerebellar network, whereas the second showed increased activity in a network including the posterior parietal and PMC regions, but not the striatum. The lack of correlated activity involving the striatum is surprising, but may be explained by the fact that the subjects were only tested in their very early learning phase with a small number (total = 30) of repetitions of the sequence, and thus that they had not reached asymptotic performance at the end of training. Nevertheless, although slightly differing with results from previous imaging studies, the work from Tamas et al. [103] is key, as it shows that multivariate data analysis techniques such as ICA are useful tools to identify neural networks associated MSL. Yet in this study, the authors focused on the early learning phase only, and consequently much more work using functional connectivity analyses is needed

in order to characterize the dynamic changes in spatially distributed patterns of coherent activity at the whole-brain level that are most probably occurring during the different learning stages.

3. Intra-system brain plasticity associated with motor learning

In addition to the brain plasticity that occurs at the systems level, accumulating data from work in animals and humans indicate that dynamic changes in motor representations during motor learning also take place within the cortico-striatal system and cerebellum (e.g., see [21,43,48] for reviews). For example, in Lehericy et al.'s study [65] described above, a gradual shift of increased activity within the putamen was observed as subjects were practicing the finger sequence task in the first training session. Very early, learning related BOLD activity over the three scans on Day 1 revealed significant activity in the associative/premotor territories of the basal ganglia, including the dorsal parts of the putamen and rostral striatal areas, the anterodorsal globus pallidus, the corresponding output nuclei of the thalamus and the subthalamic nucleus. After 10 min of practice, however, improved performance on the task was associated with a decreased of activity in the rostradorsal (associative) regions of the putamen, followed by significant activations in the posteroventral regions of the putamen that then persisted even after a month of daily practice (see Fig. 1). Our results [65] reveal that the associative region of the putamen is mainly active at the beginning of finger sequence learning, but that a gradual, "shift" of activation toward the sensorimotor area can be observed once subjects have reached asymptotic performance within the first training session, hence suggesting that newly acquired motor sequences are represented in the latter territory of the basal ganglia. These findings are consistent with other imaging studies that have reported activations in the rostral portions of the striatum during early MSL (e.g., [54]), and more posterior activations when the motor sequence is well practiced (e.g., [6,24,41]). They are also in accord with a large number of experiments in primates where reversible pharmacological blockage of the associative region of the putamen using muscimol (a GABA agonist) produced an impairment in learning new sequences, whereas a similar blockade of the sensorimotor region led to a deficit in the execution of well-learned motor sequences [76] (see [48] for a review). Finally, Lehericy et al.'s study [65] confirms and extends to humans Hikosaka's model of MSL. They support the notion of a double representation of newly learned motor sequences: the anterior (associative) region of the putamen (in link with parietal and prefrontal cortical regions) being critical for building a "spatial representation" of the sequence, and the posterior (sensorimotor) area of the putamen (related to motor cortical regions) playing a major role in creating a "motor representation" of the sequence [48].

A functional transfer of activity from the cerebellar cortex to the dentate nucleus (one of the cerebellar output nuclei), most probably reflecting a switch in representations during motor learning, has also been reported. For example, when Doyon et al., [24] scanned healthy participants on three separate sessions while they were practicing an explicitly known sequence of finger movements until their performance reached a plateau in the slow learning phase (see above for more details), BOLD signal changes evoked a very interesting pattern of results within the cerebellum (see Fig. 2). Early learning during Session 1 was correlated with increased BOLD activity in the cerebellar cortex ipsilateral to the hand used in the task. With more practice, however, activity in the cortex decreased from Session 1 to Session 2, but increased in the dentate nucleus during that same training period. Such findings suggest that the cerebellar cortex is recruited early in sequence learning, but that its contribution then declines as proficiency at performing the task improves. By contrast, this gain in performance was associated

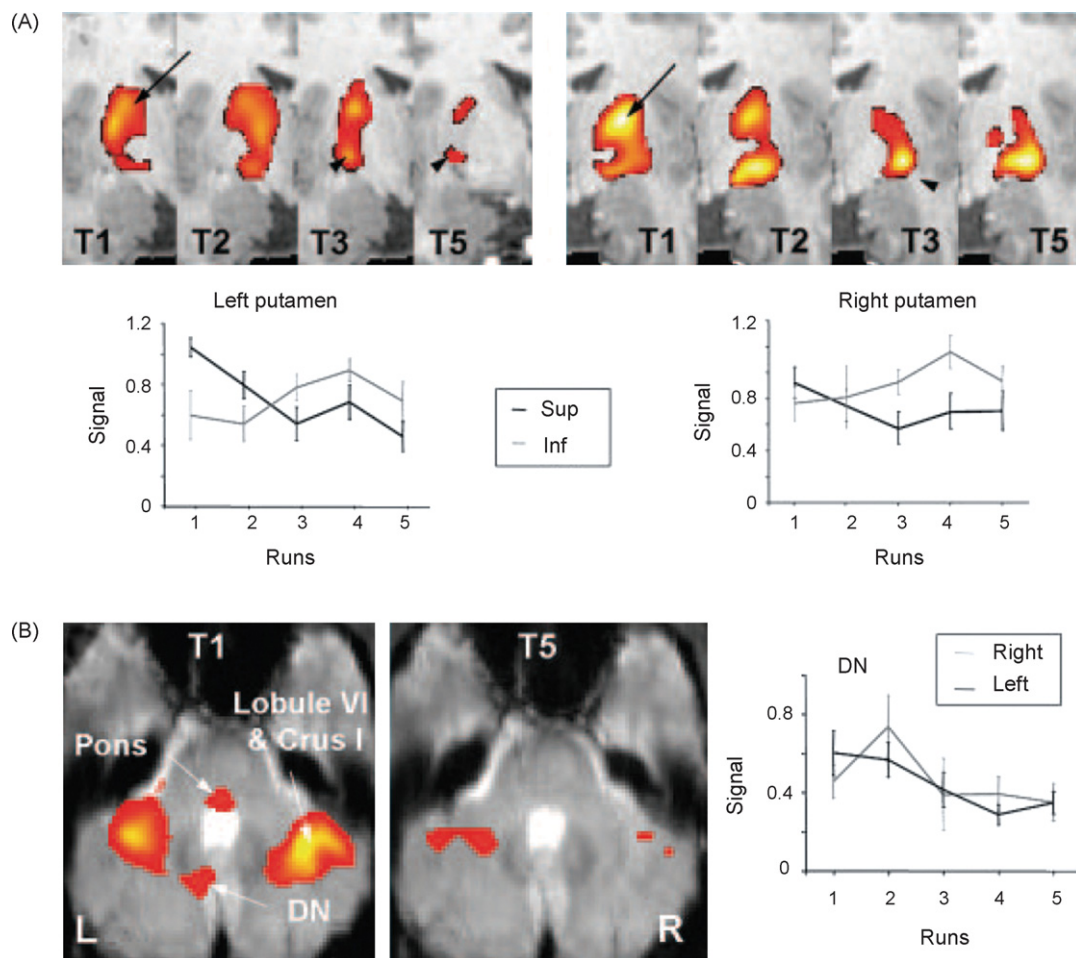


Fig. 1. Activation patterns within the basal ganglia during motor sequence learning [65]. (A, top) Activation maps obtained in the putamen superimposed on a coronal T1-weighted image. There was a progressive activation decrease in the dorsal part of the putamen (arrows) and an increase in a more ventrolateral area (arrowheads) bilaterally, which persisted after 4 weeks of training. (A, lower) Percentage signal increase SEM averaged across all subjects for each run of the trained sequence confirmed the activation decrease in the dorsal putamen and increase in the ventral putamen (RM-ANOVA). (B, left) Activation maps obtained in the cerebellum during the T-sequence (T1 on day 1 and T5 on day 28). Activation in the lateral cerebellar hemispheres, the left DN, and the pons decreased with training. (B, right) Percentage signal increase SEM averaged across all subjects for each run of the trained sequence in the left and right DN. In the right DN, activation increased transiently during T2 (10 min of practice) and returned to pre-training values. All activation maps are corrected for cluster extent at P 0.05 (height threshold P 0.0001).

with recruitment of the dentate nucleus, suggesting a transfer of plasticity in the neural representation of the motor sequence from the cerebellar cortex to the deep cerebellar nuclei. Importantly, such a pattern of findings has also been seen when young subjects are learning to track a continuously changing force target using a pressure sensor [33], or adapting to a force field in a target-reaching task [81]. Taken together with the results from the basal ganglia described above, these findings thus suggest that functional and physiological changes during the fast learning phase of a motor skill also occur at the intra-system level, that this plasticity is necessary to build the motor routines that will then be consolidated over time, and that this type of intra-system plasticity is not restricted to MSL, as it has been seen in studies using MA paradigms as well.

4. Planning motor sequences

Before executing sequential behaviors that are part of our repertoire of motor skills, one regularly needs to plan individual movement elements into a properly timed and spatially ordered sequence. Such a faculty is crucial, as it allows us to “anticipate events, select movements, specify their ordering and better control actions online” [30]. Although not studied as well as the learning process itself, recent experimental work has given us some clues regarding the brain structures that could be involved in this

premovement phase. Indeed, such an important question has previously been studied using the go, no-go and instructional delay tasks (see [38] for review). More relevant to our line of reasoning in this literature review, however, two recent imaging studies using single event fMRI designs and analyses have investigated the neural substrates involved in planning motor sequences [8,30], see also [37,78,79]. Importantly, their results demonstrate that planning-related brain activity is not only present in motor cortical regions like the SMA (and pre-SMA in particular) and CMA [9–11], but in the basal ganglia as well. First, Elsinger et al. compared BOLD signals both before and while subjects executed finger sequences with the right hand that differed in terms of the level of complexity (simple, complex) and the nature of the motor command (internally generated [IG], externally guided [EG]). In the simple sequence condition, subjects were asked to perform five consecutive key presses with only one of the three fingers used for this task (e.g., 11111), whereas in the complex sequence condition, they were required to produce heterogeneous sequences implicating all three fingers (e.g., 12131). In the IG condition, subjects were first exposed to information about the sequence (e.g., 23231) that they needed to produce after being given a cue in the “Movement Response” phase of the trial, while in the EG condition, they were given no such information (e.g., XXXXX) before being asked to produce one of the sequences (e.g., 13121) during the same “Movement Response” phase. Direct

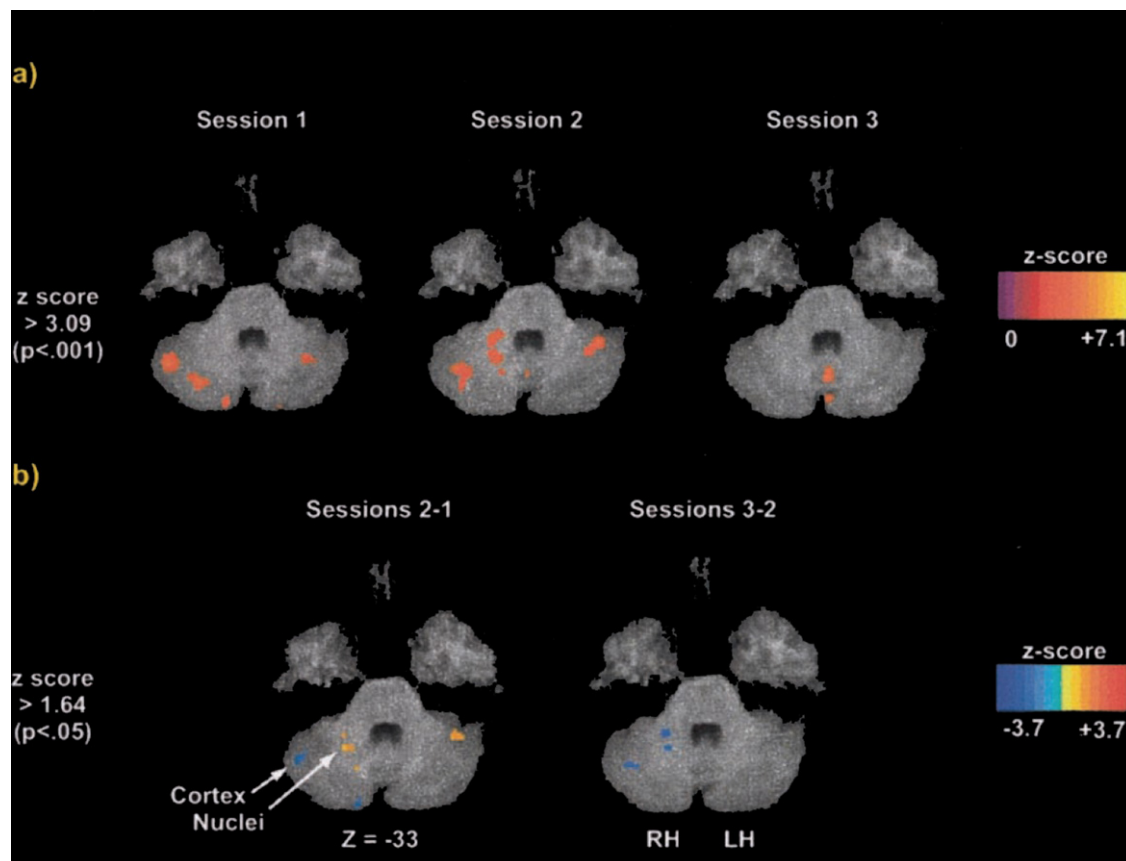


Fig. 2. Activation patterns within the cerebellum during motor sequence learning [24]. Merged fMRI–MRI horizontal sections through the cerebellum illustrating the results of the multiple regression analysis for the learning–random regressor averaged over the nine subjects. The results are shown as z score maps and reveal both increases (orange) and decreases (blue) in BOLD signal over the three scanning sessions, and are displayed overlaid on a coplanar, high-resolution MRI scan of a single subject. In the horizontal sections, the z coordinate represents the position of the section relative to the anterior–posterior commissure line. The subject's right cerebellar hemisphere is on the left. (a) Significant increases and decreases of activation in both the cerebellar cortex (lobule V and crus 1) and deep nuclei across sessions. (b) Results of the subtraction analysis comparing the z score maps obtained in Session 2 versus Session 1, and in Session 3 versus Session 2.

comparison of the premovement and movement periods revealed BOLD activity in the SMA/CMA, lateral PMC and anterior putamen that was greater in the premovement IG than in the movement IG condition, hence suggesting that the cortico-striatal system contributes to internal planning of sequential actions before they are put into operation. Second, using a similar approach, Boecker et al. [8] investigated the brain circuitry involved prior to producing either self-initiated or externally driven sequences of movements. Contrary to Elsinger et al. [30], however, subjects were required to execute a unique, well automatized four-finger motor sequence. Again, when the planning phase of the IG condition was compared to that of the EG condition, increased activity was found in a distributed network of motor-related structures including the SMA, CMA, parietal regions, midbrain nuclei (red nucleus and subthalamic nucleus), as well as the anterior putamen contralateral to the hand used. Together, the results of these studies highlight the fact that the basal ganglia and its related brain structures do not only play a major role in the cognitive processes mediating the encoding and maintenance of motor sequences over time, but that they are also implicated right before sequential behaviors are implemented in real life.

5. Motor adaptation

A large body of evidence indicates that the neuronal substrate primarily responsible for the encoding, consolidation and long-term storage of adapted movements comprises the cerebel-

lum and related structures [14,16,44,101] see [19,21,23,25,61,98] for reviews). Support to this statement comes from clinical population studies, which have demonstrated that while patients with Parkinson's or Huntington's disease show intact performance on paradigms designed to measure MA like mirror figure tracing or prism adaptation [2,36,63,64], those with damage to the cerebellum are impaired on these types of tasks [71,90,105], see [104] for review). Nevertheless, Smith and Shadmehr [101] have conducted a more refined analysis of the type of errors that patients with basal ganglia dysfunction do during the target-reaching force-field task. They have demonstrated that damage to this system produces a disturbance in error feedback control. This was reflected by a poor compensation of the motor command in the early part of the reaching movement [100], but not by a deficit in adapting to novel arm dynamics errors from trial to trial [101].

Consistent with such findings, results from imaging studies have shown that the striatum also contributes in some way to the motor commands necessary to achieve the required motion. Interestingly, however, functional interactions between the two subcortico-cortical systems while performing this type of MA task have revealed a pattern of findings opposite to the one described above with MSL. In a series of PET studies, Shadmehr and Holcomb [96,97] have found that the capacity of subjects to adapt to a perturbing force field when reaching randomly presented targets with a robotic arm was first associated with increased activity in the left putamen and dorsolateral prefrontal cortex bilaterally. Later in the

fast learning phase of the first training session when subjects failed to show further gains in performance, however, decreased activity in the putamen was seen, while increases in activation were observed in the cortico-cerebellar system. This transient increase of activity in the striatum during MA has been corroborated by Krebs et al. [62], who have used a similar force-field task with PET. In the latter study, early (fast) learning was associated with activations in the ventral striatum, as well as in the contralateral primary sensory cortex and bilateral parietal association areas. By contrast, when the skill was well learned and the subjects produced smooth reaching movements, there was a shift of activity from the striatum and parietal areas to the left motor and PMC regions, as well as the right cerebellar cortex.

A similar pattern of results has been found in one of our recent study, in which both standard peak-detection and data-driven functional connectivity analyses [7,70] were used to investigate the dynamic functional changes associated with acquisition of a kinematic MA ability. Eleven subjects were scanned while performing a target-reaching task, in which they were required to use a joystick to move a cursor from the center of a screen to one of eight targets following an elliptical trajectory within a time limit (3000 ms). In the “inversed mode” condition, the relation between movements with the joystick and direction of the cursor was inverted on each trial, while they were spatially compatible in the “direct mode” (control) condition. Subjects were scanned during five runs on two consecutive days, and additional periods of practice were administered between scanning sessions in order to ensure that subjects reached asymptotic performance on Day 2 (see Fig. 3). BOLD signals were recorded using a standard single-shot echoplanar imaging sequence (TR = 3500 ms, TE = 40 ms, 64×64 matrix, 42 slices) on a 3.0T system, as well as a combined block and event-related design. As expected, comparison of the inversed and direct modes over the two days yielded a stable activation in lobules

V–VI of the left cerebellar cortex, an increase of activity in the cingulate and primary motor regions, as well as a decrease of activity in the parietal cortex bilaterally. Furthermore, greater activity in the sensorimotor region of the putamen and globus pallidus, pre-SMA and parietal cortex were observed on Day 1 compared to Day 2, whereas greater activity in the cerebellum and medial prefrontal cortex were seen on Day 2 compared to Day 1. More interestingly, however, functional connectivity analyses revealed that the brain acquires this motor skill through interesting spatio-temporal dynamics. Experience-dependent plasticity during MA was first characterized by a transient overall increase in the number of inter-regional connectivity within a large-scale network of cerebral structures involving the cortico-striatal and cortico-cerebellar systems (see Fig. 4A). When subjects completed the fast learning phase on Day 1, however, the amplitude and number of functionally connected regions with the cortico-cerebellar system increased, and the striatum was now functionally linked with other motor cortical regions (see Fig. 4B). This was followed on Day 2 by a gradual decrease in connectivity between the striatum, cerebellum and motor-related structures, as well as the retention of functional links that were restricted to the cerebellum and related cortical structures via the thalamus (see Fig. 4C and D). Altogether, these findings suggest that interactions between the cortico-cerebellar and cortico-striatal systems are necessary at the beginning of the acquisition of a new motor skill, that this interaction is mediated through an increase in the magnitude and number of functionally connected regions within these two systems, and that the cortico-cerebellar system is sufficient to maintain this skilled behavior once the task is well learned (see [14] for a PET study describing very similar findings).

6. Motor memory consolidation

Data accumulated so far clearly demonstrate that motor sequence learning depends initially on repeated practice, but that it also continues to develop over time after training has ended. During this latent post-learning phase, the memory of a given motor experience is thought to be transformed into a robust and enduring state, a process called “memory consolidation” [58,110]. Motor memory consolidation possibly begins as early as after subjects have done a few practice trials, and thus after the brain has been exposed to sufficient relevant behavioral experience. Yet experimentally, this memory process has been defined as the intermediate process between the early (fast) and late (slow) learning phases, where the emergence of delayed, off-line, gains in performance or a diminished susceptibility to interference by a subsequent experience is observed in the post-training phase.

We and other investigators have demonstrated that sleep plays a critical role in the consolidation of memory traces for motor sequences [20,68,110]. For example, Walker et al. [111] have shown that delayed gains in performance on a motor sequence task are triggered after a period of sleep, but not following an equivalent period of daytime. Hotermans et al. [49] have reported that this process occurs very early after an initial training phase, as a transient increase (boost) in performance emerging as early as 5–30 min after practicing a motor sequence task has been shown in young volunteers. Importantly, this early ‘boost’ was predictive of the behavioral gains observed 48 h post-training, indicative of its functional significance in motor memory consolidation. Further studies [31,60] have demonstrated that this sleep-enhancing effect is independent of whether subjects slept during the night or during daytime, thus ruling out the alternative interpretation that motor consolidation on this task relates to circadian rhythm effects. Finally, other researchers have also shown that certain sleep parameters, especially Stage 2 sleep spindles, are involved in offline consolidation of sequential finger movements [80,112].

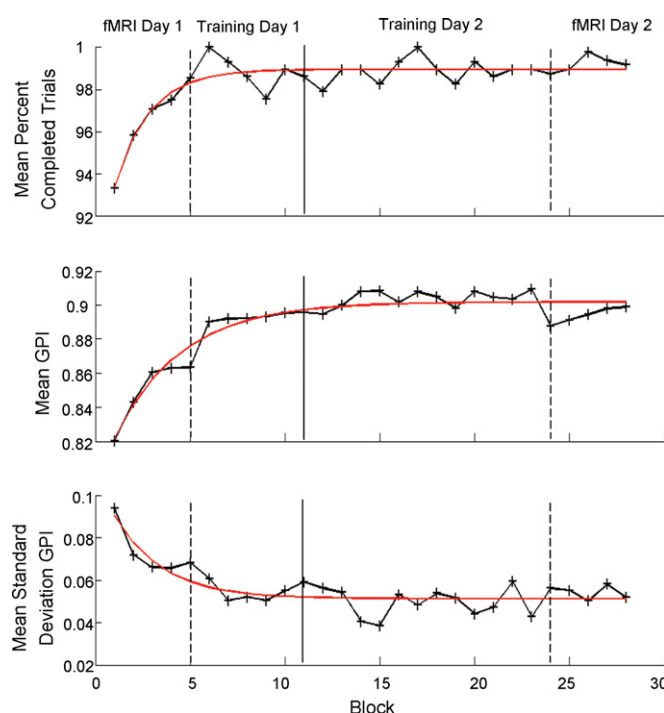


Fig. 3. Behavioral results obtained in the MA task. Performance was assessed through three different measures: Percentage of completed trials, global performance index (GPI) that is taking both precision and time in consideration, and standard deviation of the GPI. Compared to their performance during training in the first fMRI session, subjects showed a plateau in their performance in the second scanning session after two additional practice sessions.

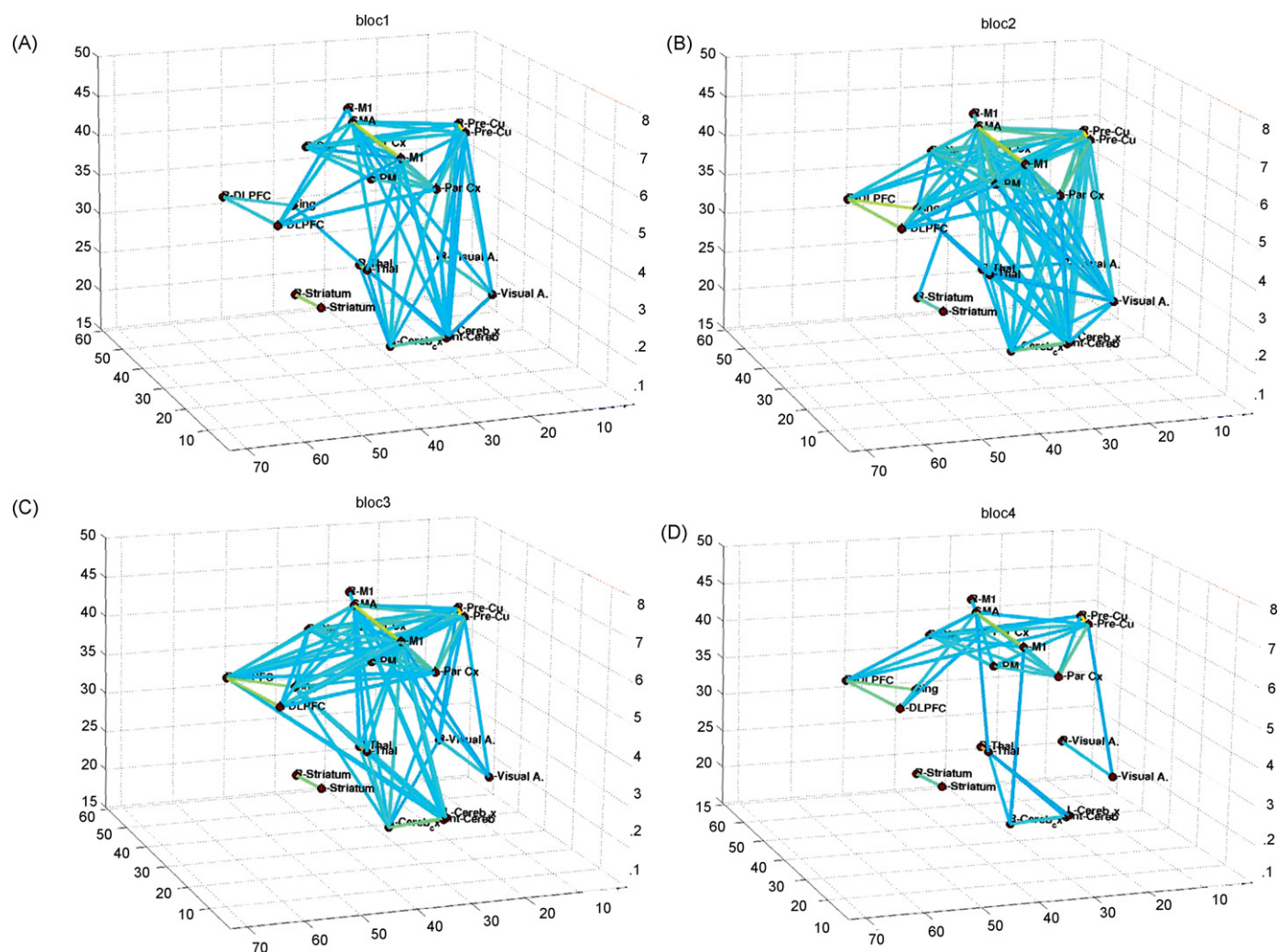


Fig. 4. Diagrams illustrating the results of functional connectivity analyses of the MA task. (A) Results demonstrating the functional connections within the cortical and subcortical structures of the cortico-cerebellar and cortico-striatal systems at the beginning of the learning process. (B) At the end of the first day of testing, when subjects have completed the fast learning phase, the amplitude and number of functionally connected regions with the cortico-cerebellar system are now significantly increased. Furthermore, as predicted by Doyon and Ungerleider's model of motor learning [21,23,25], the striatum is now functionally linked with motor cortical regions. (C) On Day 2 of testing, the network starts to show a decrease in connectivity between the striatum, cerebellum and motor-related structures. (D) Finally, the results reveal that at the end of learning when subjects have reached asymptotic performance, the regions that show sustained co-activations are limited to the cortico-cerebellar system.

Although still conjectural in humans, it is widely accepted that, during learning and immediately after, physiological and structural synaptic changes take place in the nervous system in order for the memory trace to persist and be consolidated [26,27]. After learning, memories are created by alterations in glutamate dependent excitatory synaptic transmission, which stabilizes over hours and days. During this time, experience-dependent gene expression, protein synthesis, as well as early structural changes in synaptic morphology occurring either consequent to protein synthesis or in parallel with it, are also thought to lead to long-lasting changes in synaptic efficacy, i.e., *cellular consolidation* [26,74]. Although these processes have mostly been described with respect to limbic-dependent forms of memory, this notion appears also viable for memories related to the motor system, as recent animal studies suggest that motor skill learning depends on *de novo* synthesis of proteins in motor cortex after training [67]. Finally, in addition to these cellular consolidation mechanisms, Dudai [27] has proposed that consolidation also occurs at the "system" level. Most of our knowledge base on "system consolidation" is again related to work involving tasks sensitive to the cortico-hippocampal circuitry [28,72], but there is now evidence that this global consolidation

process may also occur for motor sequence learning as well, and that the latter is sleep dependent [110]. Yet, little is known with respect to the neural substrates mediating memory consolidation of motor skills, and of motor sequences particularly, as the nature of the post-training, sleep-related cerebral changes has only been shown in the framework of a sleep-deprivation paradigm [32], or using, in the 12-h re-test session, a paced condition that prevented the full expression of the consolidation mechanism [113].

The few studies that have explored the anatomical underpinnings of motor sequence memory consolidation have all stressed the importance of the basal ganglia in this mnemonic process (see [32] for a different pattern of results revealing sleep-dependent consolidation effects in cortical regions only). For example, using a reactivation paradigm with PET, Maquet and co-workers [69,82] 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 (REM) sleep, hence suggesting that the striatum participates in the consolidation of sequential skilled behaviors. Support for this statement also comes from a recent

fMRI study carried out in Doyon's laboratory [12], during which young volunteers were assigned to two subgroups; a night/sleep and a day/awake group. Post-training performance on a 5-item finger sequence task was assessed and scanned after a 12-h break that included sleep, or not. As expected, gains in performance were only observed in the night-sleep group, confirming again that the consolidation of motor memory traces underlying sequential behaviors is sleep-dependent. The imaging results demonstrated that both groups started off with increased activity in M1 and the cerebellum during the immediate post-training session. More importantly, however, the Group $\times$ Session interaction yielded increased activity located mainly in the sensorimotor region of the putamen, hence suggesting that the latter structure contributes to the consolidation process. Finally, Albouy et al. [4] have also reported findings consistent with the striatal hypothesis using an implicit oculomotor (instead of fingers) sequence learning paradigm and fMRI in young subjects. Subjects were scanned both during initial training and at specific post-training delays: 30 min, 5 h or 24 h (the latter delay including a night of normal sleep). Consistent with their predictions, the results during the training phase revealed an increase in BOLD signal, not only in the ventral striatum, but in the hippocampus as well. Interestingly, the levels of activity within these two structures conditioned the memory consolidation process, as subsequent delayed gains in performance over night (and not over day) were associated with increased activity in the ventral striatum and hippocampus. Finally, the competitive interaction observed between these two structures during training turned into a cooperation process overnight after the memory trace was consolidated. These results confirm the involvement of the striatum and further highlight the role of the hippocampus during the initial training of a new motor sequence [91]. Altogether, these studies constitute an important step towards understanding the physiological basis of motor memory consolidation, as they stress the possibility that a functional interaction between striatum and hippocampus during post-training sleep is necessary for the consolidation of new sequential actions to occur.

Yet, post-training sleep does not appear to be necessary for the consolidation of all forms of motor sequential behaviors. Studies using an implicit [85,88] or probabilistic learning paradigm [102] have revealed delayed spontaneous increases in performance after the simple passage of daytime, suggesting that time alone may be sufficient to consolidate this type of motor sequential skill. Furthermore, we and others [17] have reported delayed gains in performance after night sleep or day/awake time on MA tasks designed to measure either kinematic (through visual rotations) or dynamic (through force-field) types of abilities. In this case, the cortico-cerebellar system (and not an interaction between the cortico-striatal and hippocampal systems) appears to play a crucial role in the consolidation process of this form of motor skill learning. Indeed, Shadmehr and Holcomb [96] have carried out a PET study, in which subjects were first scanned while being trained to adapt to force field perturbations in a target-reaching task, and again on the same day 5.5 h later while they were performing the same task. A direct comparison of the regional cerebral blood flow levels between these two phases of learning revealed increased activity in the posterior parietal region, PMC and cerebellum, suggesting that the latter structures constitute the neural substrate supporting MA consolidation processes.

In conclusion, the studies reported in this section suggest that interactions between the basal ganglia (striatum) and limbic (hippocampus) systems during sleep may be essential for consolidating memory traces representing newly learned sequences of movements that are known explicitly before practice begins. Yet this functional interplay does not appear to be critical for sequences that have been learned through other cognitive means (e.g., implicit learning). Furthermore, a distinct neural network involving the

cerebellum and associated cortical regions is elicited during the consolidation process of other types of motor skilled behaviors, like those necessitating to adapt to changes in sensorimotor mapping that are mostly independent of sleep (see [50] for a different pattern of findings).

7. Automatization of motor skills

To investigate the neural substrates associated with the “automatic” performance of a motor skill, researchers 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. The main problem with this approach is that it is difficult, if not impossible, to make sure that performance on a motor skill has become completely automatic after practice in the laboratory (even for a month like in Lehericy et al., [65]), as there is always residual interference effects on performance of the primary task when subjects are exposed to the dual-task condition. The second design consists of comparing functional and/or anatomical changes seen in individuals with over-learned skills (e.g., playing a musical instrument) to those seen in naive subjects. Using these two approaches, some investigators have reported a general decrease of activity in distributed networks of motor-related structures involving the cortico-basal ganglia and cortico-cerebellar pathways [47,114]. Such findings support the global efficiency hypothesis, which states that during automatic performance individual motor regions are simply functioning more efficiently, and thus require less energy. An alternative interpretation of these data, however, is that this pattern of results is due to the use of a rest period as the baseline control condition, hence rendering difficult to dissociate learning-dependent activity from the simple experience-independent execution of movements [114], or to the use of a between-subjects design, thus increasing variance in the data due to heterogeneity in the two samples [47].

One way to counteract the limitations reported above, and to identify the neural correlates associated with the automatization of a motor skill, would be to scan a group of volunteers using a within-subject design while they are performing a life long practiced motor skill, and to compare these imaging results to those obtained in the same subjects as they are learning the same motor skill from scratch. Knitting allows such a possibility. Indeed, as a friend of J. Doyon (R. Amsel, an expert knitter) was knitting in the back of his car while driving to a scientific conference close to Kingston, Ontario, Canada, it became apparent that she could simultaneously knit a complicated pattern of stitches and hold an intelligent and fluent conversation with him and other colleagues sitting in the car. However, one interesting fact that is not known by most of us who have not engaged in this type of recreational and creative activity, is that there exist two quite different techniques to knit the exact same stitch: an English and a Continental technique. To look at the brain structures mediating the automatization versus early learning of a motor sequence task in the same subject, we thus conducted an fMRI study while highly skilled knitters ($n=8$, male=0, mean age: 52 years old, range in knitting experience: 14–58 years) performed regular stitches in the scanner without visual feedback. These subjects were scanned in three conditions using a block design, that is: (a) while executing a series of 10 simple stitches with their usual English technique (called “old automatized condition”), (b) when executing the exact same stitches with the new Continental technique (named “newly learned condition”) that they learned prior to scanning, and (c) while performing alternating simple movements with the two needles (control condition). The number of movements made was equated across conditions by training subjects to knit one stitch/3 s using the new Continental technique. Whole-brain BOLD signal changes were acquired using

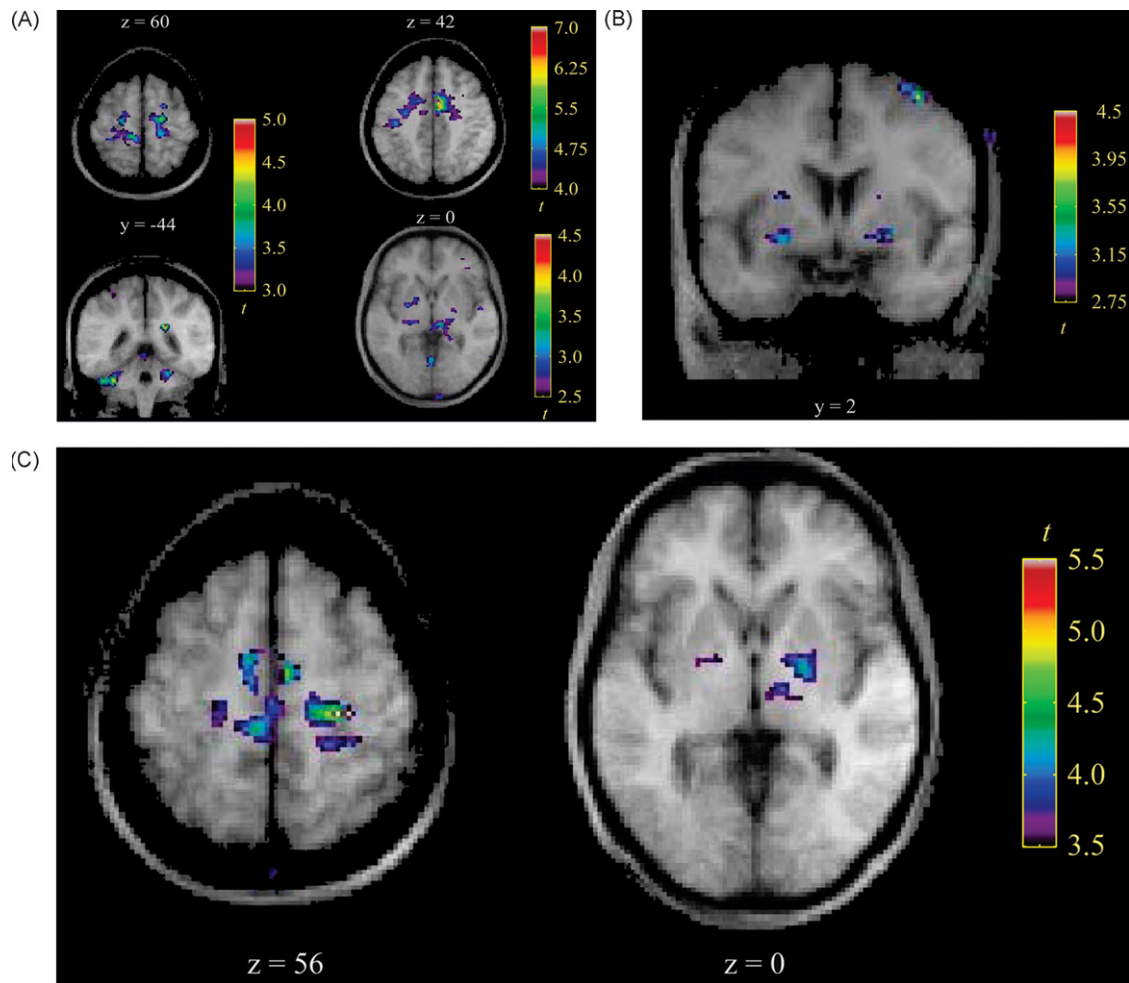


Fig. 5. Activation maps obtained in the fMRI knitting experiment. (A) Contrast between the “newly learned condition” and the “control condition”, (B) contrast between the “old automatized condition” and the “control condition”, and (C) contrast between the “old automatized condition” and the “newly learned condition”.

a standard single-shot, echo-planar imaging sequence on a 1.5T magnet. Contrasts between the “newly learned” and “control” conditions revealed increased activity in motor-related structures like the PMC, the putamen/globus pallidus and cerebellum (lobules V and VI) bilaterally, as well as in the right thalamus, anterior cingulum and SMA (see Fig. 5A). By contrast, comparison of the “old automatized” and “control” conditions yielded an increase of activity in the right inferior parietal cortex, the SMA and motor territory of the putamen/globus pallidus regions bilaterally (see Fig. 5B), the latter basal ganglia structure remaining significantly active when BOLD signals in the “newly learned” condition were subtracted from those in the “old automatized” condition (see Fig. 5C). These findings suggest that early learning of a sequential motor task necessitates the contribution of both cortico-cerebellar and cortico-striatal systems, but that after the skill has become fully automatized, the cerebellum is no longer essential, and the long-lasting representation of the skilled behavior now involves the basal ganglia and associated motor cortical regions only.

To parallel the results obtained above in knitters, Doyon et al. have recently completed a study aiming at exploring the underlying brain structures implicated in the automatization of a visuomotor adaptation task. Although we tried to find an ecological MA skill that would be MR-compatible, and for which subjects would show a level of expertise similar to that of knitters, our search was unsuccessful. Consequently, we decided to use a subject-tailored design to determine the amount of training each subject would receive on a target-reaching MA paradigm, and to scan subjects before and

after they had reached automatization on the task. In this study, subjects were required to reach one of eight targets using a joystick, where the relationship between movements of the latter and the cursor on a monitor was either inversed (MA condition) or not (control condition). Subjects were introduced to the experimental tasks on Day 1 (baseline performance) and scanned immediately thereafter. Beginning on Day 2, and for as long as they needed, subjects practiced the MA task until they reached automatic performance. Automatization on this motor skill was confirmed through the use of a dual-task paradigm, during which subjects were asked to reach targets while simultaneously identifying high or low pitch sounds. Following several practice sessions (mean = 24.0), subjects reached some level of automatization as their performance on both primary (MA) and secondary (auditory) tasks in the dual condition did not differ significantly to that in the single condition. Once they achieved this criterion, subjects underwent a second fMRI scan identical to the first. The fMRI results (see Fig. 6A) showed that the improvement in performance from the early learning to the automatic execution stage was associated with a decrease in BOLD activity in the striatum, but an increase in the cerebellum and its related cortical structures. In addition, correlation analyses revealed that distinct cerebellar regions are involved in different strategies used to complete the adaptation task, as activity within the anterior cerebellar regions was associated with the subject's speed in executing this automatized skill, whereas the posterior regions was related to the precision with which movements were executed (see Fig. 6B and C).

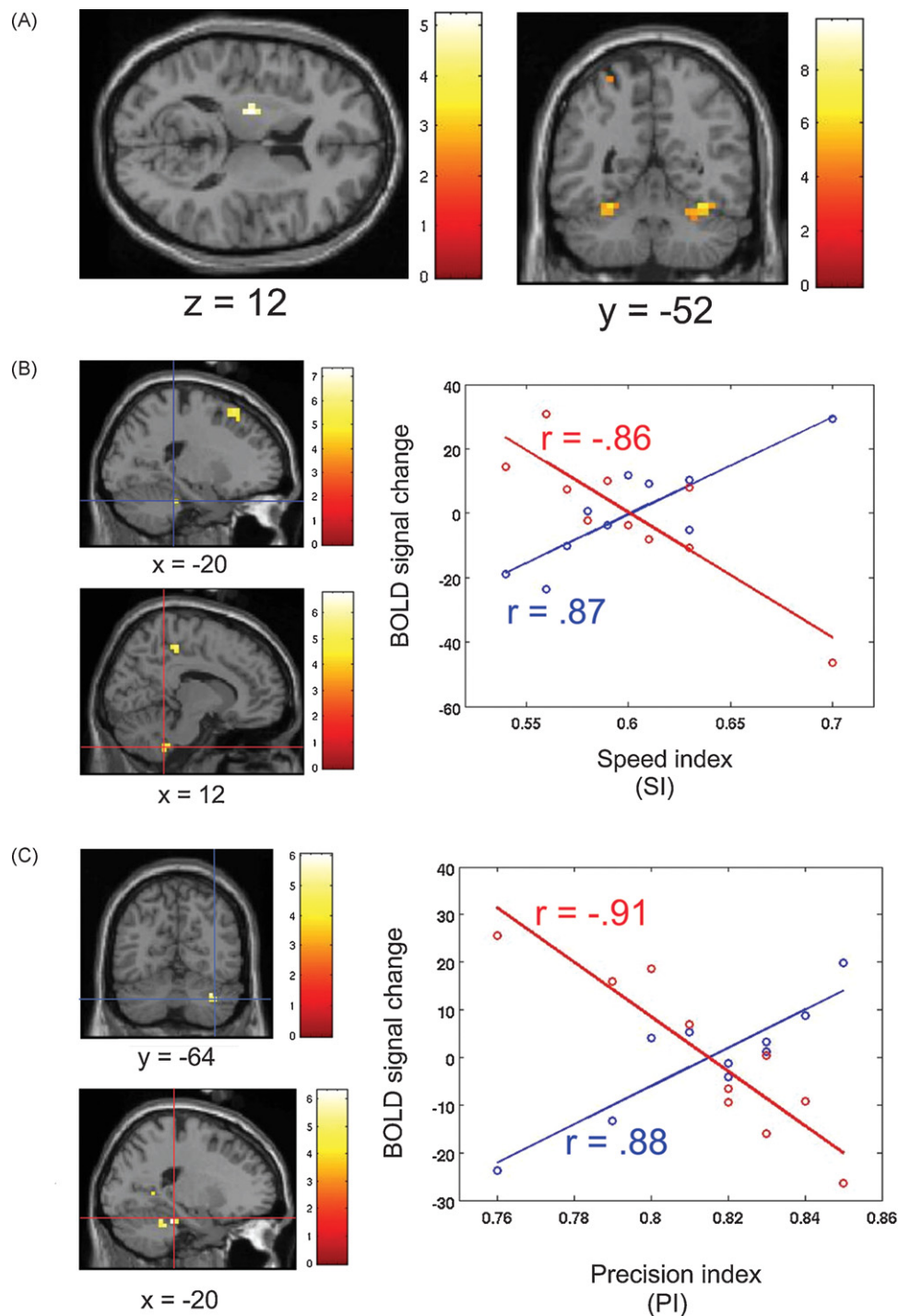


Fig. 6. Activation maps obtained in the motor adaptation task before and after automatization. (A) Striatal and bilateral cerebellar activations seen, respectively, during the early learning phase and following automatization. (B) Between-subjects regression analyses coupling the average subjects' speed index (SI) and the BOLD signal measured following automatization in the MA task. *Blue crosshair:* left cerebellar lobule IV (-20 – 32 – 28). The scatter plot shows that the brain response at this coordinate was positively correlated with the SI (blue; $r = 0.87$). *Red crosshair:* right cerebellar lobule IX (12 – 40 – 44). The scatter plot reveals that the brain response at this coordinate was negatively correlated with the SI (red; $r = -0.86$). (C) Between-subjects regression analyses coupling the subjects' average precision index (PI) and the BOLD signal after automatization of the MA task. *Blue crosshair:* right cerebellar Crus I (32 – 64 – 32). The scatter plot shows that the brain response at this coordinate was positively correlated with the PI (blue; $r = 0.88$). *Red crosshair:* left cerebellar lobule IV (-20 – 32 – 24). The scatter plot shows that the brain response at this coordinate was negatively correlated with the PI (red; $r = -0.91$).

8. Motor skill learning: A model

The large number of studies described above have not only helped us to identify the brain systems that contribute differentially to MSL and MA, but have also provided valuable information with regards to the functional dynamic changes that occur within the

cortico-striatal, cortico-cerebellar and limbic systems during the different learning stages of a motor skill (e.g., see [20,21,23,25,45, 98] for reviews). To put these results into a plausible neurobiological model, Doyon et al. [23,25] attempted first to propose an integrated view of the functional plasticity that a motor memory trace undergoes, depending on the type of learning (i.e., sequential

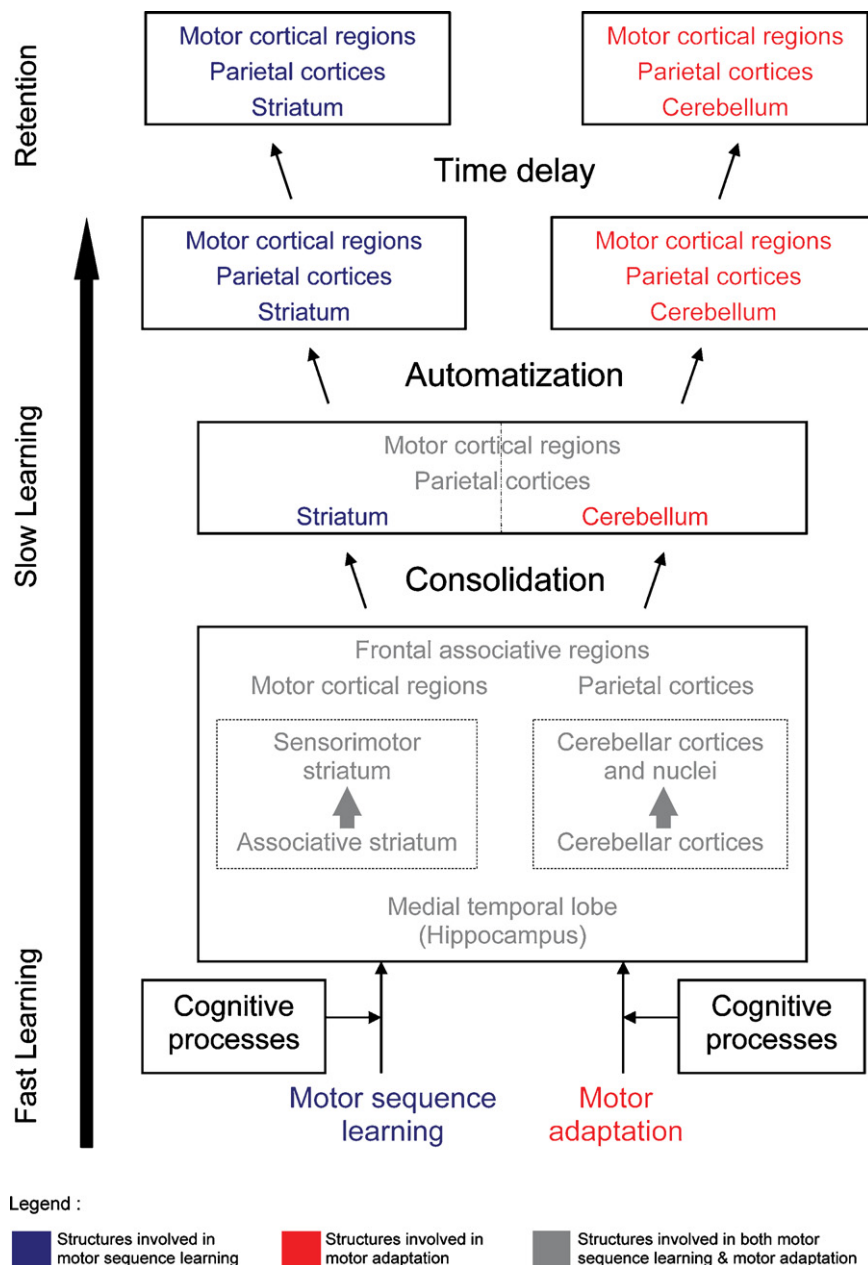


Fig. 7. Doyon and et al.'s model [21,23,25] of motor skill learning describing the cerebral plasticity within the cortico-striatal and cortico-cerebellar systems during the course of learning a new sequence of movements (motor sequence learning) or to adapt to environmental perturbations (motor adaptation).

versus kinematic or kinetic adaptation) and the different phases of the acquisition process. Importantly, this model was revisited in 2005 [21] in order to take into account new published evidence of cerebral functional plasticity within the striatum and cerebellum during MSL (e.g., [24,33,65]) and MA [81], as well as new data showing a possible role of the hippocampus in this form of learning [91].

Primarily based upon brain imaging findings, this model also attempts to explain some of the results of other studies in animals and clinical populations. The latter (see Fig. 7) suggests that in the fast encoding phase, both MSL and MA recruit similar cerebral structures: the striatum, cerebellum, motor cortical regions (e.g., PMC, SMA, pre-SMA, anterior cingulate), as well as the prefrontal cortex, parietal cortex and the hippocampus. During this stage, dynamic functional interactions between these systems are thought to be critical for establishing the motor routines necessary to learn the new motor behavior. Furthermore, a shift of motor representation

from the associative to the sensorimotor striatal territory can be seen during MSL, whereas a transfer of activity from the cerebellar cortex to the deep cerebellar nuclei can be observed in the cerebellar nuclei after practice on both MSL and MA tasks. 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 either the cortico-cerebellar or the cortico-striatal circuit, depending on the type of learning acquired. At this stage, Doyon's model suggests that for MA, the striatum is no longer necessary for the retention and execution of the acquired skill; regions representing the skill are now involving the cerebellum and related cortical regions. By contrast, a reverse pattern of plasticity is thought to occur in MSL, 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. Finally, when a well-learned motor behavior is elicited again, even after a long delay without practice, the model posits that the same cortico-subcortical systems are reactivated. For motor sequence learning skills, it is proposed that the long-term retention of this type of skill is dependent upon activity maintained in the cortico-striatal system, whereas for motor adaptation skills, the long-lasting representation of this form of learning is mediated through the cortico-cerebellar system.

Although such a model of motor learning explains most of the findings found in the motor skill learning literature and some of its inconsistencies, the latter does not offer much about the nature of the cognitive processes that bring about the functional interactions and cause the dissociations seen between the cortico-striatal and cortico-cerebellar systems over the entire course of learning. It does not explain either the specific motor functions under which each of these systems (in link with the hippocampus in some cases) operates while a new procedural skill is being acquired. These sorts of issues have been addressed, however, in other models of the cortico-striatal and cortico-cerebellar functions in motor control and learning. First, Hikosaka et al. [48] have advocated that two representations of a motor sequence (spatial, motor) is acquired during learning, and that each representation relies critically on two sets of cortico-basal ganglia and cortico-cerebellar circuits independently; the fronto-parietal cortices forming a loop with the associative regions of the basal ganglia and cerebellum being implicated in the spatial representation of the sequence, while the motor cortical regions forming a second circuit with the motor-related areas within those same structures being important for the motor representation of that sequence. The “spatial sequence” representation is thought to be effector-unspecific, processed explicitly, acquired rapidly and very demanding with regards to subjects’ attentional resources. By contrast, the “motor sequence” representation is believed to be effector-specific, processed implicitly, acquired slowly, and less demanding with respect to attentional resources. Second, using a computational viewpoint, Shadmehr and Krakauer [98] have recently proposed a functional dissociation between the basal ganglia and cerebellum; the former being implicated in optimal control of movements, that is in learning the costs (effort needed) and rewards associated with the execution of a motor skill, and the latter being important for predicting the sensory consequences of motor commands through the establishment of internal models. Finally, Doya [18] has suggested that motor learning in the cortico-striatal and cortico-cerebellar loops is guided through reward and error signals. His view, based on computational theories, proposes that the basal ganglia are critical for “reinforcement learning”, which would be guided by the reward signal encoded in the midbrain dopaminergic neurons from the substantia nigra, while the cerebellum plays a crucial role in “supervised learning”, which would be modulated by the error signal processed in the climbing fibers arising from the inferior olive. Yet, even if more enlightening from a functional and cognitive perspective, the different concepts advanced in these models cannot easily be generalized to the motor skill learning domain at large, as they appear to be applicable mostly to one form of motor skill, MSL or MA, but not to both. Consequently, we believe that much more experimental and theoretical work will be needed before one can be in a position to conceive a comprehensive behavioral/neuroanatomical model capable of explaining the multitude of behavioral, physiological and imaging findings observed across the several stages of learning and types of motor skilled behaviors.

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