Sleep Stabilizes Visuomotor Adaptation Memory: a functional Magnetic Resonance Imaging Study

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SUMMARY

The beneficial effect of sleep on motor memory consolidation is well known for motor sequence memory, but remains unsettled for visuomotor adaptation in humans. The aim of this study was to characterize more clearly the influence of sleep on consolidation of visuomotor adaptation using a between-subjects functional magnetic resonance imaging (fMRI) design contrasting sleep to total sleep deprivation. Our behavioural results, based on seven different parameters, show that sleep stabilizes performance whereas sleep deprivation deteriorates it. During training, while a set of cerebellar, striatal and cortical areas is activated in proportion to performance improvement, the recruitment of the hippocampus and frontal cortex protects motor memory against the detrimental effects of sleep deprivation. During retest after sleep loss a cerebello–cortical network, usually involved in the earliest stage of learning, was recruited to perform the task. In contrast, no changes in cerebral activity were observed after sleep, suggesting that it may only support the stabilization of the visuomotor adaptation memory trace.

INTRODUCTION

Humans use a wide variety of motor skills which they have to acquire through practice. Motor learning has been studied using two main paradigms exploring the acquisition of well-mastered sequences of movements (motor sequence learning) and the ability to execute a movement while compensating for external changes (motor adaptation) (Doyon *et al.*, 2003). The neural correlates of motor sequence memory and visuomotor adaptation memory consolidation have been described to rely on striato–cortical and cerebello–cortical networks, respectively (Doyon and Benali, 2005; Doyon *et al.*, 2003).

Some evidence suggests that, during motor sequence learning, sleep favours the occurrence of offline gains in performance, i.e. behavioural improvements occurring between training sessions without any interleaved practice (Albouy *et al.*, 2008; Doyon *et al.*, 2009; Fischer *et al.*, 2005; Korman *et al.*, 2003; Walker, 2005). By contrast, the influence of sleep on visuomotor adaptation has been characterized less frequently and remains controversial. Sleep effects

were reported either in terms of offline performance gains (Doyon *et al.*, 2009; Hill *et al.*, 2008; Huber *et al.*, 2004) or savings in performance (Debas *et al.*, 2010; Huang *et al.*, 2011; Krakauer, 2009; Krakauer *et al.*, 2005). The latter consists in the change in learning rate or average performance between the first trials of delayed testing relative to initial training. Offline performance gains were not observed systematically after sleep (but see Doyon *et al.*, 2009; Huber *et al.*, 2004), whereas performance savings were reported consistently at delayed retests (Brashers-Krug *et al.*, 1996; Debas *et al.*, 2010; Donchin *et al.*, 2002; Krakauer *et al.*, 2005; Shadmehr and Brashers-Krug, 1997) but seem to be independent of sleep (Debas *et al.*, 2010; Donchin *et al.*, 2002).

The aim of the present study was to determine whether sleep influences the consolidation of visuomotor adaptation skills, using functional magnetic resonance imaging (fMRI) and contrasting sleep-deprived individuals with volunteers who slept after training. We assessed comprehensively both offline changes and savings in performance using a panel of seven behavioural parameters.

MATERIALS AND METHODS

Ethics statement

All the participants gave their written informed consent to take part to the study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège.

Participants and experimental design

Thirty-three young (mean age: 24 ± 3 years, 16 females), right-handed (Oldfield, 1971), healthy volunteers were recruited by advertisement. They had no history of medical, neurological or psychiatric disease and none of them was on medication. The quality of subjects' sleep was normal as assessed by the Pittsburgh Sleep Quality Index question-naire (PSQI) (Buysse *et al.*, 1989). All the subjects followed a 3-day constant sleep schedule before the first visit and kept to the same schedule for three more days, until their second visit. Compliance to the schedule was assessed using both sleep diaries and wrist actigraphy (Cambridge Neuroscience, Cambridge, UK).

Subjects were scanned during two separate sessions, referred to as the training and retest sessions (Fig. 1b), while they performed a motor adaptation task (Fig. 1a) coded in Cogent2000 (http://www.vislab.ucl.ac.uk/cogent.php) implemented in MATLAB (Mathworks Inc., Sherbom, MA, USA). The task required subjects to reach for visual targets using a mouse with their (right) dominant hand while adapting to

Figure 1. Experimental protocol. SG: sleep group; SDG: sleep-deprived group; U: untrained deviation; T: trained deviation. (a) Adaptation task; (b) experimental protocol; (c) experimental functional magnetic resonance imaging (fMRI) design.

systematic rotation imposed on the perceived dot trajectory (Fig. 1a). Participants had to move a dot, displayed on the screen, corresponding to the position of the mouse, starting from the centre of the screen to a target position that would appear randomly at 10 cm in one of eight radial directions (0, 45, 90, 135, 180, 225, 270, 315°). All eight potential target positions were displayed constantly on the screen. A trial began when one of the targets was highlighted randomly. The participants had the instruction to reach the target as fast as possible using the shortest possible trajectory. In this rotation adaptation task, the dot position displayed on the screen was rotated clockwise [trained deviation (T), +60°] or anticlockwise [untrained deviation (U), −60°] relative to the mouse position. When the target was reached, the dot automatically returned to the starting central position, where the subjects had to wait 500 ms before the next target appeared.

The task was performed in 14 successive practice blocks of the trained deviation separated by 15-s rest periods (Fig. 1c). Each target had to be reached twice during each practice block (16 reaching movements per block). After training, subjects were assigned randomly to one of two groups according to whether they would be allowed to sleep [sleep group (SG)] or be totally sleep deprived [sleep-deprived group (SDG)] during the first post-training night (Fig. 1b). In the SG, subjects went home after the training session and slept regularly, as imposed by their constant sleep schedule, during the three post-training nights. In the SDG, subjects stayed awake in the laboratory during the first post-training night (from 23:00–07:00 h), under the constant supervision of experimenters. During the following day, subjects were instructed not to sleep and to continue their usual activities. They slept at home during the two remaining nights.

The retest session took place 72 h after training for subjects of both groups (SG and SDG), allowing two recovery nights for the SDG (Fig. 1b). Training and retest sessions were conducted from 08:00 to 19:00 h across participants and were performed at the same time of day for each subject in order to account for possible circadian fluctuations in performance within subjects. The retest session consisted of 20 blocks, with 14 blocks of trained and six blocks of untrained deviations (Fig. 1c).

Motor skill performance was measured with several parameters usually explored in the motor adaptation litera-ture. We first computed measures of speed with (i) block duration, representing the speed to perform the task by block, (ii) mean date of the peak velocity by block and (iii) mean time to reach the target by block. We also computed measures of accuracy with (i) mean trajectory length by block, (ii) mean area enclosed by the mouse trajectory relative to the theoretical trajectory (straight line), (iii) mean distance to the target at $t = 650$ ms and (iv) mean directional error at peak velocity, representing the angle between the position of the dot at peak velocity and the target to reach.
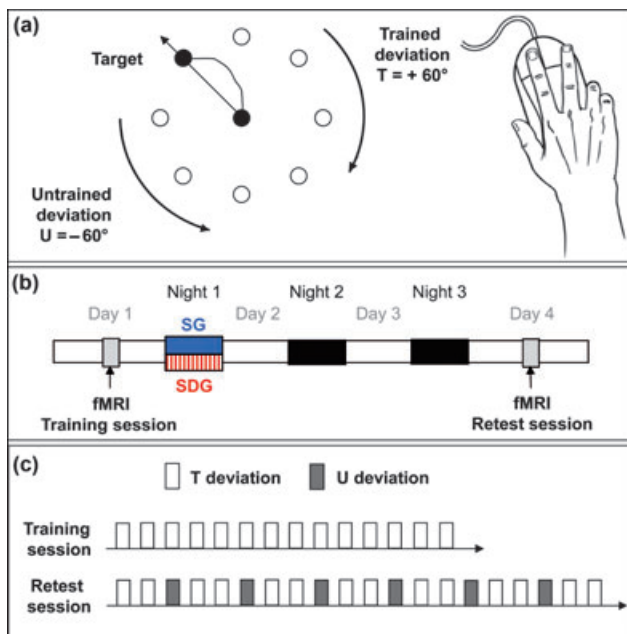
As usually conducted in motor sequence learning experiments, offline changes in performance were calculated as the difference between the average performance of the two last blocks of training versus the average of the two first blocks of retest. In order to fit the literature on the motor adaptation task, savings in performance were computed as the difference between the average performance of the two first blocks of training versus the two first blocks of retest.

fMRI data acquisition and analysis

Multi-slice 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% interslice gap, FoV = 220 × 220 mm², matrix size = 64 × 64 × 32, voxel size = 3.4 × 3.4 × 3.0 mm³). A structural T1-weighted 3D MP-RAGE sequence (TR = 1960 ms, TE = 4.43 ms, TI = 1100 ms, FA = 8°, 176 slices, FoV = 230 × 173 mm², matrix size = 256 × 192 × 176, voxel size = 0.9 × 0.9 × 0.9 mm³) was also acquired in all subjects. The analyses were performed in 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 coregistration 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 two serial steps accounting, respectively, for fixed and random effects. For each subject, changes in brain regional responses were estimated by a general linear model, including the responses to the trained and untrained deviations and their linear modulations by mean performance (mean time to reach the target in ms). These regressors consisted of box cars convolved with the canonical haemodynamic 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.

The linear contrasts generated statistical parametric maps [SPM(T)]. These summary statistics images were then further spatially smoothed (Gaussian kernel 6 mm FWHM) and entered into a second-level analysis, corresponding to a random-effects model, accounting for intersubject variance that consisted mainly of one- or two-sample t-tests. 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, as reported in the literature.

RESULTS

Population and demographic data

One subject in the SDG was excluded from the analyses because of large movements during fMRI data acquisition and another was excluded because he did not respect a regular sleep schedule after the deprivation night. Thirty-one subjects were included eventually in the analyses, 16 in the SG (mean age = 23 ± 2.7 years, 11 females) and 15 in the SDG (mean age = 25.3 ± 3.5 years, three females, unpaired t-test on age, $t_{29} = -1.96$, $P = 0.058$).

The groups did not differ either by the mean sleep duration (SG, 8 h 10 ± 57 min; SDG, 7 h 42 ± 1 h 05 min; unpaired t-test, $t_{27} = 1.24$, $P = 0.22$) or by the median PSQI score (SG, 3; SDG, 3; unpaired t-test, $t_{27} = 0.19$, $P = 0.84$) during the month preceding the recordings. Subjective sleep duration and quality did not differ between groups either during the night preceding the training session (duration: SG, 8 h 09 min ± 49 min; SDG, 7 h 51 min ± 48 min; unpaired t-test $t_{29} = 0.99$, $P = 0.32$; quality: SG, 4; SDG, 4; unpaired t-test $t_{29} = 0.24$, $P = 0.80$) or during the night preceding the retest session (duration: SG, 7 h 52 min ± 1 h 20 min; SDG, 8 h 04 min ± 1 h; unpaired t-test $t_{28} = -0.44$, $P = 0.65$; quality: SG, 4; SDG, 4; unpaired t-test $t_{28} = -0.81$, $P = 0.42$).

Actigraphic data on the six nights showed significant main effects of group ($F_{1,28} = 27.27$, $P < 0.001$) and night ($F_{5,140} = 69.07$, $P < 0.001$), as well as a group × night interaction ($F_{5,140} = 74.96$, $P < 0.001$). The activity during the three first nights did not differ between groups (all Ps > 0.2). As expected, the activity was larger in the SDG than in the SG during the deprivation night (SG = 29.73 ± 13.87 units, SDG = 285.00 ± 110.35 units, $F_{1,28} = 84.51$, $P < 0.001$). During the first recovery night, activity in the SDG tended to be lower than in the SG, suggesting a rebound of sleep after sleep deprivation (SG = 33.49 ± 24.19 units, SDG = 19.70 ± 12.29 units, $F_{1,28} = 3.69$, $P = 0.06$). This effect was no longer present on the second recovery night, which preceded the retest session (SG = 36.50 ± 24.51 units, SDG = 34.45 ± 18.70 units, $F_{1,28} = 0.06$, $P = 0.8$), suggesting that two nights were sufficient to recover from the effects of sleep deprivation.

Actigraphic data during daytime showed no significant main effects of group ($F_{1,28} = 1.59$, $P = 0.21$) and day ($F_{4,112} = 0.45$, $P = 0.77$), as well as no group × day interaction ($F_{4,112} = 1.46$, $P = 0.21$). The activity during the day following the sleep deprivation did not differ between groups (SG = 380.75 ± 106.56 units, SDG = 369.39 ± 160.99 units, $F_{1,28} = 0.05$, $P = 0.81$), suggesting that sleep-deprived subjects maintained the same activity as sleepers the day after sleep deprivation.

Behavioural results

Behavioral results are presented in Figure 2 where raw performance (Fig. 2a), mean time to reach the target (Fig. 2b), offline gains and savings in performance (Fig. 2c) are illustrated.

Training session

For the training session, repeated-measures analyses of variance (ANOVAS) on performance (each of the parameters described in the methods) with block repetition of the trained deviation and group as factors showed a main effect of repetition for all the parameters. In contrast, there was no significant group effect or repetition × group interaction for any of the parameters, indicating that performance improved similarly with practice in both groups (Table 1a, Fig. 2b, left panel, training).

Retest session

A repeated-measures ANOVA on performance of the retest session (for all the parameters) with block repetition and condition (trained versus untrained) as within-subject factors and group as between-subjects factor was performed. For each parameter, the ANOVA showed a significant effect of condition (all $F_{1,29} > 64.47$, all $Ps < 0.001$), performance being faster on the trained than on the untrained deviation, but no significant group (all $F_{1,29} < 1.02$, all $Ps > 0.32$) or group × condition interaction (all $F_{1,29} < 3.83$, all $Ps > 0.05$), suggesting that the learning effect tested at retest was not modulated by the sleep condition of the first post-training night (Fig. 2b, right panel, retest).

Further analyses were performed to explore the possible interference effect of the untrained deviation on performance of the trained deviation during retest. Planned comparisons showed that, for each parameter, performance on the trained
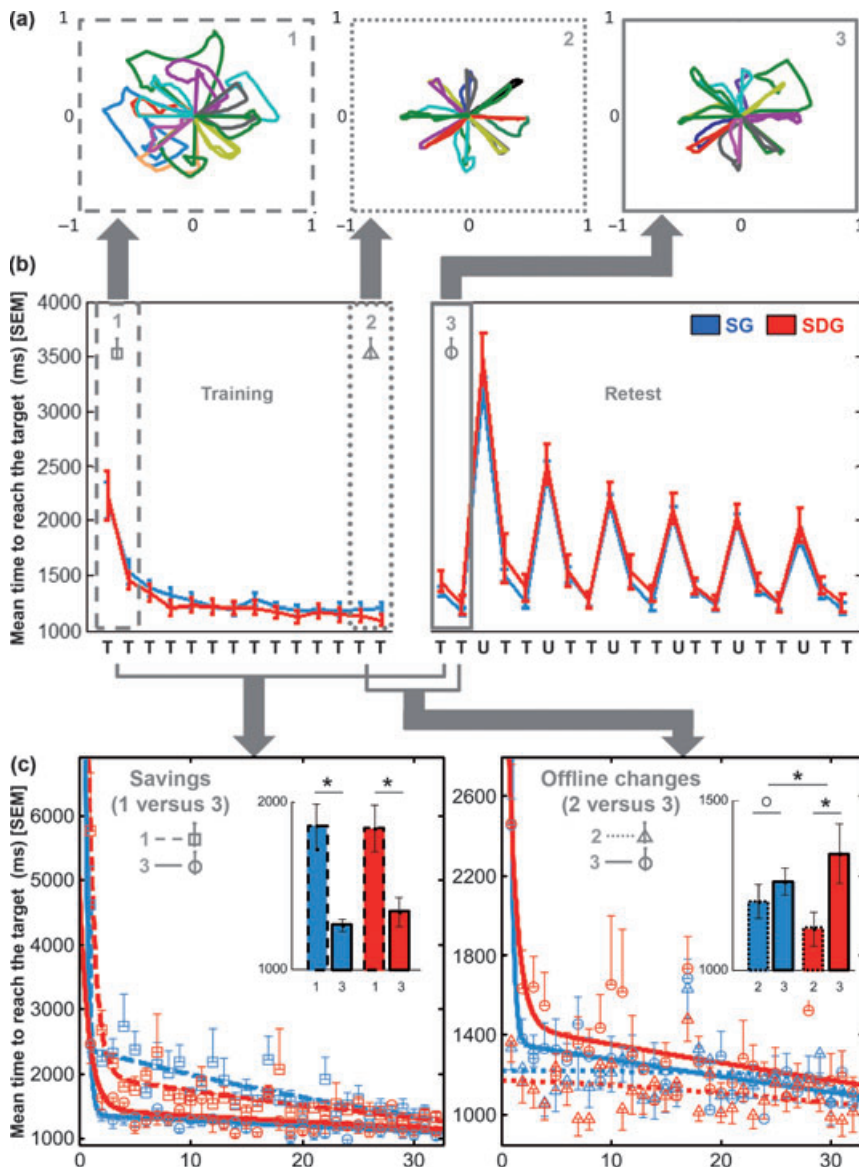

Figure 2. Behavioural results. Whiskers represent standard error of the mean (SEM). SG: sleep group; SDG: sleep-deprived group; U: untrained deviation; T: trained deviation. (a) Raw performance on the adaptation task (display of the dot trajectory) during the first block of training (1), the last block of training (2) and the first block of retest (3) for one representative subject of the SG (arbitrary units). (b) Performance [mean time to reach the target (ms)] during training (left panel) and retest (right panel) for both the trained and untrained deviations. (c) Trial by trial performance [mean time to reach the target (ms)] on the two first blocks of training (1, dashed line) versus the two first blocks of retest (3, full line) illustrating savings in performance (left panel); and on the two last blocks of training (2, dotted line) versus the two first blocks of retest (3, full line) illustrating offline changes in performance (right panel). Circles, squares and triangles points, representing the group average with SEM for each trial, are fitted by a double-exponential function (Krakauer et al., 2005). For savings and offline changes, the insets represent average performance within the two blocks encircled in each group. (*) $P < 0.05$, (o) $P > 0.05$.

Table 1 Behavioural results. In the planned comparison analyses, mean ± SD of the mean offline gains and savings in performance are presented for each parameter in each group

(a) ANOVA *testing the repetition* × *group effect during training*

Performance	Repetition	Group	Interaction
Block duration	$F_{13,377} = 47.69$, $P < 0.001$	$F_{1,29} = 0.26$, $P = 0.61$	$F = 0.32$, $P = 0.98$
Time at peak velocity	$F_{13,377} = 39.21$, $P < 0.001$	$F_{1,29} = 0.002$, $P = 0.96$	$F = 1.61$, $P = 0.07$
Time to reach the target	$F_{13,377} = 47.38$, $P < 0.001$	$F_{1,29} = 0.85$, $P = 0.36$	$F = 0.20$, $P = 0.99$
Trajectory length	$F_{13,364} = 25.28$, $P < 0.001$	$F_{1,28} = 0.02$, $P = 0.78$	$F = 0.12$, $P = 0.99$
Area	$F_{13,377} = 29.84$, $P < 0.001$	$F_{1,29} = 0.54$, $P = 0.46$	$F = 0.28$, $P = 0.99$
Distance at 650 ms	$F_{13,377} = 48.10$, $P < 0.001$	$F_{1,29} = 0.29$, $P = 0.59$	$F = 1.33$, $P = 0.18$
Directional error	$F_{13,377} = 23.82$, $P < 0.001$	$F_{1,29} = 0.93$, $P = 0.34$	$F = 0.92$, $P = 0.52$

(b) ANOVA *testing the session (offline changes)* × *group effect*

Performance	Session	Group	Interaction
Block duration	$F_{1,29} = 12.77$, $P = 0.001$	$F_{1,29} < 0.01$, $P = 0.99$	**$F = 4.34$, $P = 0.04$**
Date of peak velocity	$F_{1,29} = 15.04$, $P < 0.001$	$F_{1,29} = 0.02$, $P = 0.88$	**$F = 6.69$, $P = 0.01$**
Time to reach the target	$F_{1,29} = 11.91$, $P = 0.001$	$F_{1,29} = 0.10$, $P = 0.74$	**$F = 4.61$, $P = 0.04$**
Trajectory length	$F_{1,28} = 11.50$, $P = 0.002$	$F_{1,28} = 1.24$, $P = 0.27$	$F = 3.21$, $P = 0.08$
Area	$F_{1,29} = 13.53$, $P < 0.001$	$F_{1,29} < 0.01$, $P = 0.92$	$F = 3.15$, $P = 0.08$
Distance at 650 ms	$F_{1,29} = 20.81$, $P < 0.001$	$F_{1,29} = 0.40$, $P = 0.53$	**$F = 7.20$, $P = 0.01$**
Directional error	$F_{1,29} = 7.31$, $P = 0.01$	$F_{1,29} = 2.60$, $P = 0.11$	$F = 0.76$, $P = 0.38$

(c) Planned comparison on between-session effect (offline changes) within groups

Performance	SG	SDG
Block duration	(−) 932.09 ± 625 ms, $P = 0.29$	**(−) 3540.32 ± 1107 ms, $P < 0.001$**
Date of peak velocity	(−) 26.43 ± 20 ms, $P = 0.36$	**(−) 132.36 ± 35 ms, $P < 0.001$**
Time to reach the target	(−) 58.29 ± 39 ms, $P = 0.37$	**(−) 221.25 ± 69 ms, $P < 0.001$**
Trajectory length	(−) 1.49 ± 0.38 cm, $P = 0.26$	**(−) 4.86 ± 1.83 cm, $P = 0.001$**
Area	(−) 36.43 ± 17 cm, $P = 0.18$	**(−) 104.57 ± 34 cm, $P < 0.001$**
Distance at 650 ms	(−) 0.28 ± 0.18 cm, $P = 0.20$	**(−) 1.20 ± 0.24 cm, $P < 0.001$**
Directional error	(−) 2.05 ± 1.48°, $P = 0.19$	**(−) 4.01 ± 1.68°, $P = 0.01$**

(d) ANOVA *testing the session (savings)* × *group effects*

Performance	Session	Group	Interaction
Block duration	$F_{1,29} = 41.68$, $P < 0.001$	$F_{1,29} = 0.07$, $P = 0.79$	$F = 0.30$, $P = 0.58$
Date of peak velocity	$F_{1,29} = 55.94$, $P < 0.001$	$F_{1,29} = 0.89$, $P = 0.35$	$F = 0.20$, $P = 0.65$
Time to reach the target	$F_{1,29} = 42.87$, $P < 0.001$	$F_{1,29} < 0.01$, $P = 0.92$	$F = 0.72$, $P = 0.40$
Trajectory length	$F_{1,28} = 14.62$, $P < 0.001$	$F_{1,28} = 0.67$, $P = 0.41$	$F = 0.75$, $P = 0.39$
Area	$F_{1,29} = 24.70$, $P < 0.001$	$F_{1,29} < 0.01$, $P = 0.99$	$F = 0.44$, $P = 0.51$
Distance at 650 ms	$F_{1,29} = 96.52$, $P < 0.001$	$F_{1,29} < 0.01$, $P = 0.99$	$F = 0.55$, $P = 0.46$
Directional error	$F_{1,29} = 63.97$, $P < 0.001$	$F_{1,29} < 0.01$, $P = 0.98$	**$F = 9.00$, $P = 0.005$**

(e) Planned comparison on between-session effect (savings) within groups

Performance	SG	SDG
Block duration	**(+) 9.52 ± 1.92 ms, $P < 0.001$**	**(+) 8.02 ± 1.91 ms, $P < 0.001$**
Date of peak velocity	**(+) 200.45 ± 44 ms, $P < 0.001$**	**(+) 226.49 ± 35 ms, $P < 0.001$**
Time to reach the target	**(+) 594.62 ± 120 ms, $P < 0.001$**	**(+) 501.41 ± 119 ms, $P < 0.001$**
Trajectory length	**(+) 6.99 ± 1.75 cm, $P = 0.002$**	**(+) 4.40 ± 1.36 cm, $P = 0.04$**
Area	**(+) 312.71 ± 73 cm, $P < 0.001$**	**(+) 239.04 ± 84 cm, $P = 0.005$**
Distance at 650 ms	**(+) 2.25 ± 1.90 cm, $P < 0.001$**	**(+) 1.90 ± 0.22 cm, $P < 0.001$**
Directional error	**(+) 12.11 ± 1.83°, $P < 0.001$**	**(+) 5.50 ± 1.16°, $P = 0.001$**

ANOVA: analysis of variance; SG: sleep group; SDG: sleep-deprived group. (+) Represents an improvement in performance and (−) represents a deterioration in performance between sessions. Results presented in bold are significant ($P < 0.05$).

deviations were faster on blocks preceding (blocks 2, 5, 8, 11, 14, 17) compared to blocks following (blocks 4, 7, 10, 13, 16, 19), blocks of untrained deviation (all $F_{1,29} > 32.40$, all Ps < 0.001) and that this effect did not differ between groups (all $F_{1,29} < 1.09$, all Ps > 0.30). Taken together, these results suggest that practice on the untrained deviation interfered with performance on the following blocks of trained deviation during retest, but that these effects did not depend on the sleep condition during the first post-training night. Importantly, these interfering effects did not influence the computation of offline changes and savings in performance that were both performed on blocks of trained deviation occurring before any exposition to the untrained deviation (blocks 1 and 2 of the retest session).

Offline changes in performance

Between-session changes in performance, i.e. the offline changes in performance between the end of training and the beginning of retest, were tested with an ANOVA on blocks (average performance of the two last blocks of training versus average of the two first blocks of retest) and group as factors. For all the parameters, the ANOVA revealed a significant main effect of session but no significant group effect. The group × session interaction was significant for four of seven parameters, whereas it showed a tendency towards significance for only two other parameters (trajectory length and area) and did not reach significance for one parameter (directional error, Table 1b). Planned comparison showed a stabilization of performance for all the parameters in the SG (but no significant offline improvement). In contrast, a significant between-session deterioration of performance was observed in the SDG (Table 1c, Fig. 2c, right panel) for all parameters.

Savings in performance

Savings in performance were tested with an ANOVA on blocks (average performance of the two first blocks of training versus average of the two first blocks of retest) and group as factors. For all parameters, the analysis revealed a significant main effect of session but no group effect. The group × session interaction was not significant for all parameters except for directional error, for which savings differed between groups (Table 1d). Planned comparisons showed significant savings for all parameters in both groups (except for trajectory length that showed a tendency towards significant increase only in the SDG, Table 1e). These results indicate that significant savings appear irrespective of the sleep condition of the first post-training night, for all parameters (Fig. 2c, left panel), but preferentially after sleep for directional error only.

Brain imaging results

The main effect of practice of the learned deviation during training and retest sessions recruited a large cerebello–cortical network (Table 2a). For the training session, a contrast tested the main effect of practice of the trained deviation on subjects of both groups and its linear modulation by the changes in mean performance (mean time to reach the target). This analysis revealed that responses increased linearly with performance improvement over the training session bilaterally in the occipital cortex, ventral and dorsal putamen, motor cortex, intraparietal sulcus, in the right cerebellum, the right hippocampus and the left medial prefrontal cortex (Table 2b, Fig. 3a). In contrast, no brain responses were observed to decrease as mean performance improved over the training session.

A regression analysis assessed the relationship between brain areas recruited during training and subsequent changes in performance on the trained deviation observed between sessions in both groups. This analysis revealed that activity in the hippocampus, cerebellum and superior frontal cortex observed during initial training is correlated with subsequent offline changes in performance in the SDG, and more so than in the SG (Table 2c, Fig. 3b; note that the regression is still significant when excluding the outlier). This result suggests that the more the subjects activated this set of brain areas during training, the less was the detrimental effect shown by sleep deprivation on performance. After sleep, this relation no longer predicts subsequent changes in performance.

As sleep was not observed to influence performance savings, a regression analysis assessed the relationship between brain areas recruited during training and the subsequent savings in performance on the trained deviation overall subjects, irrespective of the sleep condition. This analysis revealed that a set of cortical areas including parietal and motor regions, as well as the cerebellar hemispheres (Table 2d), was activated during training in proportion to the subsequent savings in performance irrespective of the sleep condition.

During the retest session, the linear contrasts testing for the main effect of learning (trained–untrained) did not show any significant difference in learning-related brain activity between groups.

Finally, a linear contrast tested the main effect of session on the practice of the trained deviation (retest–training). This analysis did not reveal any change in brain responses between training and retest sessions in the SG compared to the SDG, suggesting stabilization of the cerebral network used during training to perform the task during retest. In contrast, in the SDG compared to the SG, responses increased at retest compared to training in a cerebello–cortical network, including the left cerebellar hemisphere, the right intraparietal sulcus, the right sensorimotor cortex and the right anterior cingulate cortex (Table 2e, Fig. 3c).

DISCUSSION

The present findings indicate that the influence of sleep on visuomotor adaptation skills depends on the metrics used to assess performance and behavioural consolidation. Based

Area	x mm	y mm	z mm	Z	P_svc
Table 2 Brain imaging results					
(a) Main effect of practice of the trained deviation during both training and retest sessions					
Right cerebellar hemisphere	26	−46	−28	Inf	**0.000***
	6	−66	−14	Inf	**0.000***
Left cerebellar hemisphere	−38	−82	−18	Inf	**0.000***
Right occipital cortex	46	−70	4	Inf	**0.000***
Left occiptal cortex	−44	−72	2	Inf	**0.000***
Left motor cortex	−35	−20	56	Inf	**0.000***
Right intraparietal sulcus	32	−48	56	Inf	**0.000***
Left intraparietal sulcus	−25	−48	54	Inf	**0.000***
Cingulate motor area	−2	−4	58	Inf	**0.000***
(b) Cerebral areas where responses increase with improvement of performance on the trained deviation during training					
Right occipital cortex	18	−86	−4	4.96	**0.016***
Left occipital cortex	−8	−90	0	4.93	**0.017***
Right ventral putamen	−14	8	−8	4.20	**0.001**
Left ventral putamen	20	14	−4	3.98	**0.003**
Right dorsal putamen	24	−10	18	3.94	**0.003**
Left dorsal putamen	−22	2	16	3.27	**0.025**
Right sensorimotor cortex	32	−8	46	3.47	**0.014**
Left sensorimotor cortex	−26	−28	54	3.27	**0.025**
Right intraparietal sulcus	14	−58	60	3.11	**0.038**
Left intraparietal sulcus	−24	−54	62	3.34	**0.021**
Right anterior hippocampus	34	−14	−24	3.64	**0.008**
Left medial prefrontal cortex	−12	62	0	3.20	**0.030**
Left cerebellar lobule IX	−12	−46	−46	3.26	**0.026**
(c) Regression analysis between cerebral activity during practice of the trained deviation during training and the subsequent offline changes in performance					
SG					
No significant responses					
SDG					
Right anterior hippocampus	24	−18	−20	3.48	**0.013**
Left anterior hippocampus	−26	−14	−18	3.67	**0.007**
Right parahippocampal cortex	30	−26	−26	3.73	**0.006**
Right posterior hippocampus	40	−32	−16	3.18	**0.030**
	32	−40	−2	3.45	**0.014**
Right cerebellar lobule IX	14	−46	−50	3.41	**0.016**
SG–SDG					
No significant responses					
SDG–SG					
Left crus II	−22	−76	−44	3.72	**0.006**
Left cerebellar lobule IX	14	−44	−50	3.70	**0.007**
Right superior frontal cortex	12	40	60	3.70	**0.007**
Left superior frontal cortex	−8	26	64	3.28	**0.023**
Right parahippocampal cortex	34	−26	−30	3.04	**0.042**
Right anterior hippocampus	26	−24	−16	3.01	**0.045**
	30	−20	−14	2.95	**0.053**
Right posterior hippocampus	22	−30	−12	2.92	**0.057**
(d) Regression analysis between cerebral activity during practice of the trained deviation during training and the subsequent savings in performance in both groups					
SG + SDG					
Left precuneus	−14	−64	56	6.11	**0.000***
Right precuneus	14	−58	55	5.32	**0.003***
Left intraparietal sulcus	−28	−54	50	5.76	**0.000***
	−22	−76	42	4.84	**0.024***
Right intraparietal sulcus	24	−48	44	5.33	**0.003***
	30	−74	38	5.24	**0.004***
Left supramarginal gyrus	−48	−30	34	5.60	**0.001***
	−42	−44	64	5.11	**0.008***

Area	x mm	y mm	z mm	Z	P$_{svc}$
Table 2 *Continued*					
Left precentral cortex	−56	−44	44	4.74	**0.036***
Left inferior temporal gyrus	−52	−72	2	4.92	**0.017***
	−36	−70	0	4.78	**0.031***
Right inferior temporal gyrus	56	−60	−20	4.79	**0.029***
	44	−68	2	4.70	**0.042***
Left superior frontal gyrus	−26	−2	72	4.84	**0.020***
	−36	−6	58	4.67	**0.048***
Left postcentral gyrus	−54	−24	44	4.74	**0.035***
Right cerebellar lobule V	14	−56	−16	4.71	**0.040***
	12	−78	−22	4.65	**0.051***
Left cerebellar lobule V	−18	−74	−24	4.65	**0.052***
(e) Main effect of session on the trained deviation (retest–training)					
SG					
Left superior temporal sulcus	−48	0	−34	3.43	**0.021**
SDG					
Right putamen	26	2	−6	3.86	**0.006**
Left putamen	−26	6	−4	3.40	**0.022**
Posterior cingulate cortex	12	−48	36	3.68	**0.011**
Right cingulate motor area	14	4	48	3.61	**0.013**
Right inferior frontal gyrus	8	56	−10	3.16	**0.042**
Left caudate nucleus	−16	0	16	3.25	**0.033**
SG–SDG					
No significant responses					
SDG–SG					
Anterior cingulate cortex	14	14	52	3.29	**0.022**
Right intraparietal sulcus	30	−48	50	3.42	**0.015**
Left cerebellar lobule VI	−28	−54	−20	3.37	**0.018**
Left cerebellar lobule V	−28	−34	−34	3.29	**0.022**
Right sensorimotor cortex	34	−12	72	3.28	**0.022**

SG, sleep group; SDG, sleep-deprived group.
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 (svc).

on a number of performance measures, our data speak for the absence of sleep-dependent delayed gains in performance after motor adaptation learning, but rather for a sleep-dependent stabilization of performance. In contrast, sleep deprivation had a detrimental effect on performance. Conversely, savings in performance occurred after both sleep and sleep deprivation, suggesting that this process is not sleep-dependent. At the cerebral level, activity in a cerebello–striato–cortical network increases in proportion to performance improvement during initial training. In parallel, recruitment of the hippocampus and frontal areas during training seems to protect the memory trace against the deleterious effect of sleep deprivation. In contrast, activity in the usual cerebello–cortical network during training seemed to predict the subsequent sleep-independent savings in performance. Finally, learning-related cerebral responses did not change significantly between training and retest in the SG, suggesting that sleep may participate in stabilization of the memory trace. By contrast, after sleep deprivation, brain areas usually involved in the earliest stages of learning were recruited during retest, when performance was deteriorated compared to training.

Behaviour

While the time–course of performance after a single practice of motor sequence is well known, this process is less well established for motor adaptation. Most studies on motor adaptation report that the average performance over all the sessions (Brashers-Krug *et al.*, 1996; Shadmehr and Brashers-Krug, 1997; Trempe and Proteau, 2010) or average performance at the beginning of a session (Debas *et al.*, 2010; Donchin *et al.*, 2002; Krakauer *et al.*, 2005) improves from initial training to testing 24 h later. Our results show that significant savings occurred irrespective of the sleep condition during the first post-training night. These observations are concordant with studies showing significant savings overnight (Krakauer *et al.*, 2005), but also during the day (Debas *et al.*, 2010) or even after sleep deprivation (Donchin *et al.*, 2002), suggesting that the emergence of savings is not a sleep-dependent process.

However, previous studies did not usually report whether or not performance changes from the end of training to the beginning of testing, and it seems that no delayed gain is observed overnight (Brashers-Krug *et al.*, 1996; Debas *et al.*,
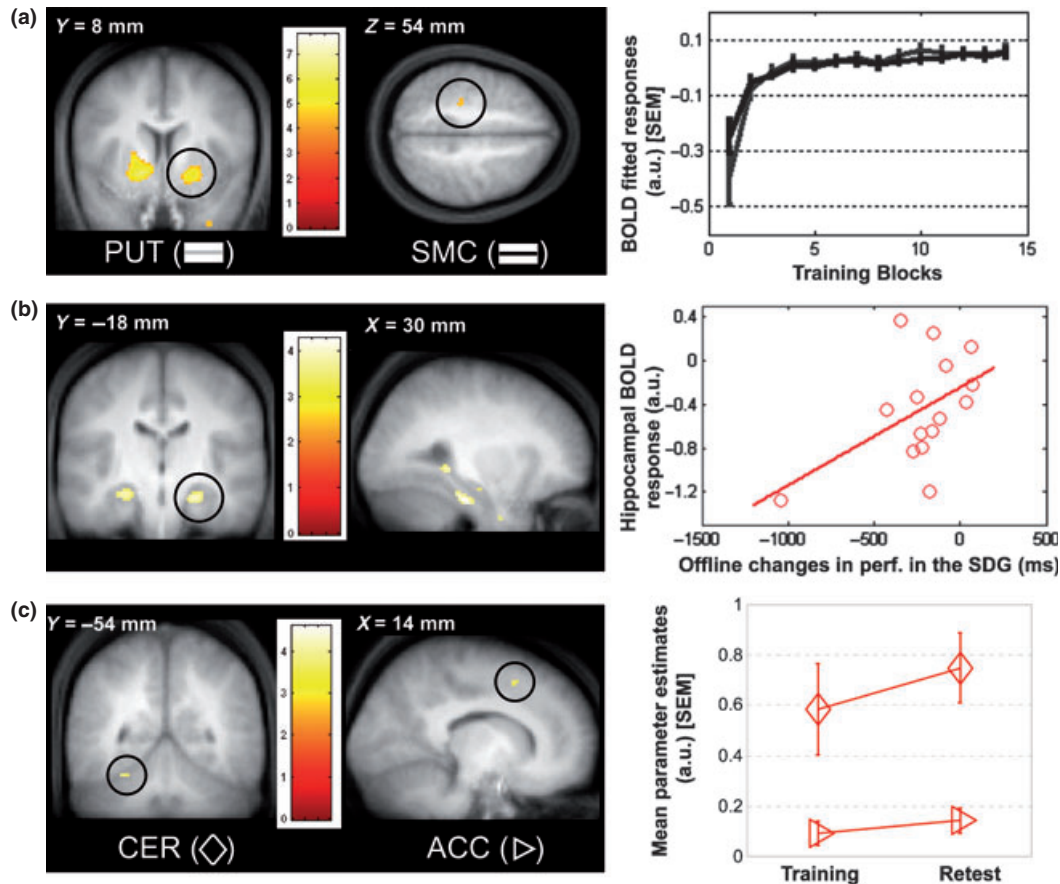
Figure 3. Functional imaging results. Functional results are displayed at $P_{uncorrected} < 0.001$ over the mean structural image of all subjects. In the insets, whiskers represent standard error of the mean; a.u.: arbitrary units. (a) Linear modulation of brain responses by mean performance. The plot illustrates the time–course of the fitted BOLD response modulated by mean performance across training blocks in the putamen (PUT) and the sensorimotor cortex (SMC). (b) Regression analysis between cerebral activity during training and subsequent offline changes in performance in the sleep-deprived group (SDG). The regression plot represents the BOLD responses in the right anterior hippocampus during training against the offline changes in performance on the learned deviation observed in the SDG. Each data point represents a single subject of the SDG. Note that the regression is still significant when excluding the outlier. (c) Main effect of session on the learned deviation on the SDG (retest–training). The plot represents the mean parameter estimates on the trained deviation during training and retest sessions for the cerebellum (CER) and the anterior cingulate cortex (ACC).

2010; Donchin *et al.*, 2002; Krakauer *et al.*, 2005; Shadmehr and Brashers-Krug, 1997; Trempe and Proteau, 2010). Nevertheless, other authors reported delayed gains in performance on a visuomotor adaptation task that would (Hill *et al.*, 2008; Huber *et al.*, 2004) or would not (Doyon *et al.*, 2009) be sleep-dependent. Various factors might account for these discrepancies: the kinematic features of the task, awareness of the deviation or the parameters used for assessing performance. The present findings, based on a number of performance measures, speak for the absence of delayed gains after motor adaptation learning, the performance levels achieved during late training being simply maintained at retest. In contrast, sleep deprivation had a detrimental effect on motor adaptation performance. The latter effect is not likely to be due to larger fatigue effect during the retest session in sleep-deprived subjects compared to sleepers, as it has been shown that following a single night of total sleep deprivation, individual performance on several tasks and subjective sleepiness are restored

completely after two nights of recovery sleep (Bonnet, 2000). One should, however, note that our results could be influenced by the menstrual cycle in females, not recorded in our study, which is known to modulate motor memory consolidation (Genzel *et al.*, 2012).

Early recruitment of cerebellum, hippocampus and frontal cortex protects against the detrimental effects of subsequent sleep loss

During the initial practice of motor adaptation task, responses in the striatum, the cerebellar hemispheres, the sensorimotor cortex, the intraparietal sulci, the prefrontal cortex and the hippocampus increased in proportion to the speeding of performance. Activity in these areas has already been described in early sensorimotor adaptation learning (Graydon *et al.*, 2005; Seidler *et al.*, 2006). Interestingly, at the same time, recruitment of the cerebellar hemisphere, the hippocampus and frontal areas is

correlated with greater maintenance in performance after sleep deprivation. The interaction between the hippocampus and the frontal cortex has already been described during the early phases of motor sequence monitoring (Albouy *et al.*, 2012) and for higher-order complex tasks (Darsaud *et al.*, 2011), and is thought to support novice performance under control processes (Chein and Schneider, 2005). Our data suggest that subjects presenting high levels of hippocampal, frontal and cerebellar activity would monitor their performance closely during training, allowing the memory trace to become more resistant to the detrimental effect of subsequent sleep deprivation. Our findings also indicate that recruitment of this network could be considered as a distinct process, paralleling the usual cerebello–cortical activations shown to predict subsequent sleep-independent savings in performance. Interestingly, a recent paper proposes that visuomotor adaptation learning is attributable to separate processes acting in parallel to the cerebellar-dependent error-based network allowing adaptation (Huang *et al.*, 2011). Our data suggest that the hippocampus and frontal cortex could participate in the monitoring of learning and even condition resistance of the memory trace to subsequent sleep deprivation.

Impact of sleep and sleep deprivation on offline cerebral response changes

Our data suggest that the maintenance in performance levels observed in sleepers was accompanied by stabilization of cerebral responses which did not change significantly between training and retest sessions. These results suggest that sleep after visuomotor adaptation may not participate in the reorganization of the memory trace, but simply in its stabilization. In contrast, the deterioration of performance in sleep-deprived subjects was contemporaneous with an increase in responses, from training to retest, in a cerebello–cortical network. Responses in cerebellar hemispheres have been described during early learning (Doyon *et al.*, 2003; Flament *et al.*, 1996; Floyer-Lea and Matthews, 2004; Nezafat *et al.*, 2001), suggesting that this part of the cerebellum would participate in the detection and correction of errors when performance is inaccurate and in the building of an internal model of the task in the early stages of learning (Graydon *et al.*, 2005; Imamizu *et al.*, 2000). Our results suggest that sleep deprivation after motor adaptation learning hinders memory trace stabilization. During retest, cerebellar hemispheres, usually involved in the earliest stage of learning, and cortical areas are recruited to perform the task when performance is non-optimal.

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