Motor skill acquisition across short and long time scales: A meta-analysis of neuroimaging data.

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Author Note: KW is supported by the Natural Sciences and Engineering Research Council of Canada. LAB is supported by the Canada Research Chairs and Michael Smith Foundation for Health Research. NJH is supported by the Natural Science and Engineering Resource Council of Canada, and the Canadian Institutes of Health Research. The authors would also like to thank Anthony Sze for his assistance with the literature search, Helena Yardley, Tal Yarkoni, and Tor Wager for their early discussion of these data, and an anonymous reviewer for their thorough analysis of and constructive comments about our work.

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Abstract

In this systematic review and meta-analysis, we explore how the time scale of practice affects patterns of brain activity associated with motor skill acquisition. Fifty-eight studies that involved skill learning with healthy participants (117 contrasts) met inclusion criteria. Two meta-contrasts were coded: *decreases*: peak coordinates that showed decreases in brain activity over time; *increases*: peak coordinates that showed increases in activity over time. Studies were grouped by practice time scale: short (≤1 hrs; 25 studies), medium (>1 and ≤24 hrs; 18 studies), and long (>24 hrs to 5 weeks; 17 studies). Coordinates were analyzed using Activation Likelihood Estimation to show brain areas that were consistently activated for each contrast. Across time scales, consistent decreases in activity were shown in prefrontal and premotor cortex, the inferior parietal lobules, and the cerebellar cortex. Across the short and medium time scales there were consistent increases in supplementary and primary motor cortex and dentate nucleus. At the long time scale, increases were seen in posterior cingulate gyrus, primary motor cortex, putamen, and globus pallidus. Comparisons between time scales showed that increased activity in M1 at medium time scales was more spatially consistent across studies than increased activity in M1 at long time scales. Further, activity in the striatum (viz. putamen and globus pallidus) was consistently more rostral in the medium time scale and consistently more caudal in the long time scale. These data support neurophysiological models that posit that both a cortico-cerebellar system and a cortico-striatal system are active, but at different time points, during motor learning, and suggest there are associative/premotor and sensorimotor networks active within each system.

1. Introduction

Numerous, non-systematic reviews have been conducted on the behavioural and physiological changes that accompany practice and the acquisition of motor skills (e.g., Hikosaka et al., 2002; Willingham, 1998). The main focus of past work has been on changes in brain activity that underlie improved speed and accuracy in sequence learning or visuomotor adaptations (e.g., Dayan & Cohen, 2011; Doyon et al., 2009; Wadden et al., 2012). Based on data from neuroimaging (e.g., fMRI, PET) and cortically-induced perturbations (e.g., TMS), neurophysiological theories of motor learning advance the idea that skill acquisition and ultimately long term learning is supported by cortico-thalamic-cerebellar and cortico-thalamic-striatal systems (e.g., Hikosaka et al., 2002; Doyon et al., 2009).

Experimental evidence from individual studies also demonstrate distinct "associative/premotor" (AP) and "sensorimotor" (SN) networks that operate within the cortico-cerebellar and cortico-striatal systems. The AP network includes the dorsolateral prefrontal cortex, rostral premotor areas, the inferior parietal cortex, cerebellar cortex, and rostral basal ganglia. The SN network consists of supplementary and primary motor cortices, caudal basal ganglia, and the dentate nucleus (Coynel et al., 2010; Lehéricy et al., 2005; see also Hikosaka et al., 2002). These networks operate on different time scales with AP areas contributing to early-stage performance and SN regions supporting performance at later stages of practice. However, the time course of shifts within and between the networks that support motor learning remains to be determined. Recently, a meta-analysis was performed to distinguish brain areas associated with learning two types of motor tasks: sensorimotor adaptation versus the serial reaction time (SRT) task (Hardwick et al. 2013). However, a limitation in this work was the omission of time-dependent analyses.

Motor learning has been defined as “relatively permanent changes in the capability for skilled behaviour" resulting from practice or experience that is typically assessed by a delayed retention test (Schmidt & Lee, 2005, p. 302). The need to differentiate performance and learning effects is based on a

substantial body of research showing differences in behaviour when it is assessed at the end of a practice session as compared to following a delay (typically 24 hours to 1 week after practice has concluded; Kantak & Winstein, 2012). Group differences noted during practice have been shown to disappear (e.g., Feijen et al., 2010; Winstein et al., 1994), appear (Abe et al., 2011), or even reverse following a retention interval (Lee & Simon, 2004). Indeed, as many as 63 % of studies show a lack of consistency in performance effects between immediate and delayed testing sessions, when those testing sessions are delayed by >24 hrs (Kantak & Winstein, 2012). There are also empirical demonstrations of change in both behavioural and neural data when a delay is introduced between practice and retention testing, referred to as motor memory consolidation (Debas et al., 2010; Robertson et al., 2004, Shadmehr & Holcomb, 1997). Thus, changes in behavior that occur within a session could represent early stages of learning and/or transitory changes in performance (what Doyon et al., 2009 have referred to as “fast learning processes”), making it important to distinguish this early or “fast” learning from more permanent "slow" learning processes which take place over longer time spans.

In view of these distinctions, the duration of practice was the primary variable of interest in our meta-analysis. Operationally, we divided practice into three time scales: short (≤1 hr), medium (>1 hr to ≤ 24 hrs), and long (>24 hrs to 5 weeks). Dividing practice sessions within a single day into short and medium time scales is motivated by similar distinctions made by Karni et al. (1998), who noted behavioural and neurophysiological changes across these time scales. Changes observed over long time scales meet the criterion of inclusion of a delayed retention test and therefore are more likely to reflect brain activity associated with learning. By controlling for the time scale of practice and combining large numbers of studies, we can delineate which brain regions are active following relatively short to moderate time scales of practice from more long-term changes and resolve some of the heterogeneous results in neuroimaging studies of skill acquisition.

2. Method

2.1 Literature search

We searched for studies published in or translated to English in the following databases: PsycINFO (EBSCO), Google Scholar, and PubMed. Search terms included combinations of "motor learning" and "skill acquisition" with one of the following, "neuroimaging", "fMRI", and "PET". The initial search was conducted in February 2013 and updated until January 2014. Further literature was obtained through reference lists of included papers.

2.2 Inclusion criteria

Analysis was restricted to experimental studies, but all time scales of learning were considered. Time scales were calculated based on methodological information provided in the study. Two coders (KRL and KW) calculated the time scale of practice for each study based on the time between first and last measurements of brain activity. When there was disagreement the authors discussed the study in question until consensus was reached. There were three time scales: short-term studies (*short*) which were ≤1 hr (the shortest of which was ~12 min; Inoue et al 1997); medium-term studies (*medium*) which were >1 hr and ≤24 hrs (the longest of which was 12 hrs[1]); and long-term studies (*long*) which were >24 hours (the longest of which was 5 weeks; Karni et al., 1995). For short studies, the comparison of the earliest to the last measurement was between brain activity at time zero to activity less than one hour later. This same contrast for long studies was based on a comparison of brain activity at time zero to several days, or even weeks later. Thus, increases or decreases (defined below) are always a comparison from the last time point measured (which could be minutes, hours, or days depending on the time scale) to the earliest brain scan.

Different tasks were included, but all involved the upper extremities. Different contrasts for assessing learning were included, provided that there was at least one learning based contrast in the study (that is, comparing performance at an early time point to a later time point, following practice).

Because we were using a coordinate-based meta-analysis, studies for which peak coordinates were not available were excluded. Four studies (Karni et al., 1995; Ma et al., 2010, Seitz et al., 1990; Seitz et al., 1992) did not directly report peak activation foci, but foci were estimated from descriptions in the text, provided figures, and consulting the Talairach daemon (Lancaster et al., 2000). Estimated coordinates accounted for 2.2% of the total data (21 out of 958 total foci).

Participants had to be healthy adults (18-50 years); developmental, geriatric, or clinical populations were excluded. After screening by title and abstract, a total of 58 studies and 117 separate contrasts were included in the meta-analysis (Table 1). All of the studies included a behavioural measure of learning in addition to neuroimaging measures.

The time scales of studies differed considerably, as did task type, and the original contrast. In order to be analyzed together, peak coordinates (foci) from these studies were re-coded to fit into one of two meta-contrasts. Comparisons were made in what we refer to as “decreases” (i.e., *Early > Late* meta-contrast), which reflects decreasing brain activation over time, or “increases” (i.e., *Late > Early* meta-contrast), reflecting increasing brain activation over time. Details of these two meta-contrasts are shown in Figure 1.

Decreases in brain activation over time included comparisons of early - late blocks (e.g., scan 1 - scan 3; Grafton et al., 1994; Grafton et al., 2002), a pre- to post-test interval (e.g., Ma et al., 2010) or across multiple scans that included baseline measures (e.g., [activation 1 - control 1]-[activation 4 - control 4]; Lehéricy et al., 2005). In some sequence learning studies a random or new sequence served as the control and activation in this condition was compared to a (pre)learned sequence (e.g., Debaere et al., 2004; Doyon et al., 1996).

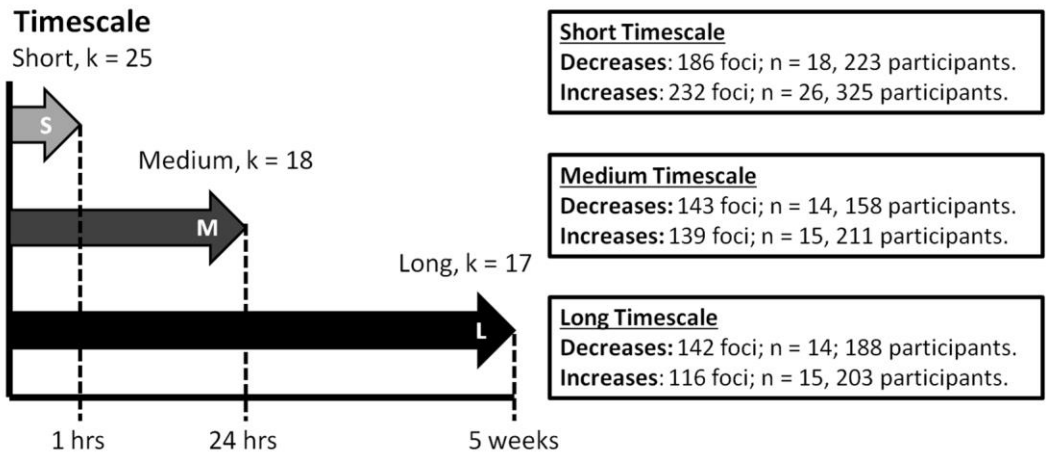

Figure 1. The number of studies at each time scale (k) and, of those studies, the number of independent groups contributing to each meta-contrast (n). In revised ALE (Turkletaub et al., 2012) data are entered by participant group rather than by published study. Thus, studies with multiple groups of participants (e.g., Sakai et al, 2002) count for k = 1 and n = 2. Time scale classification refers to the length of the experimental protocol.

Increases in brain activation over time included the opposite contrasts, where activity at a later scan was greater than an earlier scan (e.g., [activation 4 - control 4]-[activation 1 - control 1], scan 3 - scan 1 or late - early Blocks; Lehéricy et al., 2005; Ma et al., 2010; Penhune et al., 2002, respectively). Thus, both meta-contrasts reflect differences in brain activity during task performance at different time points. These meta-contrasts are sensitive to changes in the neural networks active during control of movement, but are insensitive to areas that are consistently involved in motor control.

Table 1. *Summary of studies and contrasts used in the meta-analysis.*

Reference	Modality	Contrasts Extracted	Foci Extracted by Contrast	Participants	Time Code in Meta-Analysis
Albouy et al., 2012	fMRI	1	12	30	Short
Anguera et al., 2007	fMRI	1	4	11	Short
Bischoff-Grethe et al. 2004	fMRI	2	38/15	24	Short
Debaere et al., 2004	fMRI	2	9/15	12	Long
Debas et al., 2010	fMRI	4	12/5/17/3	24/24	Medium
Deiber et al., 1997	PET	1	4	7	Long
Doyon et al., 1996	PET	2	7/4	14	Short
Doyon et al., 2002	fMRI	4	3/1/6/2	9	Medium
Fernández-Seara et al. 2009	fMRI	2	7/26	14	Short
Fischer et al. 2005	fMRI	2	9/6	8	Long
Floyer-Lea & Matthews, 2005	fMRI	3	9/3/3	15/7	Short & Long
Gheysen et al., 2010	fMRI	2	1/20	22	Short
Gobel et al., 2011	fMRI	2	2/9	18	Short
Grafton et al., 1992	PET	1	3	6	Short
Grafton et al., 1994	PET	4	9/3/4/2	8	Short & Long
Grafton et al., 1995	PET	2	7/4	12	Medium
Grafton et al., 2001	PET	2	7/3	7	Short
Grafton et al., 2002	PET	2	21/9	8	Short
Graydon et al., 2005	fMRI	2	5/12	24	Short
Hazeltine et al., 1997	PET	4	9/8/8/4	11	Medium
Honda et al., 1998	PET	1	3	21	Medium
Inoue et al., 1997	PET	1	19	6	Short
Inoue et al., 2000	PET	1	5	6	Short
Jenkins et al., 1994	PET	2	21/18	12	Medium
Jueptner et al., 1997	PET	1	21	12	Medium

Karni et al., 1995	fMRI	1	2	6	Long
Krakauer et al., 2004	PET	1	7	12	Short
Krebs et al., 1998	PET	2	15/19	8	Medium
Lefebvre et al., 2012	fMRI	1	4	20	Short
Lehéricy et al., 2005	fMRI	2	17/3	14	Long
Ma et al., 2010	fMRI	2	2/2	10	Long
Matsumura et al., 2004	PET	1	4	13	Medium
Müller et al., 2002	fMRI	2	12/7	8	Short
Olson et al., 2006	fMRI	1	3	10	Medium
Parsons et al., 2005	fMRI	2	14/3	12	Long
Penhune et al., 1998	PET	2	14/7	12	Medium
Penhune & Doyon, 2002	PET	4	4/5/11/7	9	Long
Peterson/Van Mier et al., 1998	PET	2	6/6	16	Medium
Poldrack et al, 2005	fMRI	1	8	14	Long
Puttemans et al., 2005	fMRI	4	3/5/4/6	11	Long
Remy et al., 2008	fMRI	2	5/2	12	Long
Ronsse et al., 2010	fMRI	2	8/1	38	Long
Sakai et al., 2002	PET	4	8/7/11/5	12/8	Short
Schendan et al., 2003	fMRI	2	8/8	17	Medium
Schlaug et al., 1994	PET	1	1	9	Short
Seitz et al., 1990	PET	2	3/5	9	Medium
Seitz et al., 1992	PET	2	1/6	9	Medium
Seitz et al., 1994	PET	2	3/1	8	Short
Shadmehr & Holcomb, 1997	PET	2	3/2	9	Medium
Steele et al., 2010	fMRI	4	24/12/14/26	15	Long
Toni et al., 1998	fMRI	2	9/4	3	Short
Toni et al., 1999	PET	4	4/4/4/5	10	Short
Tracy et al., 2001	fMRI	2	18/19	5	Short
Tracy et al., 2003	fMRI	1	5	12	Long
Van der Graaf et al., 2004	fMRI	2	7/6	18	Long

Van Horn et al., 1998	PET	2	22/10	15	Short
Willingham et al., 2002	fMRI	1	7	22	Medium
Wu et al., 2004	fMRI	1	13	12	Medium

***Table 1 (cont.)**. Summary of studies and contrasts used in the meta-analysis.*

Reference	Task	Hand	Foci Extracted
Albouy et al., 2012	Explicit sequence learning.	L ND	Table 1
Anguera et al., 2007	Visuomotor adaptation	R D	Table 4
Bischoff-Gerthe et al., 2004	Explicit sequence learning	R D	Table 1
Debaere et al., 2004	Bimanual coordination task	L and R	Table 2 Table 3.
Debas et al., 2010	Sequence learning and reach adaptation	L ND	Supplemental Table 1. Supplemental Table 2.
Deiber et al., 1997	Conditional joystick movements*	R D	Table 3. Table 4.
Doyon et al., 1996	Implicit sequence learning	R D	Table 1. Table 2.
Doyon et al., 2002	Explicit sequence learning	R D	[1]
Fernández-Seara et al., 2009	Explicit sequence learning	R D	Table 4.
Fischer et al., 2005	Explicit sequence learning	L ND	Table 2. Table 3.
Floyer-Lea & Matthews, 2005	Force production sequence	R D	Table 1.
Gheysen et al., 2010	Implicit sequence learning	L and R	[1]
Gobel et al., 2011	Serial Interception Sequence Learning	L and R	Table 1.
Grafton et al., 1992	Pursuit rotor task	R D	Table 2.
Grafton et al., 1994	Pursuit rotor task	R D	Table 1. Table 2.
Grafton et al., 1995	Six item serial reaction time	R D	Table 1. Table 3.
Grafton et al., 2001	Continuous tracking with an embedded and random sequence	R D	Table 2. Table 5.
Grafton et al., 2002	Implicit sequence learning	L ND	Table 2
Graydon et al., 2005	Joy stick reaches with a visuo-motor rotation.	R D	Table 2.
Hazeltine et al., 1997	Implicit and explicit sequence learning	R D	Table 1. Table 2.
Honda et al., 1998	Implicit and explicit sequence learning	R D	Table 2.
Inoue et al., 1997	Visuomotor adaptation	R D	Table 2. Table 3.
Inoue et al., 2000	Visuomotor adaptation	R D	Table 3.
Jenkins et al., 1994	Trial and error sequence	R D	Table 5.

	learning		Table 6.
Jueptner et al., 1997	Trial and error sequence learning	R D	Table 1.
Karni et al., 1995	Explicit sequence learning	ND 5L, 1R	[2]
Krebs et al., 1998	Target reaching with novel dynamics	R D	Table IIa. Table IIb.
Krakauer et al., 2004	Visuomotor adaptation	R D	Table 2.
Lefebvre et al., 2012	Implicit visuomotor learning	L ND	Table 3.
Lehéricy et al., 2005	Explicit sequence learning	L ND	[1] and supporting information.
Ma et al., 2010	Explicit sequence learning	L ND	[2]
Matsumura et al., 2004	Two ball rotation task	L and R	Table 4
Müller et al., 2002	Explicit sequence learning	D 7R, 1L	Table 5
Olson et al., 2006	Implicit sequence learning	L and R	Table 2
Parsons et al., 2005	Explicit sequence learning	R D	Table 2
Penhune et al., 1998	Audio and visual rhythm learning	R D	Table 3.
Penhune & Doyon, 2002	Visual rhythm learning	R D	Table 2. Table 4.
Peterson/Van Mier et al., 1998	Maze tracing	R D	Table 7.
Poldrack et al, 2005	Implicit sequence learning w/o secondary task	Not Clear	Table 3.
Puttemans et al., 2005	Bimanual cyclical wrist movements	L and R	Table 2. Table 3.
Remy et al., 2008	Bimanual cyclical wrist movements	L and R	Table 1.
Ronsse et al., 2010	Bimanual cyclical wrist movements	L and R	Table 1
Sakai et al., 2002	Learning of a timed sequence	R D	Table 1. Table 2.
Schendan et al., 2003	Implicit and explicit sequence learning	R D	Table 1. Table 2.
Schlaug et al., 1994	Explicit sequence learning	R D	Table 2.
Seitz et al., 1990	Explicit sequence learning	R D	[2]
Seitz et al., 1992	Explicit sequence learning	R D	[2]
Seitz et al., 1994	Writing novel ideograms	R D	Table 1
Shadmehr & Holcomb, 1997	Reaching in a novel force field	R D	[1]
Steele et al., 2010	Temporal motor sequence learning	R D	Supplemental Table 2 Supplemental Table 3
Toni et al., 1998	Trial and error sequence learning	R D	[1]

Toni et al., 1999	Conditional visuomotor task and sequence learning task	R D	Table 3 Table 4
Tracy et al., 2001	Explicit sequence learning	R D	Table 1 Table 2
Tracy et al., 2003	Knot tying	L and R	Table 1
Van der Graaf et al., 2004	Implicit sequence learning	L and R	Table 3
Van Horn et al., 1998	Maze learning in a 10 x 10 matrix	R D and ND	Table 1
Willingham et al., 2002	Explicit and implicit sequence learning	L and R	Table 2 Table 3
Wu et al., 2004	Explicit sequence trained to automaticity	R D	Table 2

Note. fMRI = functional magnetic resonance imaging. PET = positron emission tomography. If more than one number is given in the column "Foci Extracted" then multiple contrasts from the same experiment have been included in the meta-analysis. Meta-analysis time codes for experimental protocols ≤1 hrs (*short*), protocols >1 and ≤24 hrs (*medium*), and protocols > 1 day (*long*). All experiments used the upper extremities but differed with respect to the hand used, either the left hand (L), the right hand (R) or bimanual (L and R). We also indicate if this was the dominant (D) or non-dominant hand (ND) for participants. The location of extracted foci is given as either the table in the original paper, foci that were extracted from text ([1]), or foci that were estimated from the text ([2]). The full dataset of studies and peak coordinates used in the meta-analysis are available from the first author upon request.
* Deiber et al (1997) was primarily a stimulus-response learning task, but there were specific spatial and temporal motor requirements.

2.3 Meta-analysis

Analyses were performed with GingerALE 2.1 (brainmap.org) using a modified algorithm for Activation Likelihood Estimation (ALE; Turkeltaub et al., 2012). ALE converts peak activation coordinates within a study into a Gaussian probability distribution centered at the given coordinates (Eickhoff et al., 2009; Laird et al., 2005). The width of these distributions is calculated based on empirical data about variability in spatial normalization, and the relationship between sample size and inter-participant localization (Eickhoff et al., 2009). Recent modifications to the ALE algorithm (Turkeltaub et al., 2012) correct for different numbers of brain activations between experiments (reducing the influence of a single study reporting many coordinates) and reduce the influence of multiple contrasts being measured from a

single group of participants. The modified ALE algorithm allows computation of the voxel-wise joint probability of brain activation within a group of participants. The voxel-wise joint probability is then calculated between these independent activation maps, controlling for multiple foci from the same group of participants. Thus, ALE measures the spatial consistency between studies, providing a metric of brain activation weighted by the inverse of the variance across studies.

All Montreal Neurologic Institute (MNI) coordinates were converted to Talairach space before analysis (Lancaster et al., 2007). Following spatial normalization, the meta-analysis was conducted in two phases. First, we calculated main effects that show consistency (spatial convergence between studies) for increases and decreases in brain activity at the short, medium, and long time scales separately (6 main effects in total). Next, we compared the short to the medium and the medium to the long time scales, which allowed us to make relative conclusions about how well represented a brain area was within one time scale compared to another time scale (i.e., the relative consistency across studies). For example, brain regions showing increases in the short time scale were compared to brain regions showing increases in the medium time scale. For these increases, the comparison Short > Medium reflects greater consistency for increasing activity at the short time scale. Conversely, the comparison Medium > Short reflects greater spatial consistency for increasing activity across studies at the medium time scale (8 comparisons between time scales).

In all analyses, ALE maps were based on a false discovery rate (FDR) of $q < .05$ as a correction for multiple comparisons (Genovese et al., 2001) and a minimum cluster size of 200 mm^3. We also reanalyzed our data using a more conservative $q < .001$ and minimum cluster size of 50mm^3. Clusters that remained significant at $q < .001$ are indicated by a "†" in the tables and ALE values in the figures are colour-coded to show significant increases in activity (red = $q < .05$; yellow = $q < .001$) and decreases in activity (blue = $q <. 05$; green = $q <. 001$). Significant clusters were identified and labeled based on the weighted centre of the cluster in Talairach space (Lancaster et al., 2000). In our Tables we use labels

corresponding to the centre of the cluster. In the text we point out instances when clusters spanned multiple brain areas. Resulting ALE maps were superimposed on a Talairach template brain (Kochunov et al., 2002) using the Multi-Image Analysis Gui (http://ric.uthscsa.edu/mango/), shown in Figure 2.

3. Results

3.1 Short studies only

3.1.1 Decreases. Across studies, there were spatially consistent decreases centered in bilateral prefrontal cortex, left presupplementary motor area, the right inferior and bilateral superior parietal lobules, the left precuneus, and right inferior temporal gyrus (Table 2). Subcortically, there were decreases centered in the right posterior cerebellar cortex.

3.1.2 Increases. Areas of consistent increasing activity were centered in M1 bilaterally, the left SMA, the left premotor cortex, the left posterior cingulate cortex, bilateral precuneus, and the left middle occipital gyrus. Subcortically, there were increases in the left globus pallidus, the right thalamus, and the anterior and posterior cerebellar cortex. Increases in the anterior cerebellum included the dentate nucleus.

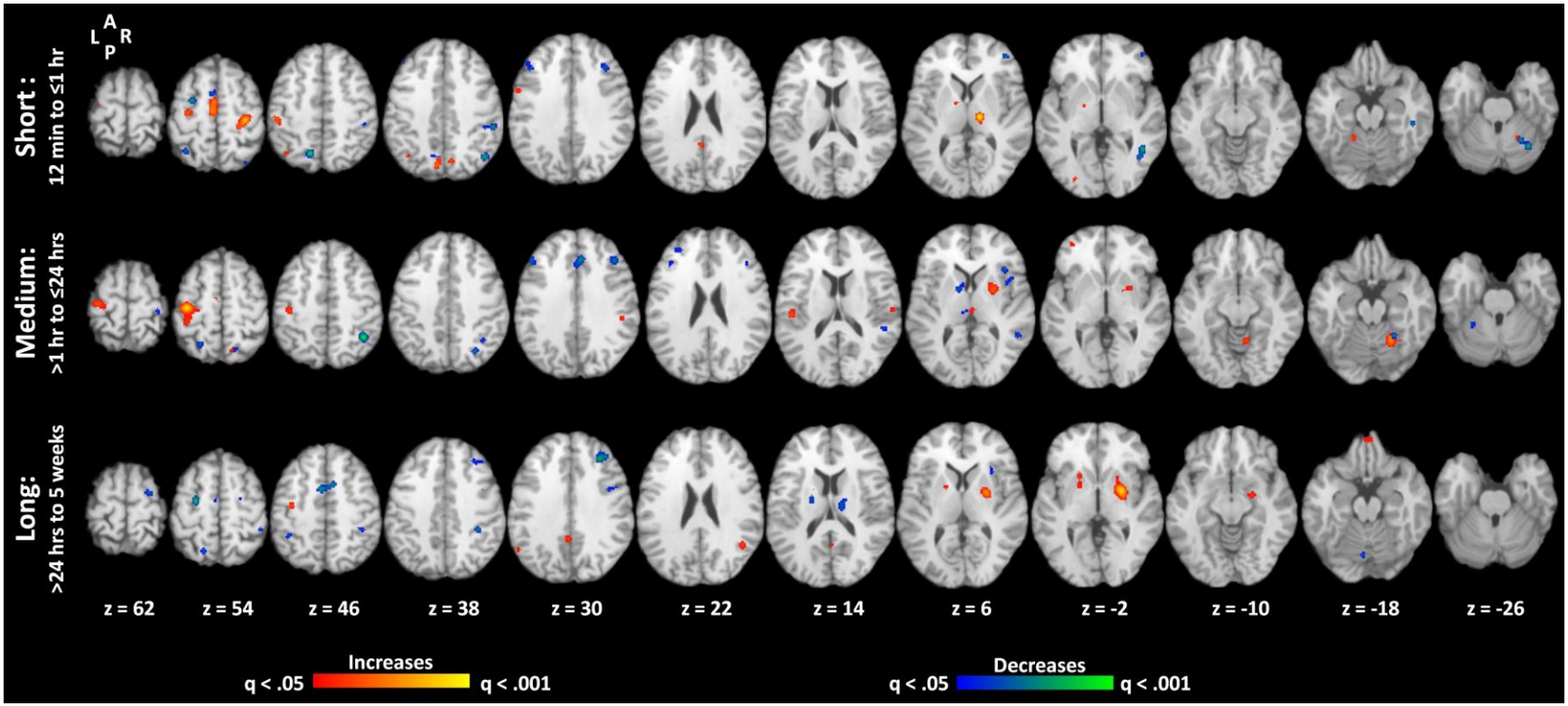

Figure 2. Significant increases and decreases for short, medium, and long time scale studies. ALE volumes significant below a brain-wise FDR = .05 are shown for decreases: blue/green and increases: red/yellow. Colour gradients reflect statistical significance for individual voxels. Red/blue areas are significant at a brain-wise FDR of q < .05; yellow/green areas remain significant at a brain-wise FDR of q < .001.

Table 2. Summary of significant clusters for studies with a short time scale (≤1 hr); FDR = .05, minimum cluster size = 200 mm^3.

			Cluster Centroid			Brain Region		
Contrast	ALE	Volume (mm^3)	X	Y	Z	Hemisphere	Label	Brodmann Area
Decreases	.014	1144	31	-62	-27	R	Post. Cere.	
	.016†	1096	46	-36	40	R	IPL	BA 40
	.016†	1064	-10	-66	45	L	Precuneus	BA 7
	.014	880	42	-57	-2	R	Temporal	BA 19
	.013	568	46	-32	-18	R	Temporal	BA 20
	.014	560	44	-66	38	R	Parietal	BA 39
	.012	464	-42	28	30	L	DLPFC	BA 9
	.013	456	42	44	3	R	DLPFC	BA 46
	.011	384	36	26	29	R	DLPFC	BA 9
	.014	360	-26	-75	42	L	Precuneus	BA 19
	.013	328	-24	-5	53	L	Sub-gyral	BA 6
	.012	296	-31	-57	55	L	SPL	BA 7
	.012	272	-3	3	52	L*	Pre-SMA	BA 6
	.011	216	31	-70	52	R	SPL	BA 7
Increases	.018†	1520	29	-26	56	R	M1	BA 4
	.016†	1392	-2	-13	52	L*	SMA	BA 6
	.017†	704	14	-20	5	R	Thalamus	
	.013	640	-4	-72	36	L	Precuneus	BA7
	.012	568	-29	-17	55	L	M1	BA 4
	.015	528	9	-72	35	R	Precuneus	BA 7
	.014	520	-45	-31	44	L	IPL	BA 40
	.013	416	-36	-65	42	L	Precuneus	BA 19
	.014	376	21	-56	-23	R	Ant. Cere.^{DN}	
	.013	360	-16	-47	-20	L	Ant. Cere.^{DN}	
	.012	280	-23	-58	-43	L	Post. Cere.	
	.011	264	-14	-7	2	L	Globus Pallidus	
	.012	232	-1	-48	21	L*	PCG	BA 30
	.012	208	-54	2	29	L	PMC	BA 6
	.012	200	-27	-85	0	L	MOG	BA 18

Note. Post. Cere. = posterior cerebellar cortex; IPL = inferior parietal lobule; DLPFC = dorsolateral pre-frontal cortex; SPL = superior parietal lobule; SMA = supplementary motor area; M1 = primary motor cortex; Ant. Cere. = anterior cerebellum; PCG = posterior cingulate gyrus; MOG = middle occipital gyrus; PMC = premotor cortex.

† = a cluster that remains significant when the false discovery rate is more conservative, $q < .001$.

^{DN} = denotes a cluster of activation that included the dentate nucleus.

* = a cluster with an x-coordinate between 3 and -3. While the centroid of the cluster lies in a particular hemisphere, the cluster extends bilaterally.

3.2 Medium studies only

3.2.1 Decreases. There were consistent decreases in activity in DLPFC bilaterally, the left anterior prefrontal cortex, the right anterior cingulate, and right somatosensory motor cortex. The cluster of decreasing activity centered in right S1 also included right M1. There were clusters of decreasing activity in the precuneus bilaterally, the right inferior and superior parietal lobules, the right insula, and the right superior temporal gyrus. Subcortically, there were decreases in the left globus pallidus and the anterior cerebellum bilaterally. See Table 3.

3.2.2 Increases. Consistent increases in cortical activity were found in left M1, the left SMA (this cluster included posterior cingulate gyrus), left sub-gyral cortex near BA 10, the left insula, the right IPL and the right precuneus. Subcortically, there were increases in the right thalamus, the right putamen, and the right anterior cerebellum. Clusters of increasing activity in the anterior cerebellum included the dentate nucleus.

Table 3. Summary of significant clusters for studies with a medium time scale (>1 hr but ≤24 hrs); FDR = .05 minimum cluster size = 200 mm^3.

			Cluster Centroid			Brain Region		
Contrast	ALE	Volume (mm^3)	X	Y	Z	Hemisphere	Label	Brodmann Area
Decreases	.018†	1312	38	-53	44	R	IPL	BA 40
	.014†	1056	38	16	4	R	Insula	BA 13
	.015†	960	4	27	29	R	ACG	BA 32
	.013	840	40	28	27	R	DLPFC	BA 9
	.012	560	-21	-59	54	L	Precuneus	BA 7
	.014†	480	28	-68	36	R	Precuneus	BA 7
	.011	440	-10	1	7	L	Globus Pallidus	
	.012	424	-45	28	29	L	DLPFC	BA 9
	.010	408	-26	-51	-27	L	Ant. Cere.	
	.012	368	24	-51	-19	R	Ant. Cere.	
	.011	312	51	-48	8	R	Temporal	BA 22
	.011	304	-31	42	20	L	APFC	BA 10
	.010	256	49	-40	13	R	Temporal	BA 21
	.009	256	15	-63	52	R	Precuneus	BA 7
	.011	256	32	-29	60	R	S1	BA 3
	.010	208	-5	-24	4	L	Thalamus	
	.009	208	23	-55	58	R	SPL	BA 7
	.009	200	-38	28	23	L	DLPFC	BA 46
Increases	.027†	3864	-33	-24	55	L	M1	BA 4
	.019†	1344	25	0	3	R	Putamen	
	.018†	1224	21	-56	-18	R	Ant. Cere.^{DN}	
	.015†	816	-46	-24	17	L	Insula	BA 41
	.013	528	-37	-45	-35	L	Post. Cere.	
	.012	496	4	-23	6	R	Thalamus	
	.013	392	9	-55	-10	R	Ant. Cere.	
	.014	368	48	-32	33	R	IPL	BA 40
	.011	352	57	-20	17	R	Parietal	BA 40
	.011	208	-34	46	0	L	Sub-gyral	
	.009	208	-4	-11	51	L	SMA	BA 6
	.011	208	12	-65	52	R	Precuneus	BA 7

Note. IPL = inferior parietal lobule; ACG = anterior cingulate gyrus; DLPFC = dorsolateral prefrontal cortex ; Ant. Cere. = anterior cerebellum; APFC = anterior prefrontal cortex; S1 = primary somatosensory cortex; SPL = superior parietal lobule; M1 = primary motor cortex; Post. Cere. = posterior cerebellum; SMA = supplementary motor area.

† = a cluster that remains significant when the false discovery rate is more conservative, $q < .001$

^{DN} = denotes a cluster of activation that included the dentate nucleus.

3.3 Long studies only

3.3.1 Decreases. Across studies, there were consistent decreases in activation in the right DLPFC, the PMC and Pre-SMA bilaterally, the left anterior cingulate, the right insula, and the right superior and bilateral inferior parietal lobules. Subcortically, there were decreases in activation across time in the thalamus and the left posterior cerebellar cortex. See Table 4.

3.3.2 Increases. Consistent increases in activation were shown in the posterior cingulate gyrus, medial frontal gyrus and precuneus bilaterally. There were also consistent increases in left M1, the right middle and left superior temporal gyri. Subcortically, consistent increases were noted in the putamen and the globus pallidus bilaterally.

Table 4. Summary of significant clusters for studies with a long time scale (>24 hrs); FDR = .05 minimum cluster size = 200 mm^3.

			Cluster Centroid			**Brain Region**		
Contrast	ALE	Volume (mm^3)	X	Y	Z	Hemisphere	Label	Brodmann Area
Decreases	.015†	1704	33	35	33	R	DLPFC	BA 9
	.013	1488	1	1	47	R*	Pre-SMA	BA 6
	.016†	704	-23	-12	52	L	PMC	BA 6
	.015†	696	36	-39	42	R	IPL	BA 40
	.012	600	43	3	33	R	PMC	BA 6
	.013	576	32	17	9	R	Insula	BA 13
	.011	536	14	-16	15	R	Thalamus	
	.011	536	24	-9	58	R	PMC	BA 6
	.014	432	-17	-71	-35	L	Post. Cere.	
	.012	328	-3	-73	-20	L	Post. Cere.	
	.011	304	-15	-63	52	L	SPL	BA 7
	.011	280	-18	-11	15	L	Thalamus	
	.011	280	13	-10	67	R	PMC	BA 6
	.011	240	-37	-47	44	L	IPL	BA 40
	.010	232	-5	-15	66	L	Pre-SMA	BA 6
	.010	200	-7	28	26	L	ACG	BA 32
	.010	200	43	-42	55	R	IPL	BA 40
Increases	.024†	3304	25	-6	-1	R	Putamen	
	.011	624	-18	5	-4	L	Putamen	
	.012	576	1	46	-15	R*	Medial Frontal	BA 11
	.012	392	-2	-49	32	L*	Precuneus	BA 31

.011	376	45	-56	22	R	Temporal	BA 39
.012	368	-34	-15	47	L	M1	BA 4
.012	352	-16	0	9	L	Globus Pallidus	
.009	240	3	-58	13	R*	PCG	BA 30
.009	200	-52	-59	29	L	Temporal	BA 39

Note. DLPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area; PMC = premotor cortex; IPL = inferior parietal lobule; Post. Cere. = posterior cerebellum; SPL = superior parietal lobule; ACG = anterior cingulate gyrus; PCG = posterior cingulate gyrus.
† = a cluster that remains significant when the false discovery rate is more conservative, $q < .001$.
* = a cluster with an x-coordinate between 3 and -3. While the centroid of the cluster lies in a particular hemisphere, the cluster extends bilaterally.

3.4 Comparison across time scales

This analysis highlights differences in the consistency of the spatial convergence across studies, for both increasing activity and decreasing activity, as a function time scale. We compared the short to the medium studies and the medium to the long studies, shown in Table 5. When the short time scale showed more consistency across studies (for increasing or decreasing activity) than the medium time scale, we denoted this with the contrast symbols; S > M and highlight the area of difference in the table. When the medium time scale showed more consistency across studies (for increasing or decreasing activity) than the medium, we denote this with the contrast symbols; M > S in the table. The same symbols apply for comparisons between medium and long time scales.

3.4.1 Comparison of short and medium studies. As displayed in Table 5, at the short time scale, there was a cluster of decreasing activity in the left precuneus that was statistically more consistent than the medium time scale. There were, however, clusters of decreasing activity in the left anterior prefrontal cortex and right inferior frontal gyrus that were more consistent for the medium than the short time scale. There was also a cluster of increasing activity in left M1/S1 that was statistically more consistent for the medium time scale than the short time scale.

Table 5. Contrast of short to medium and medium to long studies. FDR = .05 minimum cluster size = 50 mm^3.

Contrast		Volume (mm^3)	Cluster Centroid			Brain Region		
			X	Y	Z	Hemisphere	Label	Brodmann Area
Decreases	S > M	536	-10	-66	43	L	Precuneus	BA 7
	M > S	152	-31	42	19	L	APFC	BA 10
		64	38	19	6	R	IFG	BA 45
	M > L							
	L > M	80	28	46	33	R	DLPFC	BA 9
Increases	S > M							
	M > S	1464	-36	-25	55	L	M1/S1	BA 4/BA 3
	M > L	464	-38	-24	54	L	M1/S1	BA 4/BA 3
		56	21	-61	-17	R	Post. Cere.	
	L > M	72	25	-10	-5	R	Globus Pallidus	

Note. DLPFC = dorsolateral prefrontal cortex; APFC = anterior prefrontal cortex; IFG = inferior frontal gyrus; M1 = primary motor cortex; S1 = primary somatosensory cortex; Post. Cere. = posterior cerebellum. S = short-term studies; M = medium-term studies; L = long-term studies.

3.4.2 Comparison of medium and long studies. At the medium time scale, there were clusters of increasing activity in left M1 and in the right cerebellar cortex that were significantly more consistent than the long time scale. Conversely, for the long time scale, there was a cluster of increasing activity centered in the right globus pallidus that was significantly more consistent than the medium time scale, shown in Figure 3. At the long time scale, there was also a cluster of decreasing activity in the DLPFC that was more consistent than at the medium time scale.

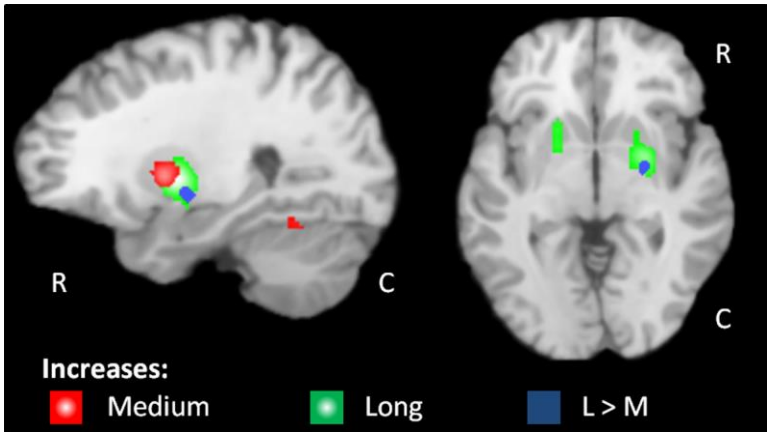

Figure 3. Imaging results showing a shift from the rostral (R) to caudal (C) striatum as a function of time scale. Increasing activity is shown for the medium (red) and long (green) time scales. Spatial convergence was greater in the caudal-ventral striatum for the long time scale compared to the medium time scale (shown in blue, $q < .05$).

4. Discussion

Pooling data from studies across different time scales allowed us to compare patterns of brain activity associated with motor learning from the very early stages of practice, to moderate time scales, to long-term changes that unfolded over days or weeks. Given these data, we show quantitative support for the hypothesis that there are cortico-cerebellar and cortico-striatal systems that are engaged during motor skill acquisition and that there is a general shift between the cortico-cerebellar to the cortio-striatal system with increased practice and motor learning. Evidence of this shift can be seen in the cerebellum. Cerebellar cortex showed decreases relative to baseline at all time scales, suggesting that activity in the cerebellar cortex is highest very early in practice. There was increased activity in the dentate nuclei at the short and medium time scales, but there was no evidence for reliable increases at the long time scale. Thus, the cerebellar cortex shows the highest levels of activity at the start of practice and then decreases as activity in the deep nuclei increase. The meta-data show, however, that these changes tend to occur within a session.

There was also evidence of a shift from an associative/premotor network to a sensorimotor network (cf. Coynel et al., 2010; Lehéricy et al., 2005). In particular, there was evidence for this shift in the striatum, where the meta-analysis showed that short and medium studies were characterized by activity in the rostral-dorsal striatum whereas long term studies were defined by activity in the caudal-ventral striatum. This is a strength of the meta-data approach, where averaging across different types of motor tasks reveals that the shift in activity from the rostral striatum to the caudal striatum is a robust pattern and that this shift occurs at time scales of 1 day or more.

Interestingly, there was also a nonlinear pattern of activity in left M1 over the three time scales. There were significant clusters of increasing activity at the short, medium, and long time scales. However, comparing short to medium, and medium to long time scales showed that the likelihood of left M1 activation was greater at the medium time scale than either the short or long time scales. This finding is consistent with experimental work showing that activation in M1 increases initially and then decreases following extended practice (Hluštik et al., 2004; Ma et al., 2010). However, other neuroimaging studies of motor sequence learning have shown increased M1 activity with long term practice (Karni et al., 1995; Floyer-Lea & Matthews 2004; Penhune & Doyon, 2005; Steele & Penhune, 2010). Thus, while increases in M1 are more consistent at the medium time scale than at the long time scale, the specific pattern of activity in M1 at the long time scale may be very specific to the task and the individual.

As with any meta-analysis, there is a concern about study selection. Our results are limited to those studies that were in English, published in peer-reviewed journals that involved the upper extremities and had neuroimaging data with published coordinates. Importantly, there were fewer long studies than short or medium studies. This may be partially a result of the expense associated with multi-day protocols in neuroimaging studies. However, delayed long-term retention and transfer tests

are critical to establishing learning effects in behavioural studies (Schmidt & Lee, 2005; Kantak & Winstein, 2012) and thus are also critical to understanding the neurophysiology of learning.

Handedness may also have influenced our data. As shown in Table 1, 36 studies reported practice with the dominant right hand, seven used the non-dominant left hand, and 11 studies used bimanual tasks that required coordination between both hands (handedness was not clear for Karni et al., 1995; Müller et al., 2002; Poldrack et al., 2005; Van Horn et al. 1998). As such, our data are sensitive but not specific to learning using the dominant right hand[2]. It is known that hand dominance and bimanual/unimanual learning conditions produce task-specific activation in the networks that support learning and performance (see Grafton et al., 2002; Debaere et al., 2004; Remy et al., 2008), whereas brain areas identified in this meta-analysis apply to motor learning more generally.

4.1 Associative/premotor to sensorimotor progressions

Our data demonstrate that when averaging across motor tasks, the AP network is more active at early compared to later intervals. Specifically, there were decreases in prefrontal and parietal cortex and the cerebellar cortex across all time scales, suggesting that these AP regions are most active at the beginning of practice. The SMA and the PMC showed increased activity at the short and medium time scales, but in long time scale studies, these areas showed decreased activity relative to baseline. This is consistent with a transitory role for the SMA/PMC (Hikosaka et al., 2002; Penhune & Steele, 2012), whereby these areas are involved in transitioning a movement from a spatial representation (supported by parietal and prefrontal cortex) to a motoric representation (supported by M1).

In the striatum, significant increases were shown in the rostral (associative) putamen, and globus pallidus at the short and medium time scales. At the long time scale, however, the caudal (sensorimotor) putamen and globus pallidus were significantly more likely to show increased activity (Table 5 and Figure 3). These patterns of subcortical activity suggest a functional gradient within the striatum, with activity shifting from associative regions to sensorimotor regions as practice progresses.

The time scale of change in the striatum was quite different from the cerebellum. Our analysis showed that the shift from cerebellar cortex to the deep nuclei (including the dentate) appears to take place within a session of practice, whereas the shift from associative to sensorimotor regions within the striatum took place over days.

These patterns of activation at the short time scale are supported by behavioural data that distinguishes a rapid motor-learning process from a slower, perceptual learning process (Dirnberger & Novak-Knollmueller, 2013). While both processes work in parallel, rapid improvements are dominated by motor processes that draw on cerebellar activation that support error corrections and externally guided movements. Slower improvements are likely based more on perceptual learning, relying on activation from the basal ganglia to self-initiate movements and predict stimulus-response associations (Dirnberger & Novak-Knollmueller, 2013). Fast learning processes, as discussed by Karni et al. (1998), are similarly thought to involve both cortical and subcortical structures related to the cerebellum. These changes in patterns of activity in the AP and SN networks also compliment behavioural data showing that early stages of motor learning are generally more cognitively demanding than later stages (Fitts & Posner, 1967; Newell, 1991). Studies comparing explicit and implicit learning have also found increased activity in prefrontal and parietal areas during explicit learning compared to implicit learning (Doyon et al., 1996; Grafton et al., 1995; Willingham et al., 2002). Similarly, when participants were instructed to attend to a previously learnt (automatized) sequence, there was an increase in activity of the prefrontal cortex and anterior cingulate gyrus (Jueptner et al., 1997). These results suggest the AP network is more active when cognitive demands of the task are increased.

4.2 Cortico-cerebellar and cortico-striatal systems

Our data support theories suggesting that there are parallel neural networks adapting at different rates which are responsible for motor control at different stages of performance and learning (Doyon et al., 2009; Penhune & Steele, 2012). These networks can be broadly classified as a cortico-

cerebellar system and a cortico-striatal system. Both systems are probably involved in motor control at all stages of learning, but the relative contributions of each system depend on the nature of the task and the time scale of practice.

The existence of the cortico-cerebellar system is supported by anatomical evidence of connections between the cerebellum and parietal, premotor, and frontal cortex (see Penhune & Steele, 2012; Ramnani, 2006 for review). The architecture of this system also fits well with computational theories of motor control that suggest internal models are located in the cerebellum (Ramnani, 2006; Shadmehr & Krakauer, 2008). In our analysis, activity decreased in the cerebellar cortex, but activity increased in the dentate nucleus at the short and medium time scales. The progression of activity from the cerebellar cortex to the deep nuclei, which then both return to baseline levels, suggests that encoding and refinement of internal models in the cerebellum likely occurs within a session (see also Penhune & Doyon, 2005). Rapid learning of the relationship between expected and actual sensory feedback may explain why adaptations in the cerebellum occur relatively quickly and are associated with decreases in activity in the cerebellar cortex (Floyer-Lea & Matthews, 2005; Lehéricy et al., 2005; Penhune & Doyon, 2002) and increases in the deep nuclei within a single practice session (Doyon et al., 2002; Lehéricy et al., 2005). In support of this role, TMS over the cerebellar cortex impaired the accuracy of reaching movements by interfering with estimation of the current position of the arm (Miall et al., 2007). Importantly, TMS disruption did not halt the movement (as would be predicted if the cerebellum was responsible for motor programming) but created dysfluency, disrupting the spatial accuracy of the movement (see also Bastian, 2006; Galea et al., 2010).

There is also a robust pattern across studies for a functional gradient in the striatum with activity shifting from the rostral-dorsal (associative) areas to the caudal-ventral (sensorimotor) areas with increased practice. The associative part of this system is hypothesized to be more important early in the learning process when prefrontal and parietal areas support a predominantly spatial

representation of a skill. The sensorimotor portion of this system is more active later in learning when cognitive demands of the task have decreased (Doyon et al., 2009; Hikosaka et al., 2002; Lehéricy et al., 2005). As a whole, the cortical-striatal system is hypothesized to be critical for encoding motor skills over long term practice, but the striatum does not seem to be the site of long-term storage of motor skills. Striatal lesions do not generally impair the recall of well learned sequences, instead lesions disrupt the learning of new sequences (Siegert et al., 2006) and slow the speed of movements (Desmurget & Turner, 2008).

4.3 Conclusion

Our data confirm and strengthen many theories of how patterns of brain activity shift over time to support motor learning. Given the difficulty and expense of neuroimaging it is challenging to assemble large imaging datasets across multiple time points in a single study, highlighting the utility of the meta-analytic approach. As more data become available there is also greater statistical power to answer meta-analytic questions about different types of tasks and moderators of learning effects. This is a direction for our future work, where we intend to expand the current database to include clinical trials for a range of neurological impairments. By subdividing our analysis across time scales, we were able to show reliable differences in the patterns of increasing and decreasing activation in motor learning that takes place over days compared to within a session (e.g., in M1, DLPFC, and the striatum), averaging across many different tasks. Short studies that do not have delayed retention tests may represent only transient effects associated with experimental variables. We recommend that future research adopt procedures that include testing brain activity following a retention interval in order for robust conclusions to be made about more permanent behavioural changes as well as the neural structures that support these changes.

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Footnotes

[1]The experiment by Debas et al (2010) had a 12 hour delay between training and retention testing. The authors were interested in the effects of sleep on motor memory consolidation. Thus, the "sleep" group practiced in the evening, slept, and 12 hours later were tested in the morning. The "no-sleep" group practiced in the morning, left the laboratory, and 12 hours later were tested in the evening. In order to avoid confounding effects of this manipulation, we only extracted learning-related foci that were common to both the sleep and no-sleep group (i.e., the extracted data represent the changes common to both groups and hence are independent of sleep effects).

[2]We conducted a supplementary analysis restricted to studies reporting dominant right hand testing. At the short time scale, there were six clusters of significantly decreased activity and three of these clusters were also significant in the main analysis. Similarly, there were seven clusters of increased activity and all seven of these clusters were also significant in the main analysis. At the medium time scale, 17/17 decreases and 6/6 increases were also found in the main analysis. At the long time scale, there were three clusters of decreased activity and two for these clusters were also significant in the main analysis. Similarly, there were four clusters of increased activity and all four were significant in the main analysis. Thus, the main analysis generally included areas of activation that are seen for the right hand, however, additional areas were found in the main analysis that were not found in the right hand analysis. It is difficult to interpret these results as there are many fewer studies per analysis when stratified by handedness and time scale, which greatly lowers the statistical power in these comparisons.