



## Brain activations underlying different patterns of performance improvement during early motor skill learning

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### ABSTRACT

**Background/Introduction:** Motor learning plays a central role in daily life and in neurorehabilitation. Several forms of motor learning have been described, among which motor skill learning, i.e. reaching a superior level of performance (a skill) through a shift of the speed/accuracy trade-off. During the first stage of learning a visuomotor skill, we observed differential patterns of evolution of the speed/accuracy trade-off in normal subjects. Half of the subjects rapidly achieved successful motor skill learning with an early shift of the speed/accuracy trade-off leading to a superior level of performance (shift pattern). The other subjects attained only minimal global improvement due to a converse evolution of speed and accuracy (i.e. a respect of the speed/accuracy trade-off: fit pattern). Functional magnetic resonance imaging (fMRI) was used to explore the neural substrates underlying these differential patterns during the first stage of motor skill learning in normal subjects.

**Methods:** Twenty right-handed normal subjects performed an implicit visuomotor learning task with their non-dominant hand. The task ("circuit game") consisted in learning to navigate a pointer along a circuit as quickly and accurately as possible using a fMRI-compatible mouse. Velocity, accuracy, and performance indexes were used to characterise the motor learning pattern (shift/fit) and to perform fMRI correlation analysis in order to find the neural substrate associated with the shift and fit patterns during early motor skill learning.

**Results:** Nine subjects showed a fit pattern (fitters), and eleven, a shift pattern ("shifters"). fMRI analyses at whole group level (ANOVA) and at sub-group level demonstrated that the supplementary motor area (SMA) was more activated in "shifters" than in the "fitters" groups and that the BOLD activation within the SMA correlated significantly with the on-line shift of the speed/accuracy trade-off in the "shifters" group.

**Conclusion:** Despite identical instructions and experimental conditions, during the first stage of motor skill learning normal subjects spontaneously adopted different patterns that can be differentiated based on distinct fMRI activation patterns. In this implicit visuomotor task, the SMA proper was the key area underlying the achievement of early successful motor skill learning, i.e. on-line shift of the speed/accuracy trade-off.

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### Background/introduction

Motor learning is a generic term encompassing several low and high level processes that co-exist and form a continuum (Krakauer and Mazzoni, 2011). These motor learning processes are active during the entire lifespan, from learning to walk to learning how to use a computer or playing tennis. The ultimate purpose of motor learning

may be to allow flexible behavioural adjustments while interacting with a changing environment. With regard to a change in motor performance, several forms of motor learning can be distinguished such as use-dependent plasticity, adaptation learning and motor skill learning (Krakauer and Mazzoni, 2011). Among these forms of motor learning, motor skill learning is particularly fascinating since it allows the apparently limitless diversification of the motor repertoire by the acquisition of new skills through training. Motor skill learning is defined as an improvement in sensorimotor performance gained through training that involves a shift in the speed/accuracy trade-off leading to a superior level of performance, i.e. the acquisition of new

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capabilities or “skills” (Dayan and Cohen, 2011; Krakauer and Mazzoni, 2011).

Functional brain imaging studies consistently showed changes in activation in a distributed network of areas involved in motor learning, overlapping with the motor execution and control networks. Several cortical areas such as the primary motor cortex (M1), the supplementary motor area (SMA), the premotor cortex (PM), the dorsolateral prefrontal cortex (DLPFC), and subcortical structures such as the cerebellum and basal ganglia are involved in motor skill learning (Debas et al., 2010; Ghilardi et al., 2000; Halsband and Lange, 2006). Other studies suggest a key role for the cerebellum in adaptation (Imamizu et al., 2000, 2003; Kawato et al., 2003). Recent observations using functional connectivity demonstrate a particular involvement of the SMA and prefrontal cortex in learning complex motor skills (Taubert et al., 2011).

During a pilot study involving 18 normal subjects who trained to improve their performance at playing with a “circuit game” involving a speed/accuracy trade-off, we noticed that despite identical instructions and experimental conditions normal subjects unconsciously developed different behavioural patterns over the first 15 min of motor skill learning. Three subjects presented a degradation of their performance (“no learning”). Eight subjects developed rapidly a superior ability involving an on-line shift in the speed/accuracy trade-off, i.e. canonical motor skill learning (shift pattern). In the seven other subjects, there was only minimal shift in the speed/accuracy trade-off since the improvement of one operant characteristic (e.g. speed) was counterbalanced by a concomitant deterioration of the other one (e.g. accuracy), leading to less successful or delayed motor skill learning (fit pattern).

The purpose of this study is to explore with functional magnetic resonance imaging (fMRI) whether different neural substrates underlie the development or the lack of an on-line speed/accuracy trade-off shift in normal subjects during the first minutes of learning an implicit visuomotor skill (“circuit game”).

## Material and methods

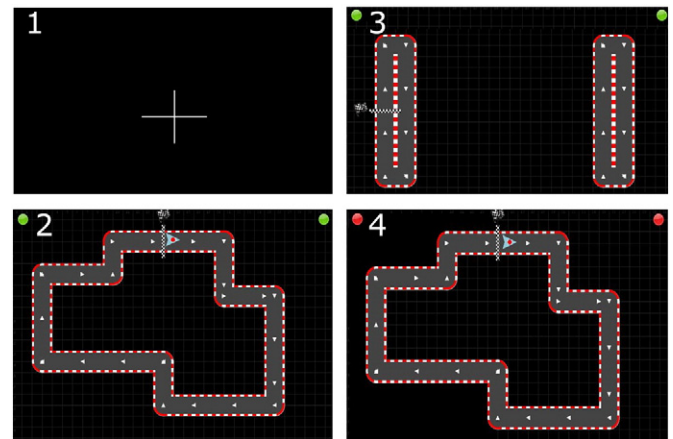
### Subjects

The experimental protocol was approved by the local Ethical Committee (Comité d'éthique médicale, CHU Mont-Godinne) and the study has been conducted according to the recommendations of the Helsinki declaration. The normal subjects provided written informed consent, after reviewing the inclusion criteria 1) being a healthy volunteer aged 18–80 years, 2) being right-handed, and exclusion criteria 1) having a pacemaker or other piece of metal in the body, 2) being pregnant, 3) having suffered from stroke or any brain damage, 4) being unable to perform the task or to understand the instruction. Eighteen subjects participated in a behavioural pilot study and 25 other subjects in the fMRI study. In the fMRI study, five subjects were excluded from further analysis for the following reasons: technical failure for one subject, another subject failed to improve any behavioural parameters, two presented deterioration of performance, and in the last subject T1 3D MRI shown the presence of numerous asymptomatic white matter lesions compatible with long-standing leukoaraiosis.

### Paradigms

#### Behavioural pilot study

For 30 min, 18 subjects trained on a motor learning task (“circuit game”) with their non-dominant left hand, alternating blocks of learning (30 s) and rest (30 s). The “circuit game” consisted of moving the pointer with a computer mouse along a circuit under visual control (Fig. 1 part 3). Subjects were instructed to perform the task as quickly and accurately as possible; accurately meaning keeping the pointer



**Fig. 1.** fMRI conditions. 1: REST: fixation cross, 2: LEARNING: the subjects had to navigate the cursor as quickly and accurately as possible, 3: EASY: the subjects had to move the cursor between the two targets at comfortable speed (50% trials with vertical movements, 50% with horizontal movements), 4: REPLAY: the subjects had to follow the cursor displacement with their eyes while watching a videoclip of their last LEARNING block, keeping the hands relaxed.

within the track of the circuit. They were informed that the goal of the session was to improve incrementally upon performance. This study was performed to explore the temporal dynamic of the first stage of learning this motor skill in normal subjects.

#### fMRI study

The subjects performed three consecutive learning runs of 8 min with a MR-compatible mouse. Each run encompassed 3 conditions and rest (fixation cross): LEARNING (circuit learning), EASY (easy motor task) and REPLAY (Fig. 1). LEARNING required to perform the “circuit game” as described previously (Behavioural pilot study section) with exactly the same instructions. EASY required moving the cursor back and forth between two bases, either in horizontal or vertical direction, with the following instructions “Move the cursor between the two targets at a comfortable speed, small overshoots and undershoots are allowed”. EASY was designed to isolate the activation related to lower aspects of movement execution under visual control. During REPLAY, a videoclip of the last LEARNING was played; the instruction being “Follow carefully with your eyes the cursor displacements, while keeping your hand as relaxed as possible on the MR-compatible mouse”. The REPLAY was designed to isolate the activation related to visual and oculomotor activity. Each condition was presented four times during each run, 84 volumes (252 s) of each of the three conditions and rest were analysed. Before these learning runs, the subjects performed a habituation run (40 activation volumes/ 40 rest volumes), which consisted of navigating the cursor on a simple square, in order to familiarise the subject with the MR environment, the concept of the task, and the manipulation of the MR-compatible mouse (this was discarded from further analysis). Visual feedback was projected on a screen; a mirror was placed on the head coil.

#### Behavioural analysis

For quantifying performance improvements and motor skill learning, the error, velocity and normalised jerk were analysed. Error was defined as the surface area generated by the difference between the real trajectory and the ideal trajectory in the midline of the track. Velocity was the first derivative of the position. Normalised jerk (NJ) was computed with the formula

$$NJ = \sqrt{1/2 * \int_{T_{start}}^{T_{end}} \text{jerk}^2(t) dt * \text{duration}^5 / \text{length}^2}$$
 (Caimmi et al., 2008; Contreras-Vidal and Buch, 2003) where the jerk is the

third derivative of the position. The NJ reflects the smoothness of the movements, with the underlying assumption that smoother movements (smaller NJ) are associated with a higher level of skill. Velocity, error and NJ, were averaged in mean error, velocity and NJ using 3 s window (corresponding to the TR) for each block of LEARNING.

Using the mean velocity and error, four indexes were computed to model subjects' behaviour (Table 1). From the behavioural pilot study, the error and velocity of the 18 subjects measured during the 15 min of actual training were averaged to extract constant error and constant velocity values. For the fMRI study, the error index (Pe) was computed as  $Pe = \text{constant error} / \text{subject mean error}$ . Pe is a normalised index designed to increase when error diminishes. The velocity index ( $Pv = \text{subject mean velocity} / \text{constant velocity}$ ) is a normalised index designed to increase when velocity increases. The Performance Index ( $PI = Pv * Pe$ ) was calculated every 3 s and averaged for each learning block. Finally, the Learning Index ( $LI = [(PI - PI \text{ initial}) / PI \text{ initial}] * 100$ ) was calculated for each learning blocks as a percentage of the PI relative to the baseline performance during the first block (PI initial). The LI was only used in order to describe the evolution of the PI over time (% of evolution across the learning blocks), i.e. to quantify the on-line performance dynamic during early motor skill learning.

Based on these indexes, three different behavioural patterns of motor skill learning were defined (Table 2). First, an on-line shift in the speed/accuracy trade-off (shift pattern), involving a substantial global performance improvement (LI) with improvement in both speed and accuracy (Pv, Pe) or in one of these two parameters without deterioration of the other one, suggesting a rapid and successful improvement in the motor skill during the first minutes of training. The subjects showing this pattern were refereed as “shifters”. Second, a fit pattern involving a minimal improvement of the LI without a significant shift of the speed/accuracy trade-off; i.e. the improvement of one of the two parameters is systematically associated with a concomitant deterioration of the other one. The subjects showing this pattern were refereed as “fitters”; they did not succeed in achieving consistent on-line performance improvement during early motor skill learning. Third, a degradation of the LI with deterioration of both speed and accuracy (Pv, Pe), or lack of any change (no change in PI, speed or accuracy). The subjects showing this pattern were excluded from analyses.

#### fMRI analysis

##### Imaging acquisition parameters

Functional MR images of brain activity were collected using a 3 T scanner (Siemens Verio, Erlangen, Germany with a 32-channels head coil) with repeated single-shot echo-planar imaging: echo time (TE) = 23 ms, flip angle (FA) = 90°, matrix size = 64 × 64, field of view (FOV) = 224 × 224 mm<sup>2</sup>, slice order descending and interleaved, slice thickness = 2 mm (no gap), number of slices = 59 (whole brain). Repetition time (TR) was 3000 ms; the whole brain was scanned 160 times per run. A three-dimensional (3D) T1-weighted data set

**Table 1**  
Behavioural indexes used in LEARNING.

Index	Formula	
Pe	Constant error* / subject error	Error index
Pv	Subject velocity* / constant velocity	Velocity index
PI	$Pe * Pv$	Performance index
LI	$(PI - PI \text{ initial}) / PI \text{ initial} * 100$	Learning index [percentage of evolution of PI across the learning session regarding to the first block of learning (30 s)]

\* Mean error and mean velocity calculated for the 18 subjects of the behavioural study.

**Table 2**  
Behavioural patterns of motor skill learning.

Motor skill learning						No learning	
Shift pattern			Fit pattern				
Pe	↗	↗	→	↗↗	↘	↘	→
Pv	↗	→	↗	↘	↗↗	↘	→
PI	↗↗	↗↗	↗↗	→	→	↘	→
LI	↗	↗	↗	↗	↗	↘	→

Pe: performance error, Pv: performance velocity, PI Performance index, LI learning index.

encompassing the whole brain was acquired to provide detailed anatomy (1 mm<sup>3</sup>) thanks to a ADNI sequence (TR = 2250 ms, TE = 2.6 ms, FA = 9°, matrix size = 256 × 256, FOV = 256 × 256 mm<sup>2</sup>, 192 slices, slice thickness = 1 mm, no gap).

#### Data analysis

fMRI data were analysed using BrainVoyager QX (Version 2.3, Brain Innovation, Maastricht, The Netherlands).

**Pre-processing.** Pre-processing consisted of a linear trend removal for excluding scanner-related signal, a temporal high-pass filtering applied to remove temporal frequencies lower than three cycles per run, and a correction for small head movements using a rigid body algorithm rotating and translating each functional volume in 3D space. The data were corrected for the difference between the scan times of the different slices and were not smoothed in the spatial domain. In order to compare the localizations of activated brain region across participants, all anatomical and functional volumes were spatially normalised (Talairach and Tournoux, 1988) and the computed statistical maps were overlaid on the 3D T1-weighted scans. All the coregistrations were performed automatically and then manually corrected. The functional data were analysed using one multiple regression model (General Linear Model; GLM) consisting of predictors, which corresponded to the particular experimental conditions, and in which the beta weights quantify the potential contribution of the predictors in explaining each voxel time course. The predictor time courses were computed on the basis of a linear model of the relation between neural activity and hemodynamic response, assuming a rectangular neural response convolved with hemodynamic function (Boynton et al., 1996).

**Contrasts of interest and statistical analyses (Supplementary Table 3).** First, a random effect group analysis was performed with the 20 subjects. In order to find the areas activated in each condition (LEARNING, EASY, and REPLAY), three basic contrasts of interests (compared to rest) were explored: [LEARNING] (contrast weight: [1 0 0]) (areas involved in motor skill learning), [EASY] [0 1 0] (areas involved in lower aspects of movement control and execution), [REPLAY] [0 0 1] (areas involved in visual and oculomotor activity). In addition, the [(LEARNING + EASY) – REPLAY] [1 1 – 2] contrast was computed in order to focus on the areas involved in motor learning and control aspects. Follow up contrasts were averaged over the whole cluster BOLD signal. All the contrasts were balanced.

Second, in all the areas found with [LEARNING], correlation analyses were performed between the beta weights of LEARNING and the performance (PI) values, in order to find out the key area(s) explaining performance evolution. For this global correlation, the PI values of the 20 subjects were averaged for each learning block (12 blocks). Then, the correlation was performed between the 12 beta weights LEARNING and the 12 PI values.

Third, to identify the neural substrates underlying the shift pattern versus the fit pattern of motor skill learning, an ANOVA (second level analysis) was computed with one within-subjects factor (conditions) and one between-subjects factor (groups).

## Results

### Behavioural results

The 20 participants were 11 female and 9 male subjects aged from 18 to 62 years (mean  $\pm$  SD:  $33.9 \pm 11$ ); all were right handed. Eleven of them displayed a shift pattern ( $36.7 \pm 11.8$  years), and 9, a fit pattern ( $30.7 \pm 9.6$  years) (Fig. 2). At the end of the learning session, the performance of the “shifters” had improved significantly more (LI:  $52.8\% \pm 87.7$ ) than that of the “fitters” (LI:  $6.2\% \pm 9.9$ ) ( $p = 0.002$ ). Furthermore, the NJ, which reflects the smoothness of the movements, diminished across the learning blocks in the “shifters” (slope  $-2799$ ) whereas it increased in the “fitters” (slope  $+3202$ ); this differential evolution was statistically significant ( $p = 0.048$ ).

### fMRI results

#### Whole group analysis

At  $q(\text{FDR}) < 0.05$  ( $t_{19} = 3.71$ ;  $p_{\text{UNCORRECTED}} < 0.0014$ ), the random effect analysis revealed 13 clusters for LEARNING, 14 clusters for EASY and 10 clusters for REPLAY (Fig. 3, Supplementary Table 1). The clusters observed in LEARNING were the right primary motor cortex (M1, Brodmann Area BA 4), bilateral premotor cortex (PMC, BA 6), supplementary motor area (SMA, BA 6), bilateral thalamus, left putamen, left anterior cerebellum, and bilateral oculomotor and visual cortical areas. The clusters found in EASY were the right M1 (BA 4), bilateral PMC (BA 6), SMA (BA 6), bilateral thalamus, bilateral putamen, left anterior cerebellum, and bilateral oculomotor and visual cortical areas. As expected, the activation in the oculomotor and visual areas found in LEARNING and EASY was also activated in REPLAY, in addition to the bilateral thalamus and PMC (BA 6), right limbic lobe (BA 24), and right prefrontal cortex (BA 9).

Correlation analyses performed between the performance index (PI) and beta weights of each area activated in LEARNING showed a statistically significant effect exclusively in the SMA ( $r = 0.60$ ,  $p < 0.0052$ ). The correlations in the other areas were not statistically significant; there was no significant correlation with the NJ (Supplementary Table 2). In

order to focus on the areas involved in motor control and learning aspects, the  $[(\text{LEARNING} + \text{EASY}) - \text{REPLAY}]$  contrast was computed at  $q(\text{FDR}) < 0.05$  ( $t_{19} = 5.93$ ,  $p_{\text{UNCORRECTED}} < 0.00001$ ). This contrast revealed significant activation in four areas: the right M1, right thalamus, left anterior cerebellum, and SMA (Table 3). A comparison between the “shifters” and “fitters” groups was performed in these four regions of interest for the following contrasts:  $[\text{EASY} - \text{REPLAY}]$   $[0 \ 1 \ -1]$ ,  $[\text{LEARNING} - \text{REPLAY}]$   $[1 \ 0 \ -1]$ , and  $[\text{LEARNING} - (\text{REPLAY} + \text{EASY})]$   $[2 \ -1 \ -1]$  (Fig. 4). Again, the SMA was the only region where a significant difference between “shifters” and “fitters” was found. Moreover, this difference was observed only for the  $[\text{LEARNING} - \text{REPLAY}]$ ,  $[\text{LEARNING} - (\text{REPLAY} + \text{EASY})]$  and  $[\text{LEARNING} - \text{EASY}]$   $[1 \ -1 \ 0]$  contrasts ( $t_{18} = 2.47$ ,  $p < 0.02$ ;  $t_{18} = 2.49$ ,  $p < 0.02$ ;  $t_{18} = 2.13$ ,  $p < 0.04$  respectively) and not for  $[\text{EASY} - \text{REPLAY}]$  contrast ( $t_{18} = 1.40$ ,  $p = 0.18$ ). There was no significant difference in the right M1 (BA 4) (respectively for each contrast:  $t_{18} = 1.09$ ,  $p = 0.29$ ;  $t_{18} = 1.14$ ,  $p = 0.26$ ;  $t_{18} = 1.09$ ,  $p = 0.29$ ;  $t_{18} = 0.49$ ,  $p = 0.63$ ), right thalamus ( $t_{18} = 0.46$ ,  $p = 0.65$ ;  $t_{18} = 0.99$ ,  $p = 0.33$ ;  $t_{18} = 1.59$ ,  $p = 0.13$ ;  $t_{18} = 1.21$ ,  $p = 0.24$ ), and left anterior cerebellum ( $t_{18} = 1.38$ ,  $p = 0.18$ ;  $t_{18} = 1.38$ ,  $p = 0.18$ ;  $t_{18} = 1.04$ ,  $p = 0.31$ ,  $t_{18} = 0.71$ ,  $p = 0.48$ ).

#### Whole-brain ANOVA

In order to compare the “shifters” and “fitters” groups for each condition, a second level ANOVA with one within-subject factor (conditions) and one between-subjects factor (groups) was computed. The  $F_{(4,72)}$  test on the within-subject factor (conditions) showed a significant activation at  $q(\text{FDR}) = 0.05$ ,  $p_{\text{UNCORRECTED}} < 0.0001$ . The  $F_{(1,18)}$  test on the between-subject factor (groups) showed no significant activation at  $q(\text{FDR}) = 0.05$ ,  $p_{\text{UNCORRECTED}} = 0.0002$ . The  $F_{(4,72)}$  test on the interaction between the two factors showed a significant activation in several areas ( $q(\text{FDR}) = 0.05$ ,  $p_{\text{UNCORRECTED}} < 0.0002$ ). To localise precisely the differences for this interaction, post-hoc analyses with specific contrasts were computed. With the  $[\text{EASY}]$  and  $[\text{REPLAY}]$ , there were no significant difference between the “shifters” and “fitters” groups. With  $[\text{LEARNING}]$ , several areas were more activated in the “shifters” than in the “fitters” group ( $q(\text{FDR}) = 0.05$ ;  $t_{76} = 3.43$ ;  $p_{\text{UNCORRECTED}} < 0.0013$ ): the right hippocampus (BA 48), SMA, left temporal cortex (BA 38), left M1, left posterior cingulate gyrus (BA 31), left putamen, left inferior parietal lobule (BA 40), left premotor cortex (BA 6), left anterior prefrontal cortex (BA 10), left parietal cortex (BA 5), right thalamus (Table 4). By contrast, no area was more activated in the “fitters” than in “shifters” group. When comparing the “shifters” and “fitters” groups, the same regions were

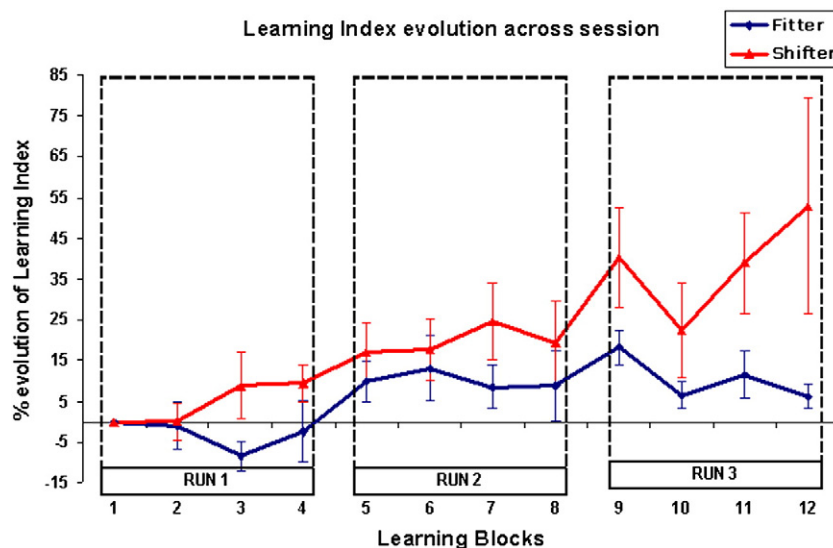
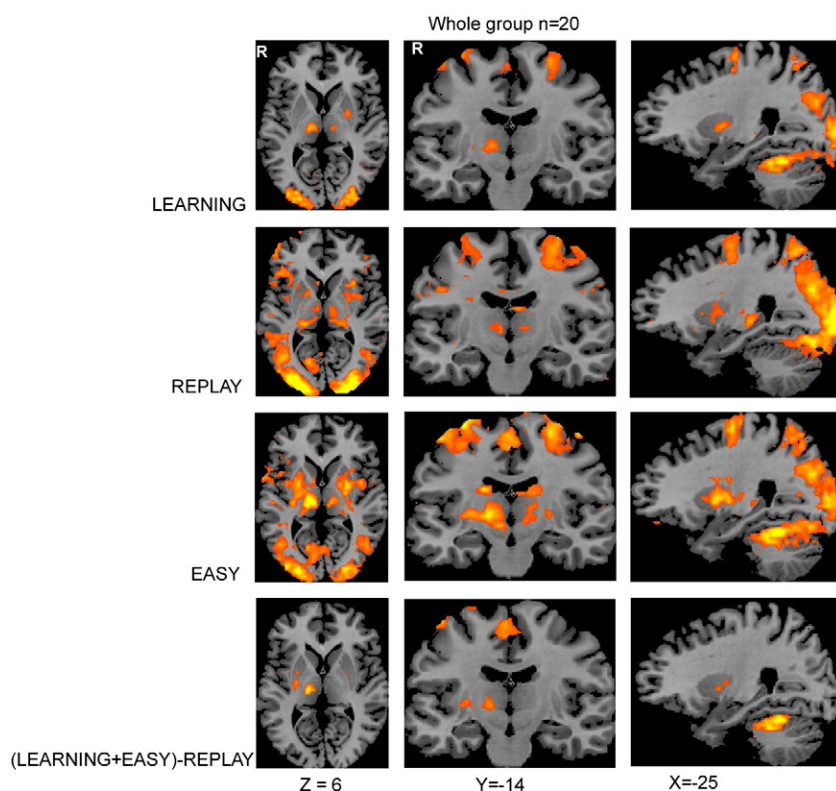


Fig. 2. Learning Index (LI) evolution across learning blocks: The 12 LI values correspond to the LI during each learning block; red line: “shifters” group, blue line: “fitters” group. Mean  $\pm$  SEM.





**Fig. 3.** Whole group activation: BOLD activation for the 20 subjects contrasting the three basic contrasts ([LEARNING], [REPLAY], [EASY]), and the [LEARNING + EASY] – REPLAY contrast, ( $q(\text{FDR}) = 0.05$  at a  $t_{19} = 3.71$ ,  $p < 0.0015$ ).

found using either [LEARNING – REPLAY] or [LEARNING], and using either [EASY – REPLAY] or [EASY]. This is consistent with the observation that there was no significant difference between the two groups for [REPLAY].

#### Sub-group analyses

In order to detail the activation patterns in the “shifters” and “fitters” groups, separate subgroup analyses were computed with the following contrasts focusing on activation related to motor skill learning: [LEARNING – REPLAY] and [LEARNING + (REPLAY + EASY)] (Table 5).

In the “shifters” group, the random effect analysis ( $df = 10$ ) showed four areas significantly activated with [LEARNING – REPLAY] ( $t_{10} = 6.7$ ,  $q\text{FDR} (0.05)$ ,  $p_{\text{UNCORRECTED}} < 0.0001$ ): the right M1, SMA, and two areas in the left anterior cerebellar hemisphere (lobule V–VI and VII). The correlation between the PI and the beta weights of these four regions of interest (ROIs) was statistically significant exclusively in the SMA ( $r = 0.63$ ,  $p < 0.0377$ ) (Supplementary Table 2). Individual correlations between the PI and the beta weights were computed, using four ROIs of 50 mm<sup>3</sup> (Fox et al., 2009) defined individually for each subject. Individual beta weights were extracted from these ROIs and were correlated with the 12 PI values of each subject. The strongest

correlation was observed in the SMA ( $r = 0.33$ ,  $p < 0.0001$ ); a significant but weaker correlation was found in the left anterior cerebellar hemisphere (lobule V–VI) ( $r = 0.22$ ,  $p < 0.0113$ ). There was no significant correlation in the right M1 ( $r = 0.1$ ;  $p = 0.36$ ) and lobule VII of the left cerebellar hemisphere ( $r = 0.1$ ,  $p = 0.36$ ). With [LEARNING – (REPLAY + EASY)], the “shifters” conserved significant activation in two areas ( $t_{10} = 6.7$ ,  $q\text{FDR} (0.05)$   $p_{\text{UNCORRECTED}} < 0.0001$ ): the SMA and left cerebellar hemisphere (lobule V–VI).

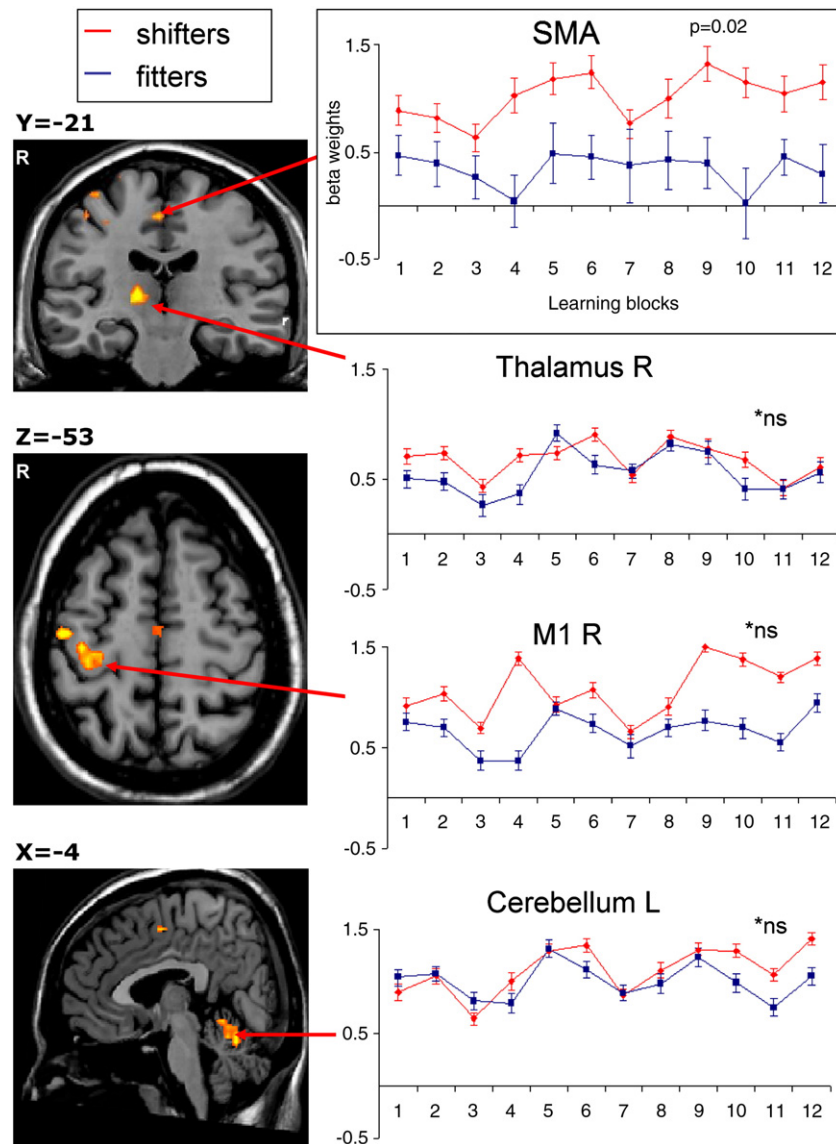
In the “fitters” group, the random effect analysis ( $df = 8$ ) showed only one area significantly activated with [LEARNING – REPLAY] ( $t_8 = 6.7$ ,  $q\text{FDR} (0.05)$   $p_{\text{UNCORRECTED}} < 0.0002$ ): the left anterior cerebellar hemisphere (lobule V–VI), where the correlation analysis suggested a non-significant trend ( $r = 0.53$ ,  $p = 0.13$ ) between the evolution of the PI and the beta weights. Individual correlations were also not significant ( $r = 0.11$ ,  $p = 0.26$ ). With [LEARNING – (REPLAY + EASY)], the activation in the left cerebellar hemisphere (lobule V–VI) was found exclusively at a  $t_8 = 4.00$  ( $p_{\text{UNCORRECTED}} < 0.004$ ).

In order to demonstrate that the performance improvement observed in healthy volunteers training to the “circuit game” with their left non-dominant hand relies on motor skill learning and implies the retention of the motor skill, an additional experiment was performed. Eighteen subjects trained during 12 min on the “circuit game” with their non-dominant left hand in front of a computer screen, alternating 12 blocks of learning (30 s) and rest (30 s), matching perfectly the fMRI paradigm. A retention test was performed the next day (5 learning blocks of 30 s alternating with rest blocks of 30 s). Thirteen subjects qualified as “shifters” (LI: +54% by the end of the learning session), and 5 as “fitters” (LI: +24%). Compared to baseline, the performance improvement at the retention test on the next day was 44% for “shifters” ( $p < 0.0005$ ) and 24% for “fitters” ( $p = 0.0062$ ) (Supplementary Fig. 1). Moreover, the slope of the LI evolution across the five retention blocks performed on the next day was steepest for the “shifters” (7.9) than for the “fitters” (2.6) ( $p = 0.0311$ ).

**Table 3**  
Whole group comparison.

Brain area/structure	Brodman Area (BA)	Mean x	Mean y	Mean z	mm <sup>3</sup>
R M1	BA 4	31	−27	55	1437
R thalamus		13	−19	6	203
L cerebellar hemisphere (lobule V–VI)		−16	−49	−18	2972
SMA proper	BA 6	1	−90	48	117

Contrast [(LEARNING + EASY) – REPLAY]; [ $q(\text{FDR}) < 0.05$ ;  $t_{19} = 5.93$ ;  $p_{\text{UNCORRECTED}} < 0.00001$ ; threshold = 100 voxels]. M1: primary motor area, SMA: supplementary motor area, R: Right, L: Left.



**Fig. 4.** Temporal evolution of the beta weights (whole group analysis). [LEARNING – REPLAY] contrast showed four ROIs (Region of Interest): SMA (BA 6), R thalamus, left M1 (BA 4) and left anterior cerebellar hemisphere (lobule V–VI); ( $q(\text{FDR}) = 0.05$ ;  $t_{19} = 4.49$ ;  $p < 0.0002$ ; threshold = 100 voxels). Each chart plots the evolution of the beta weights (Mean ± SEM) across the learning blocks for the “shifters” (red) and “fitters” (blue) groups. The difference in beta weights evolution was significantly different between the “shifters” and “fitters” groups only in the SMA ( $p = 0.02$ ).

**Table 4**  
Whole brain ANOVA.

Brain area/structure	Brodman Area (BA)	Mean x	Mean y	Mean z	mm <sup>3</sup>
L inferior parietal lobule	BA 40	−45	−34	−43	329
L anterior prefrontal cortex	BA 10	5	−62	5	517
L putamen		−30	−1	9	432
L dPMC	BA 6	−42	−9	23	146
R thalamus		23	−13	12	669
R hippocampus	BA 48	33	−34	2	318
L parietal cortex	BA 5	−18	−62	45	601
L temporal cortex	BA 38	−30	3	−28	406
L M1	BA 4	−34	−23	53	144
SMA proper	BA 6	−2	−17	52	124
L posterior cingulate gyrus	BA 31	−25	−27	41	115

[LEARNING] “shifters” > “fitters”; ( $q(\text{FDR}) < 0.05$ ;  $t_{76} = 3.62$ ;  $p_{\text{UNCORRECTED}} < 0.0005$ ; threshold = 100 voxels). M1: primary motor area, SMA: supplementary motor area, PMC: lateral dorsal premotor cortex, R: Right, L: Left.

## Discussion

Despite the fact that normal subjects received identical instructions and were studied under identical experimental conditions, they spontaneously exhibited different behavioural patterns of on-line performance improvement during the early stage of motor skill learning (shift/fit/lack of learning). Comparison of fMRI data between the group of “shifters” and “fitters” revealed that differential brain activation underlies these behavioural patterns. The SMA proper was the key area underlying the achievement of on-line shift of the speed/accuracy trade-off during early motor skill learning.

Which neural processes do reflect the fMRI changes acquired while the volunteers trained to perform the “circuit game”? On the one hand, these fMRI changes may simply reflect short-term changes related to on-line motor skill performance improvement. Short-term performances changes and/or transient improvements may be observed during a single training session involving a use-dependent

**Table 5**  
Subgroup analysis.

	Brain area/structure	Brodmann Area (BA)	Mean x	Mean y	Mean z	mm <sup>3</sup>
<b>A) [LEARNING – REPLAY]</b>						
<i>Shifters</i>	R M1	BA 4	34	–29	64	47
	SMA	BA 6	1	–19	49	126
	L cerebellar hemisphere (Lobule V–Vi)		–21	–47	–21	94
	L cerebellar hemisphere (Lobule VII)		–9	–55	–15	57
<i>Fitters</i>	L cerebellar hemisphere (Lobule V–Vi)		–20	–45	–20	161
<b>B) [LEARNING – (REPLAY + EASY)]</b>						
<i>Shifters</i>	SMA	BA 6	1	–19	49	70
	L cerebellar hemisphere (Lobule V–Vi)		–21	–45	–21	73
<i>Fitters</i> *	L cerebellar hemisphere (Lobule V–Vi)		–20	–45	–20	92

qFDR 0.05 ( $t_{10 \text{ AND } 8} = 6.7$ ; threshold: 40 voxels) M1: primary motor area, SMA: supplementary motor area, R: Right, L: Left

\* $t_8 = 4.0$ ;  $p_{\text{uncorrected}} < 0.004$ .

plasticity task such as performing a simple ballistic movement in a specific direction (Classen et al., 1998). This basic form of motor memory mainly involves M1 (Muellbacher et al., 2002) and may serve as a primer for more elaborated forms of motor learning, which mobilise a broader network of cortical areas and subcortical structures (Baraduc et al., 2004; Floyer-Lea and Matthews, 2005; Ghilardi et al., 2000). Such an interpretation would by definition imply that the performance improvements gained during training should not be retained in memory as a motor skill, i.e. that no performance gain should remain after a short washout period. The observed fMRI changes would thus simply reflect an on-line modulation of the network underlying transient performance improvement.

On the other hand, the fMRI changes acquired during the training to perform the “circuit game” may reflect the early stage of motor skill learning. Previous experiments have demonstrated early neurophysiological modifications underlying the first stages of motor skill learning evaluated over a single session of training (Albert et al., 2009; Floyer-Lea and Matthews, 2005; Orban et al., 2011; Tomassini et al., 2011; Toni et al., 1998; van Mier et al., 1998). Indeed, motor skill learning involves at least two stages developing on different timescales: a fast on-line learning process leading to large performance improvement over a single training session (as those observed in the current study), and a slower process involving smaller performance gains obtained through repeated training sessions (Dayan and Cohen, 2011). Training to perform the “circuit game” as quickly and accurately as possible not only induces on-line performance improvements, especially in “shifters”, but also results in motor skill learning as demonstrated by the retention of the motor skill on the next day in the additional experiment, both for the “shifters” and the “fitters”. Thus, the on-line performance improvements and the related fMRI changes observed during the training blocks reflect the early stage of motor skill learning as demonstrated by the retention of the motor skill on the next day in the additional experiment.

From a behavioural point of view, the shift pattern is superior to the fit pattern since shifting early the equilibrium point of the speed/accuracy trade-off allows reaching on-line a superior level of skill. By the end of the learning session, the fit pattern resulted in a smaller improvement of global performance since it did not modify rapidly the equilibrium point of the speed/accuracy trade-off (Fig. 2). This was confirmed by the differential evolution of the NJ, which reflects the smoothness of movement, with an improvement in the “shifters” and deterioration in the “fitters”. Interestingly,

when comparing how much of the skill has been retained on the next day in the additional experiment, the difference was less important between the “shifters” and the “fitters” than at the end of the learning session. This could reflect either the maintenance of the skill or the development of slight off-line learning in the “fitters” group, or some overnight degradation in the “shifters” group. Nevertheless, both the “shifters” and the “fitters” achieved motor skill learning since the test on the next day (from the first block onwards) unambiguously demonstrated retention of the performance improvement gained on the previous day during training. Even if some overnight degradation occurred in the “shifters”, they retained most of the motor skill they learned the day before. It is also noteworthy that, even during the very short retention session (five blocks of the “circuit game”), the “shifters” maintained again a faster rate of motor skill learning, confirming that their “learning strategy” was different from that of the “fitters”.

Neither the “shifters” nor the “fitters” were aware of having adopted a particular behavioural strategy, as much as we could determine during informal debriefing. Rather, it seems that the “shifters” were more efficient from the early phase of motor learning. The stronger fMRI activation in several areas of the “shifters” compared to the “fitters” group was present since the first blocks of training. The reason for these differential patterns in normal subjects during the early phase of motor learning is unclear but one could reasonably speculate that, after a longer training period or over several sessions, the “fitters” would also have achieved a shift pattern.

At the whole-group level ( $n = 20$ ), the activation patterns corresponded to those expected for each condition: predominantly visual and oculomotor activity for REPLAY (Ohlendorf et al., 2010), predominantly motor execution and control areas for EASY (Nair et al., 2003), and motor skill learning network for LEARNING (Doyon et al., 2003; Grafton et al., 1992; Jenkins et al., 1994). The ANOVA demonstrated a lack of significant difference between the shift and fit patterns for EASY (lower-level motor execution and control components) and REPLAY (oculomotor and visual components), strengthening the suggestion that the BOLD activation differences in LEARNING specifically reflect motor skill learning components in addition to “simple” motor control, oculomotor and visual processing components. In LEARNING, several areas were more activated in the “shifters” than in the “fitters” groups (see Table 3). Among these areas, the SMA (BA 6), M1 (BA 4), cingulate gyrus (BA 31), putamen, inferior parietal lobule (BA 40), premotor cortex (BA 6), anterior prefrontal cortex (BA 10), parietal cortex (BA 5), and right thalamus are known to be involved in motor skill learning (Grafton et al., 1992; Jenkins et al., 1994; Doyon et al., 2003). Interestingly, a differential activation was also observed in the right hippocampus. Traditionally, the hippocampus has been associated with episodic memory formation but not with motor learning, as initially suggested by a lack of deleterious effect of hippocampus lesion on motor skill learning (Corkin, 2002; Spiers et al., 2001). However, a recent fMRI study demonstrated that the hippocampus may indeed play a role in the earlier and later stages of implicit motor sequence learning (Gheysen et al., 2010). Our observations are consistent with such a conclusion, at least when successful learning of a visuomotor skill is involved. Similarly, the temporal cortex (BA 38) has been more classically associated with semantic memory (Clark et al., 2010) but activation has also been observed in the temporal cortex during first stage of bimanual motor skill learning (Ronsse et al., 2011), as well as during motor skill learning with the non-dominant hand (Grafton et al., 2002), suggesting an involvement of the temporal cortex during the first minutes of skill learning; which is consistent with the current observation.

There was no difference between the two groups in the M1 contralateral to the trained hand which is considered as a key area in motor skill learning (Boggio et al., 2006; Karni et al., 1995; Kim et al., 2004; Muellbacher et al., 2002; Tecchio et al., 2010). Recent studies suggested that M1 may be specifically involved in the storage



of the “low-level” executive motor learning components of a task rather than in the higher-order aspects of motor learning (Baraduc et al., 2004; Kantak et al., 2010; Robertson, 2009). Therefore, this lack of differential activation in the contralateral M1 suggests that the motor execution, motor control, and lower aspects of motor learning did not significantly differ between the “shifters” and “fitters” groups. A stronger activation in the “shifters” than in the “fitters” groups in the ipsilateral (left) M1 may suggest that the ipsilateral M1 is also involved in complex motor skill learning. Alternatively, this may also relate to the proposal that in right-handed subjects the left dominant hemisphere may be more involved in higher-order aspects of motor control than the right hemisphere, and could play a key role in motor learning whatever the hand involved (Goldenberg, 2003; Schambra et al., 2011). Thus, whereas lower aspects of motor control and motor learning were similar in terms of recruited neuronal resources between the “shifters” and “fitters”, as suggested by a lack of differential activation in the contralateral M1, the shift pattern of motor skill learning was associated with extra fMRI activation in the ipsilateral M1.

In a similar way, there was no statistically significant difference in the areas related to attentional and motivational processes such as the DLPFC or anterior cingulate cortex (Clark et al., 2010; Smith and Jonides, 1999) between the “shifters” and “fitters” groups. This may suggest that, at least for this task and under these particular experimental conditions, there was no difference in motivational and attentional processes detectable by the current fMRI design that could explain why about half of the normal subjects adopted a shift pattern, and half, a fit pattern. It is noteworthy that three subjects were excluded from further analysis since their global performance indexes remained stable (one subject) or even deteriorated (two subjects). It is unlikely that these three normal subjects were unable to learn since they did not suffer from neurological nor psychiatric disorder. Their demographical characteristics did not differ from those of the “shifters” and “fitters”; and visual comparison of their individual fMRI activation pattern did not differ from those of the “shifters” and “fitters”. We can therefore not speculate further about the reasons or neural substrates underlying these behavioural patterns. It is however likely that they lacked motivation and/or attention, or experienced fatigue during the experiment. This may fit with recent observations about the importance of context, motivation, and reward for motor learning (Abe et al., 2011).

No cortical area or subcortical brain structure was significantly more activated in the “fitters” than in the “shifters” group. This suggests that the fit pattern was characterised by a globally less intense activation, and that no area outside the network described in the “shifters” group was specifically involved in the “fitters” group. It should also be mentioned that the perception of “error” (i.e. not keeping the pointer perfectly in the middle of the track) is difficult for the subjects unless they make a broad error such as clear overshoot outside of the track. Moreover, such an error would likely lead to a transient error signal in the brain, since our “circuit game” requires performing continuous movements. In that sense, it is therefore not surprising that “errors” in the “circuit game” do not lead to dedicated brain activations such as in tasks requiring (sequential) key presses or pointing to a small target with a single movement. Thus, either the “fitters” failed to activate efficiently the key areas involved in the first stage of successful motor skill learning (see below) or this lack of an early activation resulted in a less efficient motor skill learning.

Two areas were of particular importance for achieving early successful motor skill learning of this task: the left cerebellar hemisphere and the SMA. In the “shifters” group, the BOLD signal was significantly correlated with the evolution of the PI in the left anterior cerebellar hemisphere (lobule V–VI). In the “fitters” group, this cerebellar zone was the only one disclosed when focusing on

motor skill learning, but the correlation with the PI was not significant. Thus, the cerebellar hemisphere is involved in successful motor skill learning as suggested previously (Debas et al., 2010; Ghilardi et al., 2000; Halsband and Lange, 2006; van Mier et al., 1998). It is worth noting that neither the whole-brain ANOVA nor the ROI analysis demonstrated a differential activation in the left anterior cerebellar hemisphere between the two groups (Fig. 3, Table 3) in which the same cerebellar zone (lobule V–VI) was activated in the two motor learning patterns (Table 5). In lobule V–VI, there was a non-significant trend for a negative correlation between the beta values and the NJ in the two groups; i.e. the stronger the BOLD activation, the smoother the movements. Thus, the lobule V–VI of the ipsilateral left cerebellar hemisphere was particularly important for performing smooth movements, independently of the learning pattern.

All the analyses (whole group, ANOVA, and subgroup analyses) showed that the SMA was the key area for distinguishing the two patterns of performance improvement during early motor skill learning (shift versus fit). In the “shifters” group, the temporal evolution of the BOLD signal in the SMA showed the strongest correlation with the temporal evolution of the PI. The SMA is known to be involved in sequence learning such as learning to trace a circuit, the serial reaction time task (SRTT), or finger tapping synchronisation (Lee, 2004; Lewis et al., 2004; VanMier et al., 2004). In the current experiment, the subjects had basically to learn to perform and to optimise (through a speed/accuracy trade-off) a complex sequence of precisely timed movements. In that sense, a higher level of activation in the SMA in the “shifters” is coherent with an early and efficient recruitment of the SMA allowing a better temporal implementation of a sequence of complex movements.

In the present study, the BOLD activity was restricted to the SMA proper, located caudally to the anterior vertical commissure (Kim et al., 2010; Nachev et al., 2008; Picard and Strick, 2001). From a cytoarchitectural and functional point of view, the SMA is separated in two distinct regions: the SMA proper (caudal part) and the pre-SMA (rostral part) (Kim et al., 2010; Nachev et al., 2008; Picard and Strick, 2001). It has been suggested that the SMA proper is involved in implicit motor skill learning and the pre-SMA in explicit motor skill learning (Ashe et al., 2006). The lack of activation in the pre-SMA in the current experiment fits with this observation since the skill to be acquired is implicit by nature. However, the functions of the SMA might be more complex than previously thought (Nachev et al., 2008). It has been suggested that the SMA proper is only involved when the correct sequence is already acquired, and permits to improve the performance of a known sequence; whereas the pre-SMA may be involved during the very first moments when acquiring new sequences (Hatakenaka et al., 2007; Nachev et al., 2008; Nudo, 2009). Due to the nature of our task (“circuit game”), the subjects were immediately aware of the full sequence since the circuit determines the movements to be performed. In that sense, the sequence is “known” at once and the activation of the pre-SMA might be very transient. Thus, in the “shifters” group, the rapid activation of the SMA proper and its continuous rise correlating with PI suggest that the SMA proper is the key area leading to the an early and efficient learning of this motor skill, as suggested previously (Grafton et al., 1992; Toni et al., 1998).

Another hypothesis for explaining the predominant role of the SMA proper may be the involvement of the SMA proper in inter-manual transfer of motor skills (Frings et al., 2006; Perez et al., 2007, 2008; van Mier and Petersen, 2006). In the current experience, all the subjects were familiar with computer work; they daily manipulated a computer mouse with their dominant hand. Although we did not specifically tested inter-manual transfer, one can hypothesise that the “shifters” were more efficient than the “fitters” in transferring from their dominant towards their non-dominant hand some low-level “general” (i.e. not task-specific) aptitude to



navigate the mouse (inter-manual transfer), and to improve their performance with the non-dominant hand.

## Conclusion

Despite identical instructions and experimental conditions, normal subjects may spontaneously adopt different behavioural patterns (shift/fit) during the first minutes of motor skill learning, which correlate with differential brain activation patterns. On the one hand, the ipsilateral cerebellar hemisphere is involved in the control of movement smoothness independently of the behavioural pattern (shift/fit). On the other hand, the SMA proper is the key area associated with an early shift of speed/accuracy trade-off, i.e. the most efficient motor skill learning pattern. This confirms a critical role of the SMA proper in the early stage of motor skill learning, at least when the task requires the performance of a sequence of fast and accurate movements under visual control.

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