NeuroImage 49 (2010) 694–702

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

The multifaceted nature of the relationship between performance and brain activity in motor sequence learning

Pierre Orban [a,b], Philippe Peigneux [b,c], Ovidiu Lungu [a], Geneviève Albouy [a,b], Estelle Breton [a], Frédéric Laberenne [a], Habib Benali [a,e], Pierre Maquet [b,d], Julien Doyon [a,*]

[a] Functional Neuroimaging Unit, Geriatric Institute Research Center and Department of Psychology, University of Montreal, 4565 Queen Mary, Montreal QC, Canada, H3W 1W5
[b] Cyclotron Research Center, University of Liège, 4000 Liège, Belgium
[c] UR2NF, Neuropsychology and Functional Neuroimaging Research Unit, Free University of Brussels, 1000 Bruxelles, Belgium
[d] Department of Neurology, CHU, University of Liège, 4000 Liège, Belgium
[e] UMR_S 678 INSERM-UPMC, CHU Pitié-Salpêtrière, Paris 75013, France

ARTICLE INFO

Article history:
Received 13 May 2009
Revised 27 July 2009
Accepted 24 August 2009
Available online 2 September 2009

Keywords:
Functional magnetic resonance imaging (fMRI)
Motor control
Sequencing
Performance
Movement
Striatum
Cerebellum

ABSTRACT

The 'learning and performance' conundrum has for a long time puzzled the field of cognitive neuroscience. Deciphering the genuine functional neuroanatomy of motor sequence learning, among that of other skills, has thereby been hampered. The main caveat is that changes in neural activity that inherently accompany task practice may not only reflect the learning process *per se*, but also the basic motor implementation of improved performance. Previous research has attempted to control for a performance confound in brain activity by adopting methodologies that prevent changes in performance. However, blocking the expression of performance is likely to distort the very nature of the motor sequence learning process, and may thus represent a major confound in itself. In the present study, we postulated that both learning-dependent plasticity mechanisms and learning-independent implementation processes are nested within the relationship that exists between performance and brain activity. Functional magnetic resonance imaging (fMRI) was used to map brain responses in healthy volunteers while they either (a) learned a novel sequence, (b) produced a highly automatized sequence or (c) executed non-sequential movements matched for speed frequency. In order to dissociate between qualitatively distinct, but intertwined, relationships between performance and neural activity, our analyses focused on correlations between variations in performance and brain activity, and how this relationship differs or shares commonalities between conditions. Results revealed that activity in the putamen and contralateral lobule VI of the cerebellum most strongly correlated with performance during learning *per se*, suggesting their key role in this process. By contrast, activity in a parallel cerebellar network, as well as in motor and premotor cortical areas, was modulated by performance during learning and during one or both control condition(s), suggesting the primary contribution of these areas in motor implementation, either as a function or not of the sequential content of movements. Our findings thus highlight the multifaceted nature of the link between performance and brain activity, and suggest that different components of the striato-cortical and cerebello-cortical motor loops play distinct, but complementary, roles during early motor sequence learning.

Introduction

Learning sequential motor actions is one of the fundamental properties of the brain, deemed essential for most living creatures. This type of procedural ability builds through the incremental integration of initially distinct movements into single behavioral units (Willingham, 1998). With practice, the emergence of a spontaneous rhythm temporally reorganizes the novel motor sequence in the form of serial chunks of movements (Sakai et al., 2004), and eventually, movements repetitively practiced in a specific spatial order come to be performed faster and in a more automatic fashion.

A large body of electrophysiological studies in non-human primates and neuroimaging research in humans has demonstrated that brain structures forming the cerebello-cortical and striato-cortical motor loops are engaged during the acquisition of novel motor sequences (see Ashe et al., 2006; Doyon and Benali, 2005; Doyon and Ungerleider, 2002; Hikosaka et al., 1999, 2002; Orban et al., 2008; for reviews). However, much controversy exists as to which components of these neuroanatomical loops actually code for learning *per se*, notably because performance changes inherently occur as a function of learning, and thus may contaminate imaging results in

* Corresponding author. Functional Neuroimaging Unit, Geriatric Institute Research Center, University of Montreal, 4545 Queen Mary, Montreal QC, Canada H3W 1W5. Fax: +1 514 340 3540.
E-mail address: julien.doyon@umontreal.ca (J. Doyon).

1053-8119/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2009.08.055

human studies (Ashe et al., 2006; Kelly and Garavan, 2005; Poldrack, 2000). The potential confound arises from the fact that brain activity can be parametrically modulated outside a learning process, for instance, by the frequency rate of movements produced individually (Jancke et al., 1998, 1999; Riecker et al., 2003; Schlaug et al., 1996) or in a well practiced order (Taniwaki et al., 2003, 2006). It entails that the reorganization of brain activation usually attributed to learning can be equivocal because it may actually correspond to a mere by-product of the behavioral changes, instead of reflecting the practice-driven modifications in brain representations that actively enable improved motor efficiency.

To address this issue, studies looking at motor sequence learning in humans have compared brain activity engaged during learning with that recorded under low and high speed control conditions (van Mier et al., 1998; van Mier and Petersen, 2001; van Mier et al., 2004), hence assuming that the brain circuitry reacting to a gross change in movement speed does not encode learning *per se*. Alternatively, others have aimed at preventing behavioral changes. For instance, researchers have used fixed temporal cues to pace the movements of an explicitly known sequence (Karni et al., 1995; Lehericy et al., 2005) or of a sequence to be discovered by trial-and-error (Jueptner et al., 1997a,b). Finally, others have administered a secondary distractor task that aimed at interfering with the behavioral changes observed during practice of sequential movements, thus proposing that the learning circuitry can be unraveled even when performance-induced cerebral activation is prevented (Seidler et al., 2002, 2005). Altogether, these studies have provided valuable insights into the brain networks involved in motor sequence learning, while ensuring that the observed practice-related reorganization of brain activity could not be accounted for by the mere expression of behavioral changes. Preventing the occurrence of performance improvements, nonetheless, presents its own drawbacks because it assumes that performance-related activity does not reflect learning processes, and because this methodological approach distorts the very nature of the motor sequence learning process as the emergence of optimal chunking and rhythm of movements, from which learning is inferred in essence, is blocked.

In order to address these concerns and to complement previous findings, we aimed at deciphering the neural signature of motor sequence learning while preserving the gradual optimization of the sequential output induced by practice. We further postulated that the effect that performance (i.e., speed of movements) exerts on brain activity during a learning task not only reveals learning-independent implementation processes but importantly captures learning-dependent dynamic processes of brain plasticity as well. Thus we hypothesized that a performance influence on brain activity during learning encompasses two distinct but intermingled effects, one being primary to the behavioral change (effect of interest) and another being secondary to it (confounding effect) (Poldrack, 2000). To characterize this multifaceted relationship between the brain activation changes observed during learning and the behavioral improvements that accompany them, we recorded brain activity in young healthy subjects using functional magnetic resonance imaging (fMRI) under motor training conditions in which performance expression was unconstrained, and compared performance-related changes in activity in a learning condition to those of non-learning conditions that controlled for both speed of movements and the nature (single vs. sequential) of the motoric output required in the task. More specifically, subjects were scanned during (a) the learning of a novel, but explicitly known sequence of finger movements, (b) the production of a highly automatized motor sequence and (c) the execution of single non-sequential movements. Brain imaging analyses dissociated qualitatively dissimilar but intertwined relationships between brain activity and performance by regressing the neural activity obtained in each condition with the subjects' performance, and then measuring the commonalities and differences in correlations between such conditions. It was predicted that this method would allow to better isolate the brain structures within the cortico-striatal and cortico-cerebellar systems that mediate motor sequence learning *per se*, as well as those that play a simpler supporting role in the motoric expression of the newly learned sequence of movements.

Materials and methods

Participants

Thirty two participants (17 females) aged 23.9 ± 4.1 years on average were divided in two groups of 16 subjects (Group 1: mean age $= 24.9 \pm 4.3$, 9 females; Group 2: mean age $= 23 \pm 4$, 8 females). They gave informed consent to participate in this study, which was approved by the local ethics committee at the Geriatric Institute Research Center, University of Montreal. All subjects were right-handed and had no history of neurological or psychiatric disorder. Musicians and professional typists were excluded in order to control for pre-existing skills that require highly coordinated finger dexterities.

Experimental procedure

Subjects in Groups 1 and 2 were scanned using an fMRI block-design protocol consisting of two alternating motor conditions interspersed with rest epochs, each condition comprising 12 blocks of trials that were administered within a single session. Buttons presses were performed with the left hand, and were recorded with a custom-made MRI-compatible response pad. We instructed participants to use their non-dominant hand, as performance with this hand allows greater behavioral change to be observed than with the right hand. It should be kept in mind, however, that left hand movements are typically characterized by more bilateral activation patterns than right hand movements due to the known specialization of the left hemisphere in motor control (Serrien et al., 2006), hence possibly limiting the interpretation of our results to this effector only. Both groups were tested while carrying out a control condition (*NoseqCont*), in which subjects were required to execute repeated tapping movements with a single finger (1, 2, 3, or 4, referring to the index, middle, ring and little fingers, respectively) at a pre-specified frequency (slow, ≈ 2 Hz; medium, ≈ 3 Hz; or fast, ≈ 4 Hz), for as long as a yellow square was displayed on a black screen that could be seen through mirrors embedded within the head coil. This produced twelve possible conditions of finger movements (4 fingers $\times$ 3 frequencies) that were administered in a randomized order across the 12 blocks of trials. In Group 1, the second experimental condition consisted of a sequence learning task (*SeqLearn*), in which subjects had to perform continuously, and as fast and accurately as possible, a novel, but explicitly memorized 5-element finger sequence (2-1-3-4-1) when a dark blue square was displayed. By contrast, the second motor condition administered to Group 2 required that participants execute a simple, highly automatized finger sequence (1-2-3-4) at a pre-determined frequency on each block (*SeqCont*), and for as long as a light blue square was displayed. The latter sequential movements were again executed at the same frequencies reported above (slow, ≈ 2 Hz; medium, ≈ 3 Hz; or fast, ≈ 4 Hz) during four blocks each, the order being randomized across blocks. Prior to the scanning session, subjects were trained to execute the single (*NoseqCont*) and automatized sequential (*SeqCont*) finger movements at the desired frequencies with help of a visual cue, so that the movements could be properly self-initiated later during the fMRI scanning session. Unknown to participants, each block of trials in all three conditions (*NoseqCont*, *SeqLearn*, *SeqCont*) ended when subjects had performed 60 buttons presses. This was implemented in order to control for the effect

that the quantity of movements can exert on brain activity (Kim et al., 2005). In addition, movements were self-initiated in all conditions to prevent undesired effects linked to differences in the neural underpinnings related to internally vs. externally triggered movements (Cunnington et al., 2002; Deiber et al., 1999; Taniwaki et al., 2003, 2006). Finally, all fingers were used in similar proportions to control for possible somatotopic representation effects on neuronal activity (Hlustik et al., 2001). The beginning of each rest period was notified to subjects through the appearance of a red square that remained displayed on the screen for 15 s. Instructions for each experimental condition were displayed for 2 s at the end of each rest period (e.g., "sequence" before the *SeqLearn* condition, "sequence-slow" before the *SeqCont* condition, and "3-fast" before the *NoseqCont* condition). The necessity to provide subjects with instructions regarding the type and speed of movements before each control condition led us to use a block rather than an event-related design.

FMRI procedure

Because of an intervening upgrade of the MRI infrastructure, brain imaging data were acquired using two different 3T systems and head coils from Siemens, AG: the Magnetom Trio with an 8-channel head coil was used when scanning subjects in Group 1, while the Magnetom Tim Trio with a 12-channel head coil was employed while testing participants in Group 2 (for the method and results of the analyses regarding the potential confounding effect of scanner type, see Supplemental Fig. 1). For both groups, functional T2*-weighted volumes were acquired using a similar blood-oxygen-level-dependent (BOLD) sensitive, single-shot echo planar sequence (TR = 4000 ms; TE = 30 ms; FA = 90°; FoV = 256 × 256 mm^2; matrix size = 128 × 128; voxel size = 2 × 2 × 3 mm^3; 44 slices). Structural T1*-weighted MRI scans were acquired using a standard three-dimensional flash sequence (TR = 13 ms; TE = 4.92 ms; FA = 25°; FoV = 256 × 256 mm^2; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm^3, 176 slices) in Group 1, and a Turbo flash sequence with an inversion pulse (TR = 2300 ms; TE = 2.98 ms; FA = 09°; FoV = 256 × 256 mm^2; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm^3, 176 slices) in Group 2.

Preprocessing and statistical analysis of brain images were performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7 (Mathworks Inc., Sherbom, MA). Spatial preprocessing included realignment and adjustment for in-scanner head movement related effects, coregistration of functional and anatomical images, spatial normalization into the stereotactic Montreal Neurological Institute (MNI) space, and spatial smoothing using a Gaussian kernel of 6 mm full width at half maximum (FWHM). Statistics were performed using the linear general model (Friston et al., 1995). In each group, the intra-individual design matrix modeled the two motor conditions ([SeqLearn] and [NoseqCont$_1$] in Group 1; [SeqCont] and [NoseqCont$_2$] in Group 2). Performance expressed in movement frequency was entered as a covariate for each block, allowing us to test for linear parametric modulation effects. For both groups, linear contrasts were carried out to look at block-related parametric changes convolved with a canonical hemodynamic response function, generating fixed-effects statistical parametric maps (Friston et al., 2002). In the present study, the main effects of conditions that revealed task-related activations independently of performance were not taken into account. We were rather specifically interested in contrasts testing for performance-related changes in activation. It should be noted that we solely evaluated linear relationships between brain activity and performance through first order parametric regressors (Büchel et al., 1998), and thus did not investigate nonlinear relationships that could provide a more comprehensive description of the neural processes involved in motor sequence learning (Toni et al., 1998). A first series of contrasts tested for the effect of the performance parametric regressor for each condition separately in each individual ([*SeqLearn*] and [*NoseqCont$_1$*] in Group 1; [*SeqCont*] and [*NoseqCont$_2$*] in Group 2). A second series of contrasts was then carried out to test for activation differences between the two parametric regressors in each individual ([*SeqLearn - NoseqCont$_1$*] in Group 1, and [*SeqCont - NoseqCont$_2$*] in Group 2). Hence, at the fixed-effects level, these contrasts reflected how changes in magnitude of brain activity correlated positively with improvements in performance levels in each condition, and revealed differences of correlation effects between conditions within an individual.

Summary statistics maps obtained at the fixed-effects level were then entered into random-effects level models to allow inferences at the population level. Models incorporating contrast images for one condition type only were aimed at showing the simple modulatory effect of performance on neural activity during the learning of novel sequential movements (simple modulation effect analysis [*SeqLearn*]), the execution of highly automatized sequential movements (simple modulation effect analysis [*SeqCont*]), or the production of single, non-sequential movements (a conjunction effect analysis [*NoseqCont$_1$* ∩ *NoseqCont$_2$*] was performed as both groups received this condition). Because no inference was drawn from these activation maps, they were displayed at $p<0.005$ (uncorrected for multiple comparisons) to reveal the full extent of performance-related responses. Based on the existing literature, loci of activations were identified within a brain network of interest composed of the striato-cortical and cerebello-cortical motor loops (i.e., striatum, cerebellum, primary motor cortex, lateral premotor cortex, supplementary motor area and pre-supplementary motor area), delineated using an inclusive mask created with the PickAtlas software toolbox (Maldjian et al., 2003).

Group-level models were then built at the random-effects level to specifically assess between-condition commonalities and differences in the relationship between brain activity and performance. First, we aimed at identifying shared performance-related activity across the three conditions, thus reflecting the brain regions that support the basic implementation of higher motor demands, irrespective of the content of the motor output or of the learning process. Parametric effects contrasts for the two conditions obtained from each group were modeled in a single design matrix in order to reveal the jointly

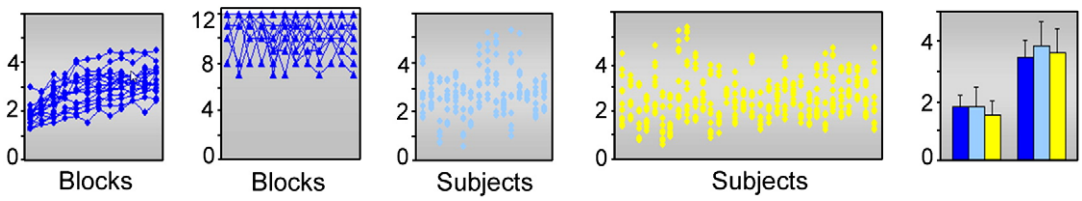

Fig. 1. Behavioral data. The series of connected dark blue dots show either the improvement in movement frequency (Hz) (circles) or the number of accurately produced sequences (triangles) in each subject over the 12 blocks of learning a novel motor sequence (*SeqLearn*). Each column of light blue and yellow dots (circles) depicts, for each subject, the range of movement frequency levels (Hz) observed in the 12 blocks of practice of an overlearned motor sequence or non-sequential movements (*SeqCont* and *NoseqCont*). Bar plots (mean and SD) show the groups' averaged movement frequencies (Hz) for the three conditions, based on each subject's slowest block and fastest block.

significant modulatory influence of performance on brain activity, independently of the movement type (conjunction analysis [*SeqLearn* ∩ *SeqCont* ∩ *NoseqCont*$_1$ ∩ *NoseqCont*$_2$]). Second, we looked for brain regions that implement higher motor demands when the motor output contains a sequential structure, irrespective of whether a learning process was involved in motor execution. Parametric contrast images obtained at the intra-individual level from the subtraction between the sequential and non-sequential conditions were entered into another model as a distinct regressor for each group (conjunction analysis [{*SeqLearn* - *NoseqCont*$_1$} ∩ {*SeqCont* - *NoseqCont*$_2$}]). This contrast was implementable because the two groups received the same non-sequential control condition, but a

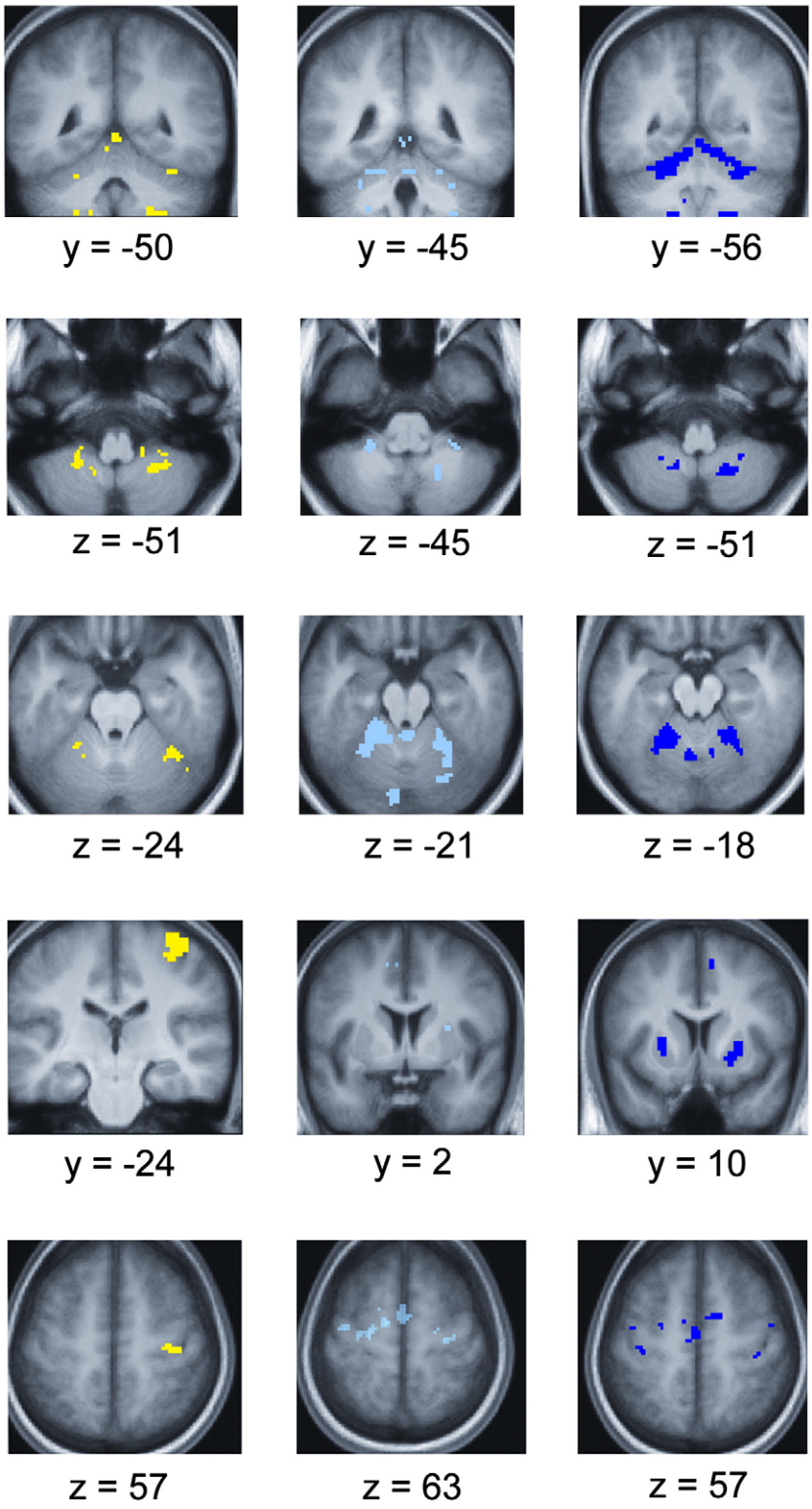

Fig. 2. Modulation of hemodynamic activity by performance in each condition. Simple parametric effects. Each column separately shows the activation effect in yellow for the *NoseqCont* condition, in light blue for the *SeqCont* condition and in dark blue for the *SeqLearn* condition. Activation maps are displayed at $p<0.005$ (uncorrected) on the groups-averaged structural scan using the neurological convention (right hemisphere on the right side). Coordinates are in the MNI space.

distinct sequential condition, which involved or not learning (i.e. the contrast [{*SeqLearn* ∩ *SeqCont*} - *NoseqCont*] could not be performed in a single group receiving all three conditions). Global null conjunction analyses (Friston et al., 2005) were used to assess commonalities across experimental conditions. It should thus be noted that a significant conjunction does not mean that all contrasts were individually significant (i.e., conjunction of significance), but rather that the contrasts were consistently and jointly significant (Friston et al., 2005). Third, the same model was most importantly used to identify links between brain activity and performance that are specific to learning of a new sequence of movements, hence revealing the neural structures whose function extends beyond the simple implementation of higher motor demands (subtraction analysis [{*SeqLearn* - $NoseqCont_1$} - {*SeqCont* - $NoseqCont_2$}]). For these three analyses of interest, activation maps were displayed and considered significant at $p<0.001$ (uncorrected for multiple comparisons). Inferences were drawn at this statistical threshold because strong *a priori* hypotheses on brain regions were driven by the large existing literature on motor sequence learning.

Results

Behavioral results

Performance levels obtained in each condition (*NoseqCont*, *SeqCont*, *SeqLearn*) are depicted in Fig. 1. Subjects that practiced the novel sequence of movements (*SeqLearn*) drastically improved their performance, as they showed a significant increase in movement frequency during training ($F_{(11,165)}=36.62$, $p<0.0001$). Demonstrating a close match in the range of movement frequencies between conditions was necessary to ensure that the reported differences and commonalities of the correlation between performance and neural activity were not confounded by between-conditions quantitative differences in performance levels. A two-way ANOVA was thus executed over block-averaged frequencies by considering the subjects' blocks with the slowest and fastest frequencies in each condition. This analysis included the type of condition (*NoseqCont*, *SeqCont*, *SeqLearn*) and range of frequencies (slowest, fastest) as independent variables (Slow: *NoseqCont* = 1.54 ± 0.44 Hz, *SeqCont* = 1.79 ± 0.66 Hz, *SeqLearn* = 1.79 ± 0.39 Hz; Fast: *NoseqCont* = 3.63 ± 0.77 Hz, *SeqCont* = 3.81 ± 0.85 Hz, *SeqLearn* = 3.44 ± 0.56 Hz). As expected, results revealed a main effect of frequency type ($F_{(1,122)}=257.17$, $p<0.0001$), but not of condition ($F_{(2,122)}=1.24$, $p=0.3$). Importantly, the interaction of Condition by Frequency type yielded no significant effect ($F_{(2,122)}=1.21$, $p=0.3$), a result further confirmed by the absence of a significant effect in all pairwise comparisons between conditions for each frequency type (all p's>0.3).

In the two control conditions, subjects did not produce any incorrect single or sequential movements. By contrast, subjects that practiced the motor learning task made some mistakes while performing the sequence of movements during the training session. Yet the rate of errors was low (mean of 10.77 ± 0.38 accurate sequences per block) and, most importantly, the number of errors did not significantly change across the 12 blocks of practice ($F_{(11,165)}=1.54$, $p>0.1$). Therefore, despite a poorer performance in the learning condition, the results of the brain imaging analyses reported below are not invalidated, because they exclusively evaluated the effect of practice on speed performance rather than the main effects of condition.

Imaging results

Positive modulations (correlations) between brain activity and performance levels were detected within the striato-cortical and cerebello-cortical motor loops for each of the three motor conditions when considered separately. The frequency of non-sequential movements (*NoseqCont* condition) modulated positively the intensity of hemodynamic responses observed bilaterally in lobules VIII and IV–V/VI of the cerebellum, as well as in the right primary motor cortex (Fig. 2, Table 1a). Performance during the execution of a simple, highly automatized motor sequence (*SeqCont*) positively correlated with increased activity in lobules VIII and IV–V/VI of the cerebellum bilaterally, the right primary motor cortex, the right and left medial and lateral (dorsal) premotor regions, as well as the right putamen (Fig. 2, Table 1b). Lastly, learning a novel sequence of finger movements (*SeqLearn*) was characterized by hemodynamic activations that positively correlated with performance in lobules VIII and IV–V/VI on both sides of the cerebellum, the right primary motor cortex, the medial and lateral (dorsal) premotor regions as well as in the right and left putamen (Fig. 2, Table 1c).

Three separate analyses were then carried out to determine, in a statistically controlled manner, the existence of significant commonalities and differences in the modulatory effect of performance between conditions. First, commonalities between the three motor conditions were observed bilaterally in lobules VIII and IV–V/VI of the cerebellum and in the hand representation area of the right primary motor cortex (Fig. 3, Table 2a). Second, a positive relationship between neural responses and performance was also found to be stronger during sequential movements than non-sequential finger taps in cerebellar lobules IV–V/VI on both sides, the supplementary motor area, the premotor cortex and the right primary motor cortex (Fig. 3, Table 2b). Third, a stronger modulation effect was observed in the right cerebellar lobule VI and the right putamen when subjects were learning novel sequential movements than when they were either executing the highly automatized motor sequence or producing non-sequential movements (Fig. 3, Table 2c). Finally, it should be noted that such analyses did not reveal any

Table 1
Modulation of hemodynamic activity by performance in each experimental condition.

Brain region	*x*	*y*	*z*	*Z*
a. NoseqCont				
R Cerebellum Lobule VIII	22	-50	-51	3.56
L Cerebellum Lobule VIII	-24	-44	-51	4.18
R Cerebellum Lobules IV–V/VI	38	-52	-24	3.71
L Cerebellum Lobules IV–V/VI	-24	-48	-27	3.49
R M1	32	-24	57	3.40
b. SeqCont				
R Cerebellum Lobule VIII	28	-40	-45	3.14
L Cerebellum Lobule VIII	-24	-40	-45	3.30
R Cerebellum Lobules IV–V/VI	26	-54	-21	4.31
L Cerebellum Lobules IV–V/VI	-20	-56	-18	4.01
R Putamen	26	2	12	3.18
L SMA	-2	-8	60	3.75
L PMd	-36	-16	66	3.32
R M1	22	-18	66	3.01
c. SeqLearn				
R Cerebellum Lobule VIII	16	-68	-48	4.77
L Cerebellum Lobule VIII	-16	-56	-51	3.27
R Cerebellum Lobules IV–V/VI	28	-54	-21	4.71
L Cerebellum Lobules IV–V/VI	-20	-56	-18	5.27
R Putamen	28	2	3	3.04
L Putamen	-26	10	3	3.32
R Pre-SMA	10	10	51	3.19
L SMA	0	-6	54	2.70
L PMd	-32	-10	66	3.80
R M1	38	-20	66	3.52

Loci of activation corresponding to the simple parametric effects for the three conditions considered separately. R and L = right and left. *x*, *y*, and *z* are stereotactic coordinates in the Montreal Neurological Institute (MNI) space. *Z* = *Z*-statistic score. Activations are significant at $p<0.005$ (uncorrected). M1 = primary motor cortex, SMA = supplementary motor area, Pmd = dorsal premotor cortex.

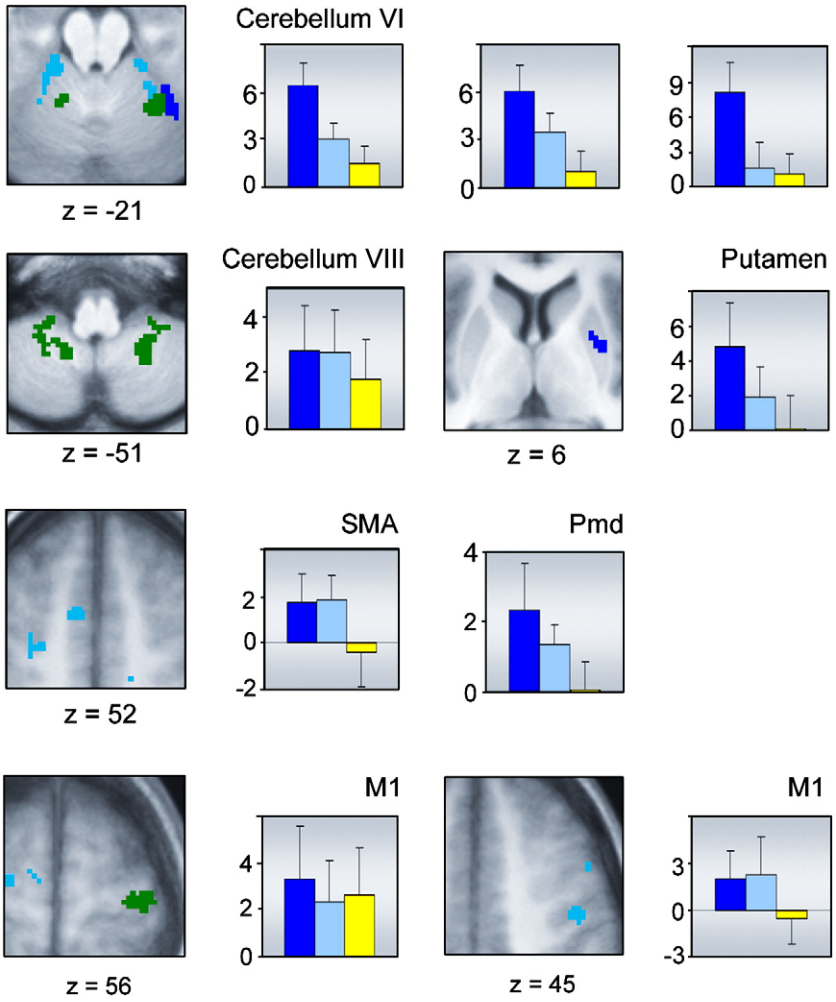

Fig. 3. Commonalities and differences between conditions in the modulation of hemodynamic activity by performance. Conjunction and subtraction of parametric effects. Activation blobs are colored in green for the [*SeqLearn* ∩ *SeqCont* ∩ *NoseqCont*$_1$ ∩ *NoseqCont*$_2$] contrast, in light blue for the [{*SeqLearn* - *NoseqCont*$_1$} ∩ {*SeqCont* - *NoseqCont*$_2$}] contrast and in dark blue for the [{*SeqLearn* - *NoseqCont*$_1$} - {*SeqCont* - *NoseqCont*$_2$}] contrast. Activation maps are displayed at $p<0.001$ (uncorrected) on the groups-averaged structural scan using the neurological convention (right hemisphere on the right side). Coordinates are in the MNI space. Bar plots (mean and SD) show the effect size (parameter estimates, arbitrary units) in yellow, light blue and dark blue (*NoseqCont*, *SeqCont* and *SeqLearn*, respectively) for peak voxels in lobules VIII [-22 -38 -51] and VI [28 -54 -21, 26 -52 -21, 36 -60 -21; from left to right] of the cerebellum, the putamen [28 0 6], the supplementary motor area [-8 4 52], the lateral premotor cortex [-24 -14 52], and the primary motor cortex [42 -22 66, 48 -18 45; from left to right].

weaker correlation effects in the learning condition compared to the two control conditions.

Discussion

The aim of the present study was to portray the complex nature of the relationship between the modifications in performance and brain activity that occur during practice on a novel sequence of movements, thereby further characterizing the specific functions of the various components of the human striato-cortical and cerebello-cortical motor loops known to be recruited in early motor sequence learning (see Ashe et al., 2006; Doyon and Benali, 2005; Doyon and Ungerleider, 2002; Hikosaka et al., 1999, 2002; Orban et al., 2008 for reviews). Results indicate that the magnitude of activity positively correlated with the subjects' level of improvements in performance during the learning task in numerous territories of the striato-cortical and cerebello-cortical motor loops. Based on the idea that the reorganization of brain activity observed with training bears some form of connection with the parallel improvement in performance, one might interpret such changes in activity as entirely reflecting learning-related brain plasticity mechanisms. However, the present results also indicate that changes of activity in some of the structures of that brain network are also modulated by the subjects' performance in the control conditions that do not involve a learning process, hence indicating that the changes in brain activation that develop with practice of a motor sequence do not reflect learning-related neural plasticity in all brain regions. Indeed, our results demonstrate that performance-related changes in activity were greater in the learning than in the control conditions solely in the putamen and cerebellar lobule VI, hence showing that only these brain areas play a key role in the learning process *per se*. By contrast, a parallel network of cerebellar and (pre)motor cortical regions not only increased its activity as a function of performance during learning, but in motor control conditions as well. This shows that such regions are mostly recruited as a by-product of learning, and thus that they contribute to the implementation of the behavioral changes that are actively induced by practice.

Contrary to previous brain imaging studies that constrained the production of movements during motor sequence learning (Bapi et al., 2006; Doyon et al., 2002; Grafton et al., 2002; Jueptner et al., 1997a,b; Karni et al., 1995; Lehericy et al., 2005; Penhune and Doyon, 2002; Seidler et al., 2002, 2005), we employed a learning task that required the unconfined production of explicitly memorized movements, as used in many recent studies looking at the precise determinants of

Table 2
Commonalities and differences between conditions in the relationship between hemodynamic activity and performance.

Brain region	*x*	*y*	*z*	*Z*	Cluster
a. (SeqLearn) ∩ (SeqCont) ∩ (NoseqCont)					
R Cerebellum Lobule VIII	22	-50	-51	4.80	270
L Cerebellum Lobule VIII	-22	-38	-51	4.68	270
R Cerebellum Lobules IV–V/VI	28	-54	-21	4.83	51
L Cerebellum Lobules IV–V/VI	-16	-54	-18	4.73	56
R M1 R	42	-22	66	4.74	103
b. (SeqLearn - NoseqCont) ∩ (SeqCont - NoseqCont)					
R Cerebellum Lobules IV–V/VI	26	-52	-21	3.48	10
L Cerebellum Lobules IV–V/VI	-20	-36	-21	3.50	22
R M1	48	-18	45	4.00	16
L SMA	-10	2	52	4.05	10
L PMd	-28	12	69	3.94	35
L PMd	-24	-14	52	3.65	28
c. (SeqLearn - NoseqCont) - (SeqCont - NoseqCont)					
R Cerebellum Lobule VI	36	-60	-21	4.09	24
R Putamen	28	0	6	3.69	11

Loci of activation resulting from the conjunction and subtraction of parametric effects. R and L = right and left. *x*, *y*, and *z* are stereotactic coordinates in the Montreal Neurological Institute (MNI) space. *Z* = *Z*-statistic score. The cluster size shows the extent of activation at $p<0.001$ (uncorrected). M1 = primary motor cortex, SMA = supplementary motor area, Pmd = dorsal premotor cortex.

motor sequence learning in humans (Hotermans et al., 2006, 2008; Korman et al., 2003, 2007; Kuriyama et al., 2004; Walker et al., 2003a,b). This allowed us to investigate the performance-related neural correlates of the acquisition process of sequential movements, while additionally controlling for performance effects on activation unrelated to learning *per se* using control conditions. Yet, a potential methodological concern with the learning and control tasks employed here is that these experimental conditions did not differ solely in terms of whether motor learning took place or not, but also whether they differed with respect to the level of movement complexity involved. It is possible that movement execution engaged distinct cognitive strategies in the learning versus control conditions. Indeed, it has been shown that motor sequence complexity, defined as the length of the sequence, the number of fingers used, the presence of repeating single finger movements or the number of movement transitions between different fingers, modulates brain activity (Boecker et al., 1998; Catalan et al., 1998; Harrington et al., 2000; Haslinger et al., 2002; Lehericy et al., 2006). Nonetheless, we believe that the condition-specific activation patterns reported in this study can best be explained through qualitative differences between movement types (i.e., linked to the content of movements and learning processes involved) rather than through quantitative variations in complexity levels. First, the three conditions used the four fingers in almost identical proportions over the twelve blocks of trials. Second, the two sequences (2-1-3-4-1 vs. 1-2-3-4) were very similar in terms of the length and number of transitions, while previous studies compared very short sequences with others that contained up to 16 elements in order to show an effect related to these sequence characteristics (Boecker et al., 1998; Catalan et al., 1998; Harrington et al., 2000; Haslinger et al., 2002; Lehericy et al., 2006). Another concern lies in the fact that different levels of familiarity and attentional demands may have been engaged while executing the diverse conditions. Increased demands on control and attentional processes may have been elicited during the motor learning task, compared to the two control conditions that required the execution of automatized movements. The attentional brain network, composed of the prefrontal, anterior cingulate and posterior parietal cortices, has previously been proposed to have a "scaffolding" role that allows coping with unskilled performance (Kelly and Garavan, 2005; Petersen et al., 1998). Again, however, the differences observed between conditions are unlikely to arise from this effect because we reported increases in activity linked to the subjects' improvement in performance, whereas activations within attentional brain areas have been shown to decrease as subjects reach asymptotic performance.

Our results indicate that the relationship between the improvement in performance and brain activity changes in the putamen mostly reflects learning-dependent mechanisms that are primary to the behavioral change, rather than learning-independent processes that merely allow coping with increased motor demands. Such a finding indicates that the striatal activation usually observed during motor sequence learning (Bapi et al., 2006; Destrebecqz et al., 2005; Doyon et al., 2002; Grafton et al., 2002; Jueptner et al., 1997a,b; Karni et al., 1995; Lehericy et al., 2005; Peigneux et al., 2000; Penhune and Doyon, 2002; Seidler et al., 2005) cannot be accounted for by a simple motoric confound secondary to the behavioral change. Thus this supports current models of motor skill learning, which view the striatum as a cardinal component of the brain machinery necessary for acquiring sequential motor actions (Doyon and Benali, 2005; Doyon and Ungerleider, 2002; Hikosaka et al., 1999, 2002). Although still conjectural, the pivotal role of the putamen in motor sequence learning may be inherent to its capacity to process reinforcement signals originating from midbrain neurons that provide the basal ganglia with dopaminergic inputs (Doya, 2000; Hikosaka et al., 2002; Schultz et al., 2003). In line with this proposal, the importance of striatal dopaminergic neurotransmission in motor sequence learning has been demonstrated in animals (Matsumoto et al., 1999) and in healthy humans using ^{11}C-raclopride positron emission tomography (Badgaiyan et al., 2007; Garraux et al., 2007). Reinforcement signals that attach a positive value to movements accurately produced in a sequence during the early stage of learning could then be stored on the long term as a single motor program, such that the initiation and execution of a well integrated behavioral unit could then be mediated efficiently by the striatum (Doya, 2000; Hikosaka et al., 2002).

Our results also suggest that the cerebellum is not exclusively dedicated functionally to motor learning *per se*, nor to the motoric implementation of the sequential movements. Indeed, distinct cerebellar territories exhibited qualitatively different types of responses with regards to the observed improvement in performance. A large cerebellar network, composed of lobules IV–V and VIII (pyramis) bilaterally and lobule VI ipsilaterally, mediated the fine-tuning of motor parameters, independently of the motor learning process. By contrast, the contralateral lobule VI (declive) of the cerebellar cortex displayed a gradient in activation intensity that depended upon the context in which performance changes occurred. Neuronal populations localized in lateral portion of the right cerebellar lobule VI were recruited exclusively (or more so) during learning of a new motor sequence, as compared to the control conditions. Thus, although much of the increased activity in the cerebellum occurred as a by-product of the learning process, a limited portion of the cerebellar involvement did appear to reflect learning-dependent plasticity. Such a pattern of results extends that of previous investigators who reported that the cerebellum, as a whole, does not play an active role in motor sequence learning (Seidler et al., 2002). In fact, our results show that different sub-regions of the cerebellum may have separate motor functions: the lobules VIII and IV–V bilaterally and ipsilateral lobule VI would be implicated in the motoric expression of movements whereas the contralateral lobule VI would be specifically involved in the learning process *per se*. A role for the cerebellum in correcting motor errors has been documented on multiple occasions (Imamizu et al., 2000; van Mier et al., 1998; van Mier and Petersen, 2001; van Mier et al., 2004). The latter hypothesis cannot explain our results, however, because the number of errors remained unchanged throughout the training session, and because our results revealed velocity-related increases in activation in this cerebellar region and not a decrease in cerebellar activity, the latter pattern being classically seen with a reduction in error rate (Imamizu et al., 2000; van Mier et al., 1998, 2004; van Mier and Petersen, 2001).

Alternatively, our findings may be consistent with the hypothesis that lobule VI on the contralateral side of the cerebellum contributes to the temporal restructuring (i.e., chunking) of a sequence of discontinuous movements, and to the emergence of a spontaneous rhythm (Sakai et al., 2004). Although suggesting the necessary involvement of the cerebellum in establishing the temporal properties of a new motor sequence, this study does not however exclude the possibility that the cerebellum may not be a critical node of the brain network that stores the automatized motor program once the sequential movement can be executed in a continuous fashion (Spencer et al., 2003).

The detection of a common performance/neural activity correlation from the motor learning and control conditions in the primary motor cortex suggests that this cortical region does not code for learning mechanisms *per se* in the early phase of practice, but rather that it acts as a low-level relay in the chain of motor commands eliciting the motor behavior. It is however important to consider that this conclusion may not hold true for all motor tasks as the recruitment of the primary motor cortex might be contingent on the level of awareness involved during the learning process. Indeed, it is known that the degree to which explicit and implicit processes are involved in a task may alter the brain network engaged in the execution of motor sequences (Ashe et al., 2006; Destrebecqz et al., 2005; Orban et al., 2008). In addition, it has to be stressed that our results pertain to the early learning phase only, and therefore do not preclude the fact that the primary motor cortex may play a major role in subsequent stages of the learning process. For example, repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex has been reported to disrupt the consolidation of a motor sequence memory trace in humans when applied after implicit sequence learning using the SRT task (Robertson et al., 2005), but not after explicit learning of a finger sequence tapping task (Hotermans et al., 2008). Moreover, long-term practice in healthy humans has also been characterized through fMRI by a more extensive neural representation of a motor sequence in the primary motor cortex (Karni et al., 1995). Furthermore, single-cell recording studies in over-trained monkeys have demonstrated that neurons in the primary motor cortex may code for serial knowledge (Carpenter et al., 1999) and sequential movements (Lu and Ashe, 2005).

In addition to the primary motor cortex, our results show that the medial and lateral motor cortical frontal areas do not appear to constitute essential learning modules during the early phase of training. These findings suggest that their function is to implement higher motor demands for movements specifically produced in sequence, irrespective of the level of practice. A role for medial premotor areas in the processing of ordinal and temporal properties of sequential motor actions is consistent with numerous findings both from animal (Shima and Tanji, 2000; Tanji, 2001) and human (Picard and Strick, 2001; Schubotz and von Cramon, 2001) studies. Research in non-human primates has shown that the lateral dorsal premotor cortex participates in the planning and selection of appropriate actions by integrating the spatial and temporal information necessary for the accurate sequencing of motor movements (Hoshi and Tanji, 2007), the predominant ipsilateral activation being consistent with the dominance of the left hemisphere in the selection of motor actions in humans (Rushworth et al., 2003).

In conclusion, the present findings highlight the multifaceted nature of the complex connection between brain activity and performance improvements, which in essence define motor sequence learning. We aimed at distinguishing between the learning-independent aspects of the modulations of brain responses by performance levels that reflect the motoric, executive feature of the task and the learning-dependent component of this relationship that points to the existence of the functional plasticity mechanisms that subtend learning *per se*. Our findings reveal that modules dedicated to motor sequence learning essentially reside in the putamen and a restricted lateral territory of the contralateral cerebellum, whereas a larger brain network involving both cerebellar and (pre)motor cortical areas are not critical learning nodes in the initial phase of training. The latter set of brain areas appears instead to be necessary to express learning and to implement the improvements in velocity performance induced by learning. It should however be stressed that the function of these regions may be contingent on the extent to which explicit and implicit processes are involved during task practice. In addition, the fact that cortical motor regions do not serve as engram stores in the early learning phase does not preclude the critical role that these areas may play once a motor sequence has been extensively practiced and consolidated.

Acknowledgments

This work was funded by a CRSNG grant (Canada) to JD. PO and PM are supported by FNRS (Belgium). The authors are most grateful to Vo An Nguyen for his skillful support and to Stéphane Lehéricy, Mélanie Pélégrini-Issac and Christophe Phillips for their comments on the research protocol.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.08.055.

References

Ashe, J., Lungu, O.V., Basford, A.T., Lu, X., 2006. Cortical control of motor sequences. Curr. Opin. Neurobiol. 16, 213–221.
Badgaiyan, R.D., Fischman, A.J., Alpert, N.M., 2007. Striatal dopamine release in sequential learning. NeuroImage 38, 549–556.
Bapi, R.S., Miyapuram, K.P., Graydon, F.X., Doya, K., 2006. BfMRI investigation of cortical and subcortical networks in the learning of abstract and effector-specific representations of motor sequences. NeuroImage 32, 714–727.
Boecker, H., Dagher, A., Ceballos-Baumann, A.O., Passingham, R.E., Samuel, M., Friston, K.J., Poline, J., Dettmers, C., Conrad, B., Brooks, D.J., 1998. Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with H2 15O PET. J. Neurophysiol. 79, 1070–1080.
Büchel, C., Holmes, A.P., Rees, G., Friston, K.J., 1998. Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. NeuroImage 8, 140–148.
Carpenter, A.F., Georgopoulos, A.P., Pellizzer, G., 1999. Motor cortical encoding of serial order in a context-recall task. Science 283, 1752–1757.
Catalan, M.J., Honda, M., Weeks, R.A., Cohen, L.G., Hallett, M., 1998. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. Brain 121, 253–264.
Cunnington, R., Windischberger, C., Deecke, L., Moser, E., 2002. The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. NeuroImage 15, 373–385.
Deiber, M.P., Honda, M., Ibanez, V., Sadato, N., Hallett, M., 1999. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. J. Neurophysiol. 81, 3065–3077.
Destrebecqz, A., Peigneux, P., Laureys, S., Degueldre, C., Del Fiore, G., Aerts, J., Luxen, A., Van Der Linden, M., Cleeremans, A., Maquet, P., 2005. The neural correlates of implicit and explicit sequence learning: interacting networks revealed by the process dissociation procedure. Learn. Mem. 12, 480–490.
Doya, K., 2000. Complementary roles of basal ganglia and cerebellum in learning and motor control. Curr. Opin. Neurobiol. 10, 732–739.
Doyon, J., Benali, H., 2005. Reorganization and plasticity in the adult brain during learning of motor skills. Curr. Opin. Neurobiol. 15, 161–167.
Doyon, J., Ungerleider, L.G., 2002. Functional anatomy of motor skill learning. In: Squire, L.R., Schacter, D.L. (Eds.), Neuropsychology of Memory. The Guilford Press, New York.
Doyon, J., Song, A.W., Karni, A., Lalonde, F., Adams, M.M., Ungerleider, L.G., 2002. Experience-dependent changes in cerebellar contributions to motor sequence learning. Proc. Natl. Acad. Sci. U. S. A. 99, 1017–1022.
Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiak, R.S., Turner, R., 1995. Analysis of fMRI time-series revisited. NeuroImage 2, 45–53.
Friston, K.J., Glaser, D.E., Henson, R.N., Kiebel, S., Phillips, C., Ashburner, J., 2002. Classical and Bayesian inference in neuroimaging: applications. NeuroImage 16, 484–512.
Friston, K.J., Penny, W.D., Glaser, D.E., 2005. Conjunction revisited. NeuroImage 25, 661–667.
Garraux, G., Peigneux, P., Carson, R.E., Hallett, M., 2007. Task-related interaction between basal ganglia and cortical dopamine release. J. Neurosci. 27, 14434–14441.
Grafton, S.T., Hazeltine, E., Ivry, R.B., 2002. Motor sequence learning with the nondominant left hand. A PET functional imaging study. Exp. Brain Res. 146, 369–378.

Harrington, D.L., Rao, S.M., Haaland, K.Y., Bobholz, J.A., Mayer, A.R., Binderx, J.R., Cox, R.W., 2000. Specialized neural systems underlying representations of sequential movements. J. Cogn. Neurosci. 12, 56–77.
Haslinger, B., Erhard, P., Weilke, F., Ceballos-Baumann, A.O., Bartenstein, P., Grafin von Einsiedel, H., Schwaiger, M., Conrad, B., Boecker, H., 2002. The role of lateral premotor-cerebellar-parietal circuits in motor sequence control: a parametric fMRI study. Brain Res. Cogn. Brain Res. 13, 159–168.
Hikosaka, O., Nakahara, H., Rand, M.K., Sakai, K., Lu, X., Nakamura, K., Miyachi, S., Doya, K., 1999. Parallel neural networks for learning sequential procedures. Trends Neurosci. 22, 464–471.
Hikosaka, O., Nakamura, K., Sakai, K., Nakahara, H., 2002. Central mechanisms of motor skill learning. Curr. Opin. Neurobiol. 12, 217–222.
Hlustik, P., Solodkin, A., Gullapalli, R.P., Noll, D.C., Small, S.L., 2001. Somatotopy in human primary motor and somatosensory hand representations revisited. Cereb. Cortex 11, 312–321.
Hoshi, E., Tanji, J., 2007. Distinctions between dorsal and ventral premotor areas: anatomical connectivity and functional properties. Curr. Opin. Neurobiol. 17, 234–242.
Hotermans, C., Peigneux, P., Maertens de Noordhout, A., Moonen, G., Maquet, P., 2006. Early boost and slow consolidation in motor skill learning. Learn. Mem. 13, 580–583.
Hotermans, C., Peigneux, P., de Noordhout, A.M., Moonen, G., Maquet, P., 2008. Repetitive transcranial magnetic stimulation over the primary motor cortex disrupts early boost but not delayed gains in performance in motor sequence learning. Eur. J. Neurosci. 28, 1216–1221.
Imamizu, H., Miyauchi, S., Tamada, T., Sasaki, Y., Takino, R., Pütz, B., Yoshioka, T., Kawato, M., 2000. Human cerebellar activity reflecting an acquired internal model of a new tool. Nature 403, 192–195.
Jancke, L., Specht, K., Mirzazade, S., Loose, R., Himmelbach, M., Lutz, K., Shah, N.J., 1998. A parametric analysis of the 'rate effect' in the sensorimotor cortex: a functional magnetic resonance imaging analysis in human subjects. Neurosci. Lett. 252, 37–40.
Jancke, L., Specht, K., Mirzazade, S., Peters, M., 1999. The effect of finger-movement speed of the dominant and the subdominant hand on cerebellar activation: a functional magnetic resonance imaging study. NeuroImage 9, 497–507.
Jueptner, M., Frith, C.D., Brooks, D.J., Frackowiak, R.S., Passingham, R.E., 1997a. Anatomy of motor learning: II. Subcortical structures and learning by trial and error. J. Neurophysiol. 77, 1325–1337.
Jueptner, M., Stephan, K.M., Frith, C.D., Brooks, D.J., Frackowiak, R.S., Passingham, R.E., 1997b. Anatomy of motor learning: I. Frontal cortex and attention to action. J. Neurophysiol. 77, 1313–1324.
Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., Ungerleider, L.G., 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 377, 155–158.
Kelly, A.M., Garavan, H., 2005. Human functional neuroimaging of brain changes associated with practice. Cereb. Cortex 15, 1089–1102.
Kim, J.A., Eliassen, J.C., Sanes, J.N., 2005. Movement quantity and frequency coding in human motor areas. J. Neurophysiol. 94, 2504–2511.
Korman, M., Raz, N., Flash, T., Karni, A., 2003. Multiple shifts in the representation of a motor sequence during the acquisition of skilled performance. Proc. Natl. Acad. Sci. U. S. A. 100, 12492–12497.
Korman, M., Doyon, J., Doljansky, J., Carrier, J., Dagan, Y., Karni, A., 2007. Daytime sleep condenses the time course of motor memory consolidation. Nat. Neurosci. 10, 1206–1213.
Kuriyama, K., Stickgold, R., Walker, M.P., 2004. Sleep-dependent learning and motor-skill complexity. Learn. Mem. 11, 705–713.
Lehericy, S., Benali, H., Van de Moortele, P.F., Pelegrini-Issac, M., Waechter, T., Ugurbil, K., Doyon, J., 2005. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. Proc. Natl. Acad. Sci. U. S. A. 102, 12566–12571.
Lehericy, S., Bardinet, E., Tremblay, L., Van de Moortele, P.F., Pochon, J.B., Dormont, D., Kim, D.S., Yelnik, J., Ugurbil, K., 2006. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. Cereb. Cortex 16, 149–161.
Lu, X., Ashe, J., 2005. Anticipatory activity in primary motor cortex codes memorized movement sequences. Neuron 45, 967–973.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19, 1233–1239.
Matsumoto, N., Hanakawa, T., Maki, S., Graybiel, A.M., Kimura, M., 1999. Role of nigrostriatal dopamine system in learning to perform sequential motor tasks in a predictive manner. J. Neurophysiol. 82, 978–998.
Orban, P., Lungu, O., Doyon, J., 2008. Motor sequence learning and developmental dyslexia. Ann. N.Y. Acad. Sci. 1145, 151–172.
Peigneux, P., Maquet, P., Meulemans, T., Destrebecqz, A., Laureys, S., Degueldre, C., Delfiore, G., Aerts, J., Luxen, A., Franck, G., Van der Linden, M., Cleeremans, A., 2000. Striatum forever, despite sequence learning variability: a random effect analysis of PET data. Hum. Brain Mapp. 10, 179–194.
Penhune, V.B., Doyon, J., 2002. Dynamic cortical and subcortical networks in learning and delayed recall of timed motor sequences. J. Neurosci. 22, 1397–1406.
Petersen, S.E., van Mier, H., Fiez, J.A., Raichle, M.E., 1998. The effects of practice on the functional anatomy of task performance. Proc. Natl. Acad. Sci. U. S. A. 95, 853–860.
Picard, N., Strick, P.L., 2001. Imaging the premotor areas. Curr. Opin. Neurobiol. 11, 663–672.
Poldrack, R.A., 2000. Imaging brain plasticity: conceptual and methodological issues—a theoretical review. NeuroImage 12, 1–13.
Riecker, A., Wildgruber, D., Mathiak, K., Grodd, W., Ackermann, H., 2003. Parametric analysis of rate-dependent hemodynamic response functions of cortical and subcortical brain structures during auditorily cued finger tapping: a fMRI study. NeuroImage 18, 731–739.
Robertson, E.M., Press, D.Z., Pascual-Leone, A., 2005. Off-line learning and the primary motor cortex. J. Neurosci. 25, 6372–6378.
Rushworth, M.F., Johansen-Berg, H., Gobel, S.M., Devlin, J.T., 2003. The left parietal and premotor cortices: motor attention and selection. NeuroImage 20 (Suppl 1), S89–S100.
Sakai, K., Hikosaka, O., Nakamura, K., 2004. Emergence of rhythm during motor learning. Trends Cogn. Sci. 8, 547–553.
Schlaug, G., Sanes, J.N., Thangaraj, V., Darby, D.G., Jancke, L., Edelman, R.R., Warach, S., 1996. Cerebral activation covaries with movement rate. NeuroReport 7, 879–883.
Schubotz, R.I., von Cramon, D.Y., 2001. Interval and ordinal properties of sequences are associated with distinct premotor areas. Cereb. Cortex 11, 210–222.
Schultz, W., Tremblay, L., Hollerman, J.R., 2003. Changes in behavior-related neuronal activity in the striatum during learning. Trends Neurosci. 26, 321–328.
Seidler, R.D., Purushotham, A., Kim, S.G., Ugurbil, K., Willingham, D., Ashe, J., 2002. Cerebellum activation associated with performance change but not motor learning. Science 296, 2043–2046.
Seidler, R.D., Purushotham, A., Kim, S.G., Ugurbil, K., Willingham, D., Ashe, J., 2005. Neural correlates of encoding and expression in implicit sequence learning. Exp. Brain Res. 165, 114–124.
Serrien, D.J., Ivry, R.B., Swinnen, S.P., 2006. Dynamics of hemispheric specialization and integration in the context of motor control. Nat. Rev., Neurosci. 7, 160–166.
Shima, K., Tanji, J., 2000. Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. J. Neurophysiol. 84, 2148–2160.
Spencer, R.M., Zelaznik, H.N., Diedrichsen, J., Ivry, R.B., 2003. Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. Science 300, 1437–1439.
Taniwaki, T., Okayama, A., Yoshiura, T., Nakamura, Y., Goto, Y., Kira, J., Tobimatsu, S., 2003. Reappraisal of the motor role of basal ganglia: a functional magnetic resonance image study. J. Neurosci. 23, 3432–3438.
Taniwaki, T., Okayama, A., Yoshiura, T., Togao, O., Nakamura, Y., Yamasaki, T., Ogata, K., Shigeto, H., Ohyagi, Y., Kira, J., Tobimatsu, S., 2006. Functional network of the basal ganglia and cerebellar motor loops in vivo: different activation patterns between self-initiated and externally triggered movements. NeuroImage 31, 745–753.
Tanji, J., 2001. Sequential organization of multiple movements: involvement of cortical motor areas. Annu. Rev. Neurosci. 24, 631–651.
Toni, I., Krams, M., Turner, R., Passingham, R.E., 1998. The time course of changes during motor sequence learning: a whole-brain fMRI study. NeuroImage 8, 50–61.
van Mier, H., Petersen, S.E., 2001. Role of the cerebellum in motor cognition. Ann. N.Y. Acad. Sci. 978, 334–353.
van Mier, H., Tempel, L.W., Perlmutter, J.S., Raichle, M.E., Petersen, S.E., 1998. Changes in brain activity during motor learning measured with PET: effects of hand of performance and practice. J. Neurophysiol. 80, 2177–2199.
van Mier, H., Perlmutter, J.S., Petersen, S.E., 2004. Functional changes in brain activity during acquisition and practice of movement sequences. Motor Control 8, 500–520.
Walker, M.P., Brakefield, T., Hobson, J.A., Stickgold, R., 2003a. Dissociable stages of human memory consolidation and reconsolidation. Nature 425, 616–620.
Walker, M.P., Brakefield, T., Seidman, J., Morgan, A., Hobson, J.A., Stickgold, R., 2003b. Sleep and the time course of motor skill learning. Learn. Mem. 10, 275–284.
Willingham, D.B., 1998. A neuropsychological theory of motor skill learning. Psychol. Rev. 105, 558–584.