

Neural correlates of performance variability during motor sequence acquisition

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ABSTRACT

During the initial training of a motor sequence, performance becomes progressively faster but also increasingly reproducible and consistent. However, performance temporarily becomes more variable at mid-training, reflecting a change in the motor representation and the eventual selection of the optimal performance mode (Adi-Japha et al., 2008). At the cerebral level, whereas performance speed is known to be related to the activity in cerebello-cortical and striato-cortical networks, the neural correlates of performance variability remain unknown. We characterized the latter using functional magnetic resonance imaging (fMRI) during the initial training to the Finger Tapping Task (FTT), during which participants produced a 5-element finger sequence on a keyboard with their left non-dominant hand. Our results show that responses in the precuneus decrease whereas responses in the caudate nucleus increase as performance becomes more consistent. In addition, a variable performance is associated with enhanced interaction between the hippocampus and fronto-parietal areas and between the striatum and frontal areas. Our results suggest that these dynamic large-scale interactions represent a cornerstone in the implementation of consistent motor behavior in humans.

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Introduction

Motor skills are acquired through repeated practice allowing the development of an automatized and crystallized motor program (Grafton, 2008). However, motor skills are constantly adjusted, even when they are automatized, in a “balancing-act” between exploitative and exploratory behaviors (Grafton, 2008). While the first behavior is efficient by allowing reproducibility of motor performance, the latter reflects continued experimentation enabling the development of new strategies, which will introduce some variability in the movement but might favor the optimization of motor behavior (Tumer and Brainard, 2007). Such variability may be adaptative, allowing plasticity in apparently crystallized skills (Grafton, 2008; Tumer and Brainard, 2007). Accordingly, during the initial practice of a new finger motor sequence, performance typically becomes progressively faster (Karni et al., 1995) and more reproducible (Adi-Japha et al., 2008). However, after several blocks of training, a transient phase of increased variability in performance is observed without any concurrent change in performance speed (Adi-Japha et al., 2008). This transient performance instability is thought to reflect a competition between different routines before the most effective one is set and mastered, presumably establishing a sequence-specific neural representation (Adi-Japha et al., 2008).

Cerebral correlates of motor sequence learning have been extensively studied and mainly involve cerebello-cortical and striato-cortical networks (Albouy et al., 2008; Doyon and Benali, 2005; Orban et al., 2010). The hippocampus is also recruited in the course of motor sequence learning (Albouy et al., 2008; Fernandez-Seara et al., 2009; Gheysen et al., 2009; Schendan et al., 2003) during which it can competitively interact with the striatum (Albouy et al., 2008). More specifically, recent studies were interested in distinguishing cerebral areas the activity of which is modulated by different components of motor performance, for example, by exploring learning-dependent plasticity mechanisms vs learning-independent implementation processes (Orban et al., 2010), accuracy vs synchrony of sequential movements (Steele and Penhune, 2010) or more generally, automaticity of visuomotor skills (Floyer-Lea and Matthews, 2004, 2005). However, the cerebral correlates of performance variability have never been specifically explored, despite its importance as a potential marker of the progress of learning strategies during training. To address this issue, we used functional magnetic resonance imaging (fMRI) to characterize the brain responses that change according to performance variability during a short (about 10 min) initial training to the Finger Tapping Task (FTT), a common motor sequence learning task during which participants have to produce an explicitly known 5-element finger sequence on a keyboard, with their non-dominant hand (Fig. 1, left panel).

Our results show that during initial motor sequence learning, responses in the caudate nucleus increase as performance becomes more

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consistent. In contrast, high variability in performance is associated with increased activity in the precuneus, an enhanced functional connectivity between the precuneus, the hippocampus, and frontal regions, on the one hand and between the caudate nucleus and frontal areas on the other hand. This finding suggests that the implementation of performance modes which eventually ensure the consistency of sequential motor output is related to functional interactions within striato-frontal and hippocampo-neocortical networks.

Material and methods

Population

Thirty-four young (mean age: 23 ± 3 years, 17 males and 17 females) right-handed (Oldfield, 1971) healthy volunteers were recruited by advertisement. They had no history of medical, neurological or psychiatric disease. None of them was on medication. None had ever played a musical instrument nor was trained as a typist. The quality of their sleep was normal as assessed by the Pittsburgh Sleep Quality Index questionnaire (Buysse et al., 1989). They followed a 3-day constant sleep schedule (according to their own rhythm ± 1 h) before the experiment. Compliance to the schedule was assessed using both sleep diaries and wrist actigraphy (Cambridge Neuroscience, Cambridge, UK).

Task and general experimental design

Subjects were scanned during 2 separate sessions referred to as the training and retest sessions while they performed a finger tapping task (FTT) coded in Cogent2000 (<http://www.vislab.ucl.ac.uk/cogent.php>) implemented in MATLAB (Mathworks Inc, Sherborn, MA). The results reported here only concern the training session. The FTT required the subjects to tap on a keyboard, with their (left) non-dominant hand, a five-element finger sequence as rapidly and as accurately as possible (Fig. 1, left panel). The sequence to perform was explicitly known by the participants and constantly displayed on the screen (4 1 3 2 4). The task was performed in 14 successive practice blocks of the trained sequence separated by 15-second rest periods. The task has been coded to keep track of the number of key presses within a block (maximum 60 key presses). After 60 key presses, the "practice block" automatically turned into a "rest block" (fixation cross). Consequently, the

duration of the practice blocks progressively decreased with learning, subjects becoming faster on performing the 60 key presses (12 possible sequences). This was done in order to control for the number of movements realized per block to make sure that differences in cerebral responses observed were not contaminated by any change in motor output during practice and implied that block duration progressively decreased through training with the speeding in performance.

Motor skill performance was measured in term of speed (actually its inverse, i.e. the mean time to perform a correct sequence per block computed over the 12 possible correct sequences), error rates (mean number of errors per block) and variability. Variability of performance was computed as variability of the residuals with respect to a single power-law fit that was calculated over the whole training session (i.e., over 168 points representing the time to perform each correct sequence (12 possible correct sequences) over the 14 blocks of training). The variability of the residuals with respect to the single power-law fit consisted in the standard deviation of the difference between the data points (time to perform each correct sequence) and their power-law fit, computed over the 12 possible correct sequences for each block of practice. This method of variability analysis, adapted from Adi-Japha et al. (2008), implies that estimates of performance variability are orthogonal from performance speed estimates.

Finally, fine-grained analyses on error type were done by exploring within and between-sequence errors as an index of changes in strategy during training. To do so, a sliding-window of 3 elements was applied on the data, trial by trial, to extract all the possible triplets of 3-element from the data, i.e. for a correct sequence 4 1 3 2 4, the 5 possible correct 3-element triplets were 413, 132, 324 (within-sequence triplets) and 244, 441 (between-sequence triplets). All the remaining triplets that were extracted were considered as "incorrect 3-element triplets" and were categorized as within- or between-sequence incorrect triplets (example: 131 was categorized as an incorrect within-sequence triplet and 442 as an incorrect between-sequence triplet). The number of elements in the sliding window was chosen to maximize the number of possible correct between-sequence triplets (with a 2 elements sliding window, there is just one possible correct between-session transition (44) whereas with a 3 element sliding window, there are 2 possible correct between-sequence triplets (244 and 441)). Number of incorrect triplets were then computed for each block in each subject and classified according to their type, as mentioned above: within-sequence incorrect triplet (over 3 possible correct within-sequence triplets) and between-sequence incorrect triplet (over the 2 possible correct between-sequence triplets).

Behavioral data analyses

Repeated-measure analyses of variance (ANOVA) on performance (speed, error rate, variability) with block repetition as within-subjects factor assessed the practice-related changes in performance during the training session. Planned comparisons were performed in order to compare performance between blocks within the training session. Furthermore, a repeated-measure analysis of variance (ANOVA) on number of incorrect triplets was computed with block repetition and error type (within-sequence or between-sequence errors) as within-subjects factor. This analysis assessed the practice-related changes in committed errors during the training session. Planned comparisons were performed in order to compare performance between blocks and error type within the training session.

Functional MRI data acquisition and analysis

Functional MRI-series were acquired using a head-only 3 T scanner (Siemens, Allegra, Erlangen, Germany). Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation (TR = 2130 ms, TE = 40 ms, FA = 90°, 32 transverse slices, 3 mm slice thickness, 30% inter-slice gap, FoV = 220 × 220 mm²,

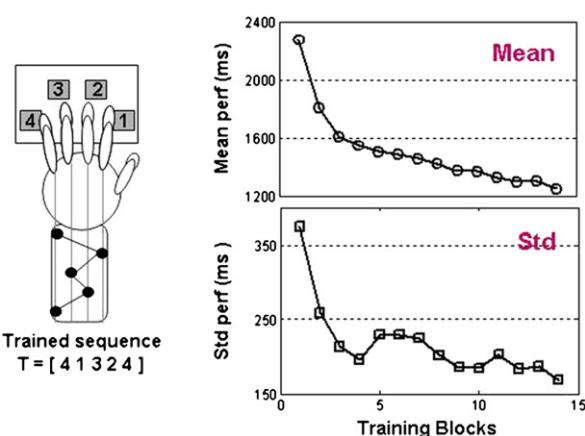


Fig. 1. Experimental task and behavioral results. Left panel — Finger Tapping Task, FTT. Right panel — Dynamics of mean time to perform a correct sequence (Mean, upper panel) and the standard deviation of difference between the data points (time to perform each correct sequence) and their power-law fit (Std, lower panel) computed over all subjects during training. Note that variability of performance follows a specific dynamics during training which does not parallel mean performance. The standard error of the mean (SEM) is not represented on the plot to conserve a scale allowing the illustration of the variability dynamics. SEM ranged across blocks from 51.10 to 109.88 ms for performance speed (Mean) and from 19.21 to 38.07 ms for performance variability (Std).

matrix size = $64 \times 64 \times 32$, voxel size = $3.4 \times 3.4 \times 3.0 \text{ mm}^3$). Training session consisted in 271 ± 37 scans. A structural T1-weighted 3D MP-RAGE sequence (TR = 1960 ms, TE = 4.43 ms, TI = 1100 ms, FA = 8°, 176 slices, FoV = $230 \times 173 \text{ mm}^2$, matrix size = $256 \times 192 \times 176$, voxel size = $0.9 \times 0.9 \times 0.9 \text{ mm}^3$) was also acquired in all subjects. Head movements were minimized using a vacuum cushion.

The 3 initial scans were discarded to allow for magnetic saturation effects. Functional volumes were pre-processed and analysed using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>; Wellcome Department of Imaging Neuroscience, London, UK). Pre-processing included the realignment of functional time series, the co-registration of functional and anatomical data, a spatial normalization to an EPI template conforming to the Montreal Neurological Institute space, and a spatial smoothing (Gaussian kernel, 8 mm full-width at half-maximum, FWHM).

The analysis of fMRI data, based on a mixed effects model, was conducted in 2 serial steps, accounting respectively for fixed and random effects. For each subject, changes in brain regional responses were estimated by a model including the responses to the trained sequence and their linear modulations by performance speed (mean time to perform a correct sequence by block) and variability (standard deviation of the residuals with respect to a single power-law fit, per block). Variability was orthogonalized with respect to speed, to account for potential collinearity. Practice blocks were modeled as box cars and convolved with the canonical hemodynamic response function. Movement parameters derived from realignment of the functional volumes were also included as covariates of no interest. High-pass filtering was implemented in the design matrix using a cut-off period of 128 s to remove slow drifts from the time series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm.

Contrasts tested the main effect of practice of the trained sequence and its linear modulation by performance speed and variability. Modulation by speed identified regions where response amplitude increased (or decreased) as time to complete a sequence decreased across training. Modulation by variability identified regions where response amplitude increased (or decreased) as motor behavior became more consistent (i.e., less variable) across training. Repeated-measure analyses of variance (ANOVA) on the fitted BOLD response of areas which activity is modulated by performance variability were performed with block repetition as within-subjects factor to assess the practice-related changes in BOLD response during the training session. Planned comparisons were performed in order to compare the BOLD response between blocks within the training session.

The fitted BOLD responses modulated by performance were estimated to illustrate the temporal dynamics block by block of cerebral responses in areas showing modulation of activity by performance (Fig. 2, ventral putamen, Fig. 3, caudate nucleus and precuneus). The fitted BOLD response represents the interaction between the parameter estimates of the regressor of interest (regressor modulated by performance) by the box-car design convolved by the canonical hemodynamic response function. The plots presented in Figs. 2 and 3 show the averaged fitted BOLD response modulated by performance for each block and across subjects.

Finally, psychophysiological interaction (PPI) analyses were computed on all the cerebral areas that showed significant modulation of activity by performance variability changes (right caudate nucleus, right motor cortex, bilateral precunei, Tables 2–3 and 2–5). These analyses were done in order to test the functional connectivity of these areas with the rest of the brain, in proportion to performance variability changes during training. Significant results were only observed for PPI analyses on the right caudate nucleus and on the right precuneus, as reported in Tables 2–4 and 2–6. For PPI analyses, new linear models were generated at the individual level, using three regressors. One regressor represented the practice of the learned sequence modulated by performance variability. The second regressor was the activity in the reference area. The third regressor represented the interaction of interest between the first (psychological) and the second (physiological)

Modulation by performance speed

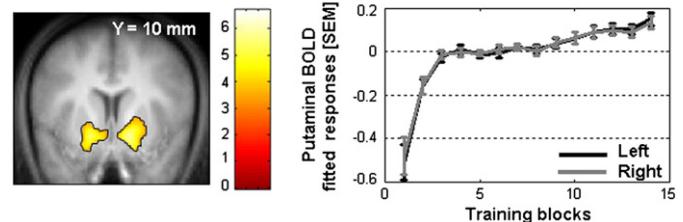


Fig. 2. Linear modulation of brain responses by performance speed. Bilateral ventral putamen responses increased during training with performance speed improvement. Functional results are displayed at $p_{\text{uncorrected}} < 0.001$ over the mean structural image of all subjects. In the insets, whiskers represent SEM. The plot represents the averaged fitted BOLD response by block (a.u., arbitrary units) modulated by performance speed across subjects.

regressors. To build this regressor, the underlying neuronal activity was first estimated by a parametric empirical Bayes formulation, combined with the psychological factor and subsequently convolved with the hemodynamic response function (Gitelman et al., 2003). The design matrix also included movement parameters. A significant PPI indicated a change in the regression coefficients (i.e. a change in the strength of the functional interaction) between any reported brain area and the reference region (caudate nucleus or precuneus), related to performance variability changes during training.

These linear contrasts generated statistical parametric maps [SPM(T)]. These summary statistics images were entered in a second-level analysis, corresponding to a random effects model, accounting for inter-subject variance. One-sample t tests characterized (1) the main effect of practice of the trained sequence and (2) the temporal modulation of brain responses by performance speed and variability.

The resulting set of voxel values for each contrast constituted a map of the t statistic [SPM(T)], thresholded at $p < 0.001$ (uncorrected for multiple comparisons). Statistical inferences were performed at a threshold of $p < 0.05$ after correction for multiple comparisons over either the entire brain volume or over small spherical volumes (10 mm radius), located in structures of interest.

Coordinates of areas of interest used for spherical small volume corrections

Striatal locations: right caudate nucleus 18 8 20 mm (Albuoy et al., 2008); left ventral putamen –14 10–10 mm (Albuoy et al., 2008); **Cerebellar locations:** left cerebellar hemisphere –22 –64 –26 mm (Penhune and Doyon, 2005), –26 –44 –42 mm (Penhune and Doyon, 2002); right cerebellar hemisphere 32 –56 –32 mm, 22 –38 –36 mm, 14 –70 –28 mm (Albuoy et al., 2008), 18 –72 –36 mm, 38 –66 –38 mm (Penhune and Doyon, 2005); **Hippocampal locations:** right posterior hippocampus 42 –34 –12 mm (Albuoy et al., 2008); left anterior hippocampus –34 –10 –28 mm (Degonda et al., 2005); left posterior hippocampus –28 –26 –22 mm, –26 –34 –6 mm; right anterior hippocampus 16 –14 –28 mm, 26 –24 –10 mm (Albuoy et al., 2008); **Motor cortex locations:** right sensorimotor cortex 36.2 ± 3.0 – 22.3 ± 4.6 57.0 ± 6.1 mm (Lehericy et al., 2006); **Parietal cortex locations:** right precuneus 16 –66 48 mm (Penhune and Doyon, 2005); left precuneus –10 –68 24 mm, –14 –72 48 mm (Penhune and Doyon, 2002); **Frontal cortex locations:** right superior frontal cortex 32 54 22 mm (Oishi et al., 2005), 18 40 46 mm, 14 26 54 mm, 10 56 26 mm (Penhune and Doyon, 2005); left superior frontal cortex –14 26 54 mm, –32 14 50 mm (Penhune and Doyon, 2005); medial prefrontal cortex –6 62 2 mm (Sterpenich et al., 2007); **Temporal cortex locations:** ±42 –8 –38 mm (Penhune and Doyon, 2002); **Occipital cortex locations:** left occipital cortex –36 –90 –2 mm (Albuoy et al., 2008).

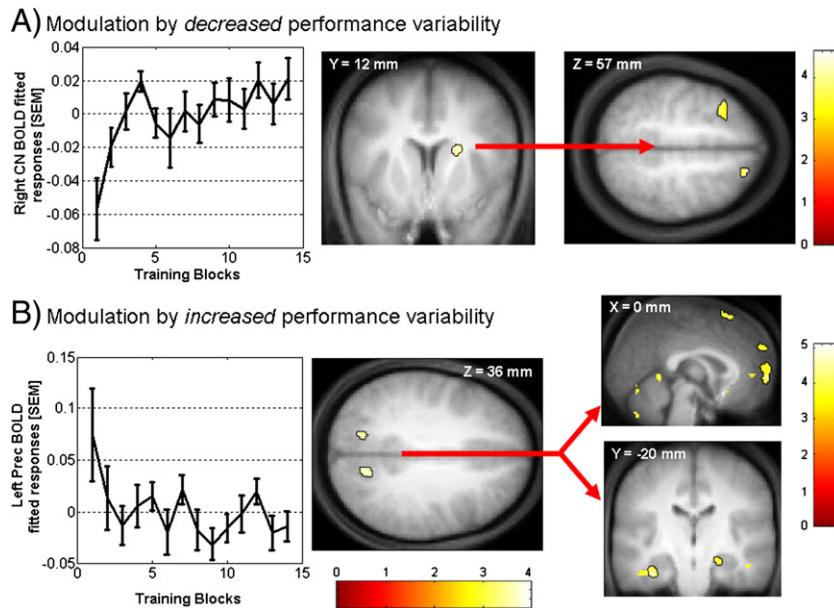


Fig. 3. Linear modulation of brain responses by performance variability. Functional results are displayed at $p_{\text{uncorrected}} < 0.001$ over the mean structural image of all subjects. In the insets, whiskers represent SEM. CN: Caudate Nucleus, Prec: Precuneus. The plot represents the averaged fitted BOLD response by block (a.u., arbitrary units) modulated by performance variability across subjects. A – Responses in the caudate nucleus decrease in proportion to performance variability. Note that the dynamics of caudate nucleus activity follows a similar non-linear dynamics as performance consistency during training, with an increasing recruitment in the first half part of training, a decrease in activity in the middle of the training session and a second increasing contribution at the end of training. The functional connectivity between the caudate nucleus and frontal areas decreases in proportion to performance consistency improvement. B – Responses in bilateral precunei increase in proportion to performance variability. Note that the dynamics of precuneus activity follows a similar non-linear dynamics as performance variability. The functional connectivity between right precuneus and hippocampo-frontal areas decreases in proportion to performance consistency improvement.

Results

Population

Four subjects were discarded from the analyses because of large movements during the acquisition (2 subjects) or because they practiced a wrong sequence in the scanner (2 subjects). Eventually, 30 subjects were included for the analyses (mean age = 23.3 ± 2.5 years, 15 males and 15 females).

Behavioral results

Error rates

A repeated-measure ANOVA conducted on the number of errors by blocks with blocks of training (14 blocks of trained sequence) as within-subjects factor, did not show significant main effect of blocks ($F(13,364) = 1.04, p = 0.40$), the mean number of error remaining stable and low (1.05 ± 1.32 errors per blocks) throughout training.

Performance speed

A repeated-measure ANOVA conducted on performance speed with blocks of training as within-subjects factor showed a main effect of block ($F(13,377) = 61.57, p < 0.0001$), the average time to complete a correct sequence decreasing with practice (Fig. 1, right panel, Mean).

Performance variability

A repeated-measure ANOVA conducted on power law fit residual variability with block as within-subjects factor showed a main effect of block ($F(13,377) = 5.69, p < 0.0001$), indicating that performance variability significantly changed across training blocks. As shown in Fig. 1 (right panel, Std), performance became progressively more consistent across blocks (i.e., standard deviation decreased), except during blocks 5 to 7 during which behavior becomes temporarily more variable. This time course is strikingly similar to the change in performance consistency reported for the finger opposition task by Adi-Japha et al. (2008). Planned comparisons showed that performance variability

during block 2 did not differ significantly from blocks 5 to 7 (Block 2 vs 5, $F(1,29) = 0.85, p = 0.36$, Block 2 vs 6, $F(1,29) = 0.47, p = 0.49$, Block 2 vs 7, $F(1,29) = 1.55, p = 0.22$), indicating that performance was as variable during these 3 blocks as during early training. The comparison between block 3 and blocks 5 to 7 did not show any significant difference (Block 3 vs Blocks 5, 6, 7, $F(1,29) = 0.29, p = 0.58$) whereas, by contrast, a trend was observed between block 4 and blocks 5 to 7 (Block 4 vs Blocks 5, 6, 7, $F(1,29) = 3.26, p = 0.08$) confirming a tendency for a transient increase in variability at mid-training. In addition, performance variability during blocks 5–7 was significantly larger than during blocks 8–10 (Blocks 5, 6, 7 vs 8, 9, 10, $F(1,29) = 4.78, p = 0.03$), indicating a significant lower variability level after the transient increase of variability observed on blocks 5–7. These changes in performance consistency occurred without concurrent changes in performance speed. Planned comparison did not indicate any decrease in speed on blocks 5–7 (Fig. 1, right panel, Mean). Indeed, in contrast to performance variability, performance speed on block 2 significantly differed from all other blocks including blocks 5 to 7 (Block 2 vs 5, $F(1,29) = 45.60, p < 0.001$, Block 2 vs 6, $F(1,29) = 29.57, p < 0.001$, Block 2 vs 7, $F(1,29) = 66.90, p < 0.001$), indicating that the dynamics of performance variability did not parallel the monotonic decrease in speed during training.

Type of errors

A repeated-measure ANOVA conducted on number of incorrect triplets produced during training with block and error type (within-sequence or between-sequence incorrect triplets) as within-subjects factor showed a main effect of error type ($F(1,29) = 21.37, p < 0.001$) indicating that subjects made more between-sequence than within-sequence errors during training. No significant block ($F(13,377) = 1.22, p = 0.26$) or error type by block effect ($F(13,377) = 0.97, p = 0.47$) was observed, indicating that number of errors globally remained stable during training whatever their type (see error rates paragraph). However, planned comparisons indicated a significant increase in within-sequence errors from early- to mid-training (within-sequence errors, blocks 1 to 4 vs 5 to 8, $F(1,29) = 5.21, p = 0.02$) that was not observed in between-sequence errors (between-sequence errors, blocks 1 to 4 vs 5 to 8,

$F(1,29)=0.03$, $p=0.86$). In contrast, between-sequence errors tended to increase between mid- and late-training (between-sequence errors, blocks 7 to 10 vs 11 to 14, $F(1,29)=3.01$, $p=0.09$) whereas within-sequence errors remained stable (within-sequence errors, blocks 7 to 10 vs 11 to 14, $F(1,29)=0.08$, $p=0.76$).

These results suggest that the increase in variability of performance at mid-training is accompanied by an increase in within-sequence errors. At the end of training, when variability is lower, an increase in between-sequence errors is observed.

Brain imaging data

Practice of the finger motor sequence recruited a distributed network including cerebellum, basal ganglia and cortical areas, as reported in Table 1.

During training, two behavioral parameters were considered as potentially important modulators of brain responses in brain imaging analyses: performance speed (Fig. 1, Mean) and variability (Fig. 1, Std). Whereas performance speed measures the progressive acceleration in movement execution and co-articulation, performance variability progressively decreases as performance becomes more consistent within a block.

Modulation of cerebral activity by performance speed

During training, responses increased in proportion to performance speed in the cerebellar hemispheres, bilaterally in the ventral putamen, the occipital cortex and in the right sensorimotor cortex (Fig. 2). In contrast, no significant responses decreased in proportion to performance speed (Tables 2–1 and 2–2).

Modulation of cerebral activity by performance variability

During training, amplitude of the cerebral responses increased in the right caudate nucleus, as performance became more consistent (i.e., as variability of the residuals with respect to the power law fit decreased, Table 2–3). The time course of responses in this area followed a non-linear dynamics which globally mirrored the evolution of performance variability, with a significant increase in activity through the session ($F(13,377)=2.47$, $p=0.003$) and a decrease in activity at mid-training that tended to differ from the level of activation at the end of training (Blocks 5, 6, 7 vs 12, 13, 14, $F(1,29)=3.07$, $p=0.09$; Fig. 3A, left panel). Furthermore, functional connectivity analyses revealed that the activity in the right caudate nucleus was coupled with a set of frontal areas, in proportion to performance variability. In other words, the strength of the functional connectivity between caudate and this set of frontal areas was modulated by performance variability. This result implies that the striato-frontal interaction was strong when performance was variable, diminished in proportion to the decrease in performance variability and was transiently strengthened at mid-training when performance was

Table 2

Functional results for the practice of the trained sequence modulated by performance. Significant brain responses after correction over the entire volume (*) or over small volume of interest (svc) are reported here.

Area	x mm	y mm	z mm	Z	p _{svc}
<i>1- Cerebral areas where responses decrease in proportion to speed</i>					
No significant responses					
<i>2- Cerebral areas where responses increase in proportion to speed</i>					
Left occipital cortex	-22	-104	14	5.13	0.007*
Right occipital cortex	16	-102	6	6.23	0.017*
Right ventral putamen	16	14	-10	4.79	0.03*
Left ventral putamen	-18	12	-12	4.45	0.000
Left cerebellar lobule V/VI	-18	-58	-18	4.25	0.000
Right cerebellar lobule VI	28	-56	-24	3.52	0.012
Right sensorimotor cortex	36	-24	64	3.30	0.022
<i>3- Cerebral areas where responses increase in proportion to performance variability decrease</i>					
Right caudate nucleus	22	12	18	3.64	0.004
Right motor cortex	10	-24	56	3.98	0.003
<i>4- Psychophysiological interaction with the right caudate nucleus modulated by performance variability increase</i>					
Right superior frontal gyrus	22	38	54	4.05	0.003
	18	34	58	3.25	0.03
Left superior frontal gyrus	-20	26	62	3.18	0.036
	-34	18	58	3.39	0.021
<i>5- Cerebral areas where responses are proportional to performance variability</i>					
Right precuneus	14	-68	40	3.31	0.022
Left precuneus	-14	-70	34	3.15	0.042
	-8	-78	50	3.20	0.030
<i>6- Psychophysiological interaction with the right precuneus modulated by performance variability increase</i>					
Left anterior hippocampus	-36	-18	-30	4.14	0.002
Right anterior hippocampus	22	-20	-18	3.48	0.016
Left posterior hippocampus	-22	-34	-4	3.43	0.019
Right cerebellar crus i	46	-68	-36	4.27	0.001
Right cerebellar lobule VI	30	-38	-44	3.54	0.014
	20	-72	-30	3.69	0.009
Left cerebellar lobule vi	-22	-56	-20	3.23	0.033
Left cerebellar lobule VIIIb	-26	-38	-50	3.98	0.003
Left occipital cortex	-30	-88	4	3.96	0.004
Right superior frontal gyrus	8	26	62	3.42	0.019
	4	58	32	3.74	0.007
Right medial prefrontal cortex	12	62	-2	3.74	0.008
	0	62	0	3.79	0.006
Left middle temporal gyrus	-48	-8	-30	4.00	0.003
Right middle temporal gyrus	50	-4	-42	3.51	0.015

more variable (Table 2–4). It is to note that the caudate nucleus and its associated circuit differ in their response to movement variability in the sense that the caudate nucleus activity increases as performance becomes consistent whereas the interaction with its associated circuit decreases as performance becomes more consistent.

In contrast, amplitude of the cerebral responses decreased as performance became more consistent (i.e., as variability of residuals with respect to the power law fit decreased) in bilateral precunei (Fig. 3B, left panel, Tables 2–5). These responses generally paralleled performance variability, with a decrease across practice blocks except at mid-training during which they transiently rose (BOLD response during blocks 5 and 7 was significantly larger than during blocks 8 and 9, $F(1,29)=4.40$, $p=0.04$; Fig. 3B, left panel). Note that the increase in BOLD response observed on block 12 did not significantly differ from block 11 ($F(1,29)=1.03$, $p=0.31$) and was paralleled by a non significant change in performance variability (Fig. 1, Right panel, Std), suggesting that these late changes could be due to non significant fluctuations. In parallel, functional connectivity analyses revealed that the activity in the right precuneus was related to responses in a network involving bilateral hippocampus and frontal, temporal, occipital and cerebellar areas, in proportion to performance

Table 1

Functional results for the practice of the trained sequence. Only significant brain responses after correction over the entire volume are reported.

Area	x mm	y mm	z mm	Z	p
Right motor cortex	36	-18	62	Inf	0.000
Left motor cortex	-50	-24	48	6.75	0.000
	-32	-6	68	6.55	0.000
	-60	6	28	9.53	0.000
Left cerebellar lobule V/VI	-18	-50	-26	Inf	0.000
	-4	-58	-12	7.69	0.000
Right cerebellar lobule V/VI	24	-60	-24	7.43	0.000
Right globus pallidus	16	-6	-8	5.20	0.005
Left globus pallidus	-16	-8	-4	4.87	0.021
Left intraparietal sulcus	-26	-52	68	5.44	0.002
Right intraparietal sulcus	32	-50	72	5.82	0.000
Cingulate motor area	2	2	56	6.20	0.000

variability. In other words, the strength of the correlation between activity in the precuneus and these areas was modulated by performance variability. The functional cooperation between these areas was strong when performance was variable, decreased in parallel to the decrease in variability and was particularly enhanced at mid-training when performance was temporarily variable (Table 2–6). It is to note that, unlike the caudate nucleus, the precuneus and its associated circuit have similar responses to movement variability in the sense that the precuneus activity and the interaction with its associated circuit decrease as performance becomes more consistent.

Discussion

In this study, we aimed at characterizing the neural correlates of performance speed and consistency during a short (about 10 min) motor sequence training. Behavioral data confirm that performance, although increasingly consistent across training, becomes transiently more variable at mid-training. Neuroimaging data show that performance speed relates to the activity in cerebello-cortical and striato-cortical networks. Our main finding is that task-related responses increase in the caudate nucleus and decrease in precuneus as performance becomes more consistent. Moreover, high variability in performance is associated with a tight cooperation between precuneus, hippocampus and frontal areas on the one hand and between caudate nucleus and frontal areas on the other hand. We proposed that these dynamic large-scale interactions allow the implementation of preferential performance modes, which ensure the reproducibility of sequential motor output during training.

Brain responses modulated by speed

During the initial practice of finger sequence learning, responses in striatum, cerebellum and sensorimotor cortex increased in proportion to the speeding of performance. Activity in these brain areas have already been described in the literature to be involved either in motor sequence learning proper or in non specific motor execution (Desmurget and Turner, 2010; Orban et al., 2010; Seidler et al., 2002, 2005). Indeed, numerous neuroimaging studies exploring cerebral correlates of motor sequence learning during initial or extended training, using speed, accuracy or even asynchrony as motor performance, reported increases in activity in the motor cortex during motor sequence learning (Karni et al., 1995, 1998; Pascual-Leone et al., 1994; Penhune and Doyon, 2002, 2005). These studies showed experience-specific reorganization in the motor cortex during sequence learning but it should be noted that a recent study proposes that the motor cortex would participate in the implementation of movement execution rather than in the sequence learning proper (Orban et al., 2010).

The progressive recruitment of the striatum has already been observed during both finger (Doyon et al., 1996; Jueptner et al., 1997; Lehericy et al., 2005; Steele and Penhune, 2010) and ocular motor sequence learnings (Albouy et al., 2008). Responses related to the progressive speeding of performance were localized in the ventral putamen, which potentially corresponds to the caudo-ventral sensorimotor part of the striatum. Indeed, the latter was previously associated with fast execution of over learned sequences (Lehericy et al., 2005). Importantly, striatal activity has been specifically related to sequence learning rather than to an unspecific speeding of movement execution (Orban et al., 2010; Seidler et al., 2005) but these findings have recently been challenged by a pharmacological inactivation study in monkeys (Desmurget and Turner, 2010).

A decrease in cerebellar responses is usually reported during motor learning as accuracy increases and as corrections required to achieve optimal behavior are less demanding (Doyon et al., 2002; Lehericy et al., 2005; Penhune and Doyon, 2002, 2005). However, a recent study showed that cerebellar responses could globally decrease with days of practice but locally increase in proportion to performance enhancement on a motor sequence task (Steele and Penhune, 2010). Similarly, our

results show a progressive increase in activity in different cerebellar regions as performance improves, as described in Orban et al. (2010). These specific cerebellar structures have been implicated in both movement implementation and acquisition of sequential knowledge (Orban et al., 2010; Seidler et al., 2002).

Importantly, unlike the studies reported above (Desmurget and Turner, 2010; Orban et al., 2010; Seidler et al., 2002, 2005), our design did not allow to tease apart improvement of simple movement execution from sequence learning proper. However, the impact of a change in motor output on the observed modifications in brain responses was limited by the fixed number of key presses per block.

Brain responses modulated by performance variability

The data confirm that the variability in performance does not progress monotonically during the initial training to a motor sequence. After a fast and substantial decrease during the first part of training, performance variability transiently increases before it further declines at the end of training (Adi-Japha et al., 2008).

Functional MRI data suggest that performance consistency is associated with a decrease in precuneus activity and an increase in caudate response. The activity in the precuneus would support novice performance by deploying controlled processes such as attention, working memory and response monitoring thereby implementing flexible and adaptive performance strategies at the expense of a slow and effortful behavioral output (Chein and Schneider, 2005). The large variability in performance at the beginning of training presumably relates to such identification of available performance modes and their adaptation to the actual experimental conditions under controlled cortical processes (Chein and Schneider, 2005; Thelen and Smith, 1993). Large responses in precuneus have already been observed during the early stages of learning (Penhune and Doyon, 2002, 2005) when performance drastically improves (Oishi et al., 2005). The activity in the precuneus linearly increases with motor complexity (Sadato et al., 1996) which suggests its role in the coordination of complex motor behavior (Cavanna and Trimble, 2006). Due to its implication in motor imagery (Cavanna and Trimble, 2006), the precuneus might also facilitate the storage of motor sequences in spatial working memory and allow the production of ongoing sequential movement with reference to that of buffered memory (Sadato et al., 1996).

The progressive involvement of the striatum which parallels performance consistency would instantiate a skilled automatic performance strategy (Hikosaka et al., 1999). Whereas the implementation of speeding in performance seems to rely on the caudo-ventral sensorimotor part of the striatum (ventral putamen described above), the establishment of reproducible behavior recruits the rostro-dorsal associative part of the striatum (caudate nucleus). Indeed, the caudate nucleus belongs to the associative part of motor striato-cortical loops and has been described to be recruited during the early phases of learning (Lehericy et al., 2005). At a higher level, the caudate nucleus has been described to play an essential role for associative learning strategies (Moses et al., 2010). Responses in the caudate nucleus were characterized by a non linear time course which significantly regressed with the specific dynamics of performance consistency. This finding is consistent with the view that the caudate nucleus is related to the implementation of preferential performance modes which ensure the reproducibility of sequential motor output during initial training, and are further optimized through practice (Rickard, 1999).

Functional integration of these networks for the implementation of consistent motor behavior

Functional MRI data suggest that the consistency in performance is related to a decreased coupling within two distinct systems: a precuneus/hippocampus/prefrontal network and a lateral prefrontal/striatum network.

The interaction between the precuneus, the hippocampus and prefrontal areas would support novice performance under controlled processes, as mentioned above (Chein and Schneider, 2005). More particularly, the precuneus was functionally connected to the medial prefrontal cortex and to lateral prefrontal areas (BA8–9) which correspond to the principal extraparietal corticocortical connections of the precuneus with the frontal lobes (Cavanna and Trimble, 2006). The prefrontal cortex is believed to code for an abstract representation of the temporal order in a sequence which is rehearsed during learning (Ashe et al., 2006). In addition, the prefrontal cortex would participate in the control of strategic processes through goal selection processes or sequence monitoring in working memory (Robertson et al., 2001; Schendan et al., 2003; Willingham et al., 2002). A decrease in prefrontal activity is usually observed when performance is automated, i.e. when there is a decrease in the need for consciously regulating and self-monitoring the ongoing finger movements (Fischer et al., 2005; Jenkins et al., 1994; Jueptner et al., 1997; Willingham et al., 2002).

The hippocampal responses recorded during motor sequence learning are usually believed to reflect the ability of the hippocampus to associate temporally discontiguous but structured information (Albouy et al., 2008; Schendan et al., 2003). The association of consecutive finger movements would account for the recruitment of the hippocampus during the early phase of motor sequence learning (Albouy et al., 2008; Schendan et al., 2003). Alternatively, given the role of the hippocampus in spatial processing (Burgess, 2008), hippocampal involvement in motor sequence learning might reflect the inherently spatial nature of the task. It is tempting to speculate that the hippocampus participates in the creation of an allocentric map of motor sequences during initial training, i.e. the organization of finger movements in space, irrespective of the fingers actually involved in its execution. This mechanism would be favored by the precuneus (Byrne et al., 2007), that would participate in the encoding of egocentric representation of the task and would, by its connectivity with the medial temporal lobe, support the translation between egocentric and allocentric representations of the task (Burgess, 2008).

The interaction observed between striatum and frontal cortex [lateral premotor cortex (BA6) and dorso-lateral prefrontal cortex (BA9)] is tighter when performance is highly variable. This network has already been described as the associative portion of the motor striato-cortical loops (Lehericy et al., 2005). Indeed, the anterior part of the striatum is known to be anatomically connected with the premotor and dorso-lateral prefrontal cortices (Lehericy et al., 2004) and these circuits would be involved in the early stages of motor sequence learning (Lehericy et al., 2005). Learning is usually thought to be associated with a progressive shift from the cortical control system to the automatic striatal system, resulting in a systematic and consistent decrease in activity in the controlled network with practice (Chein and Schneider, 2005). In keeping with this view, strong fronto-striatal interactions when performance is highly variable, during early learning, would materialize the influence of sequence representations elaborated in cortical circuits upon striatal representations. A reproducible motor behavior would be associated with a decrease of cortical weight upon the striatum.

The temporary overriding of controlled process implemented in cortical networks over automatic strategies supported by the striatum potentially explains the transient increase in performance variability and within-sequence error rates arising at mid-training. Our results on incorrect triplets concord with those of Adi-Japha et al. (2008) and show a shift in error type from within to between-sequence errors between mid- and late- training. These findings suggest that a change in strategy occurred at mid-training and that these qualitative behavioral changes reflect the adoption of a final coherent and stable representation of the sequence.

In consequence, the current study provides an objective evidence that the frontal cortex plays an important role in the balance between exploitative and exploratory behaviors (Grafton, 2008). Early during

learning and at mid-training, the cortical control of motor behavior at the expense of automaticity would involve interactions of the prefrontal cortex with on the one hand the precuneus and the hippocampus, and on the other hand, the striatum. These interactions would constitute a crucial process in sequence acquisition by which various performance modes are serially tried before the most effective mode is set to represent the whole sequence of movements in motor memory (Adi-Japha et al., 2008). The final coherent representation specific to the well-mastered sequence is associated with a decrease in the interactions within both the precuneus/hippocampus/frontal network and striato-frontal circuits.

Conclusions

Motor sequence acquisition implies the recruitment of distributed brain networks. The striatum would implement stereotyped performance strategies which promote performance consistency whereas fronto-parietal areas would serially elaborate various performance modes, among which an allocentric representation of the motor sequence could be mapped by the hippocampus. Future research should characterize the potential impact of these early representations on the subsequent consolidation of motor sequence memory.

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