

Brain plasticity related to the consolidation of motor sequence learning and motor adaptation

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This study aimed to investigate, through functional MRI (fMRI), the neuronal substrates associated with the consolidation process of two motor skills: motor sequence learning (MSL) and motor adaptation (MA). Four groups of young healthy individuals were assigned to either (i) a night/sleep condition, in which they were scanned while practicing a finger sequence learning task or an eight-target adaptation pointing task in the evening (test) and were scanned again 12 h later in the morning (retest) or (ii) a day/awake condition, in which they were scanned on the MSL or the MA tasks in the morning and were rescanned 12 h later in the evening. As expected and consistent with the behavioral results, the functional data revealed increased test–retest changes of activity in the striatum for the night/sleep group compared with the day/awake group in the MSL task. By contrast, the results of the MA task did not show any difference in test–retest activity between the night/sleep and day/awake groups. When the two MA task groups were combined, however, increased test–retest activity was found in lobule VI of the cerebellar cortex. Together, these findings highlight the presence of both functional and structural dissociations reflecting the off-line consolidation processes of MSL and MA. They suggest that MSL consolidation is sleep dependent and reflected by a differential increase of neural activity within the corticostriatal system, whereas MA consolidation necessitates either a period of daytime or sleep and is associated with increased neuronal activity within the corticocerebellar system.

functional MRI | memory consolidation | motor learning | sleep | wakefulness

Motor memory consolidation refers to the “off-line” process by which a memory trace initially labile becomes more robust and fixed. Accumulated evidence has shown that sleep contributes to this physiological process, but that its effect depends on the nature of the motor learning demands (see ref. 1 for a review). For example, several researchers have demonstrated that the consolidation of a newly learned sequence of movements (motor sequence learning, MSL) acquired through explicit mechanisms is sleep dependent, as performance gains have been observed after nocturnal sleep, but not after the simple passage of time (2–5). By contrast, the role of sleep in the consolidation of skills, in which subjects have to adapt to sensorimotor perturbations (motor adaptation, MA), has been more controversial. Whereas Huber and colleagues (6) have reported that better performance on such a task was only observed in subjects who slept following training, Doyon et al. (2) have recently demonstrated that similar performance gains could be seen after a night of sleep or an equivalent period of daytime.

Numerous studies have previously demonstrated that the striatum, cerebellum, and motor-related cortical regions play a critical role in the acquisition of MSL and MA skill behaviors (7–9). Investigations of the brain regions mediating the consolidation process of these motor abilities, and how they relate to sleep,

however, have revealed inconsistent findings. Whereas sleep-dependent posttraining improvement in performance on MSL has been associated with a reduction in brain activation in prefrontal, premotor, and primary motor cortex (M1) areas, as well as increased activity in parietal regions (10), a different pattern of results characterized by increases of activation in M1, medial prefrontal, hippocampus, and cerebellum, along with a decrease of activity in parietal cortices, have also been reported (11). Furthermore, the neural correlates associated with the consolidation of MA skill during sleep have never been fully studied. Using electroencephalography (EEG), it was suggested that slow wave activity localized in the parietal cortex contributes to the consolidation of a rotation adaptation task during sleep (6). However, EEG recordings do not allow the measurement of subcortical activity changes in purportedly critical structures like the cerebellum.

The goal of this study was to determine, using functional MRI (fMRI), the cerebral structures affected by the off-line consolidation of both MSL and MA skills, and how they relate to sleep vs. passage of time. To do so, we compared activation maps between night/sleep and day/awake groups of young healthy subjects that were asked to execute motor tasks designed to measure one of these two forms of motor skills. The night/sleep groups were thus trained and scanned in a posttraining session after having reached asymptotic performance on a version of a five-item finger sequence learning task (MSL) or an eight-target reaching task (MA) in the evening. They were then retested in the morning after a 12-h delay encompassing a night of sleep in the laboratory. The day/awake groups followed the same procedure, except that they were trained and scanned on either of these two tasks in the morning and retested 12 h later in the evening (Fig. 1). On the basis of previous behavioral (3, 4) and imaging data (9), we hypothesized that MSL would elicit sleep-dependent changes in the corticostriatal system, whereas MA would produce sleep-independent changes in the corticocerebellar network.

Results

Behavioral Data: Motor Sequence Learning. Performance on this task was measured using the execution time per sequence (TpS) for each block of trials. All subjects improved during the training session and reached asymptotic performance. (For additional information regarding this initial session, see *SI Text* as only

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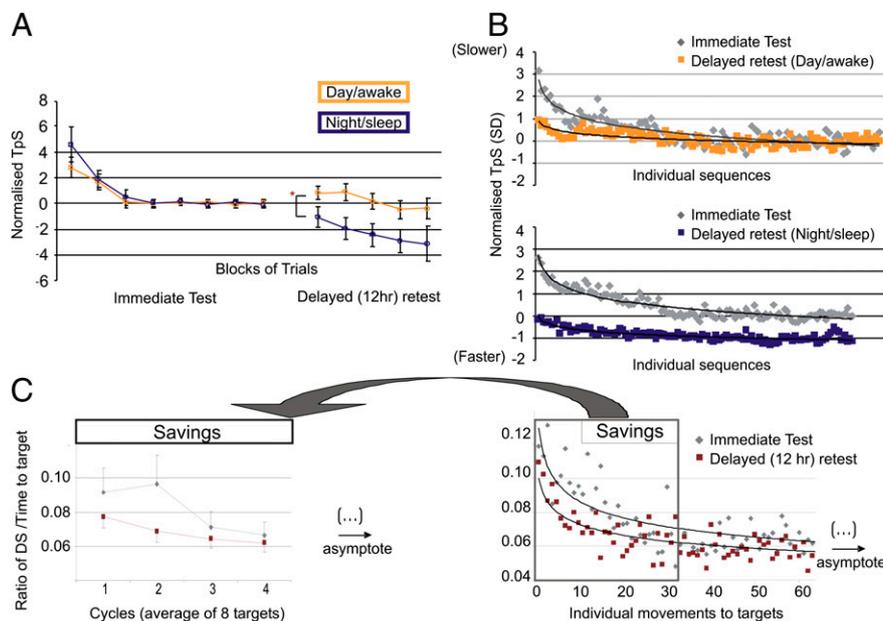


Fig. 2. Behavioral results. (A) Behavioral results of the MSL task. Performance of the two groups across blocks in both immediate and retest sessions are illustrated. (B) Illustration of the groups' performance at the individual sequence level, with each curve representing a session. (Upper) The performance for the day/awake group. (Lower) The night/sleep group. (C) Behavioral results for the MA task. The y axis represents the ratio of DS relative to the time taken to reach each target. Left graph shows averaged subject's performance for each cycle. Right graph shows performance on each individual movement to a single target. Each curve represents a session. Savings occurred within the first four cycles of the retest session. Yet there was no significant interaction or between-group differences (night/sleep vs. day/awake) with respect to the amount of savings, and thus the results of both groups were pooled together to look at test-retest differences (consolidation).

therefore assessed through a global conjunction analysis of the two groups in the delayed > immediate contrast. This contrast revealed that activity in the right cerebellum (lobule VI) ($X = 36$, $Y = -72$, $Z = -21$), was significantly greater in the retest than in the test session ($\text{svc}_{10\text{mm}}$, $P_{\text{Fwe-corr}} = 0.04$) (Fig. 3B). Finally, multiple regression analyses revealed that this region of the cerebellum (lobule VI), albeit slightly anterior ($X = 36$, $Y = -60$, $Z = -21$), correlated with the amount of savings found between the two sessions in the two groups (Fig. 3B and Table S2).

Discussion

This study aimed at identifying the brain regions associated with the off-line consolidation process of two forms of motor skill learning: MSL and MA. As expected, the behavioral results yielded significant spontaneous gains in performance on an explicitly known MSL task that were observed following a night of sleep, but not after an equivalent diurnal period (2–5). Importantly, such improvements were present as soon as participants began executing the sequence task in the retest session. This suggests that performance gains were not due to data averaging across trial blocks, hence masking a simple end product of continued learning within that session (12), but rather that they reflect the expression of a real motor memory consolidation process.

By contrast, the amount of savings observed on the MA task was similar in both night/sleep and day/awake groups, thus implying that time alone is necessary, but sufficient, for consolidation of that memory trace to occur (2, 13, 15). The latter results do not corroborate those of Huber and colleagues (6) who reported evidence of a sleep-dependent consolidation effect on a rotation adaptation task, but this apparent discrepancy may be explained by methodological differences in the two studies, as they differed in terms of their demands on upper-arm effectors and extent of kinematic adaptation needed.

Although the design of the present study does not allow us to exclude entirely the possibility of circadian influences on our

pattern of results, most of the evidence to date suggests that such a confounding factor does not seem to play a major role in motor memory consolidation. Indeed, our own behavioral and imaging data did not yield any significant functional difference between the first evening and morning sessions. Gains in performance on motor sequence learning have also been demonstrated after diurnal sleep (3) or following an afternoon nap of 90 min (16), hence suggesting further that the present results are probably not due to circadian effects, but rather to the sleep-dependent consolidation process of a motor memory trace.

Motor Memory Consolidation: Functional Imaging Data. The present study demonstrates that, as predicted, the effects of sleep and passage of time on motor memory consolidation of skills measuring MSL or MA are associated with distinct neuronal changes. For the MSL task, activity within the basal ganglia (and in the putamen, in particular) was significantly greater during the retest session in subjects who slept than in those who did not. Brain regions involved in the execution of the task after sleep included the striatum, as well as the cerebellum (lobules IV, V, and VIII), bilateral primary motor cortex, the right sensory cortex, and the SMA. Yet, only the striatal activity was strongly influenced by a night of sleep relative to daytime. Because scanning did not take place during sleep, it is not possible to state whether the striatum has an active role during sleep or appears as a consequence of it. Nevertheless, our results suggest that this structure does not only reflect the consolidation of a newly learned sequence of movements (6, 7, 17, 18), but that this physiological process is facilitated by sleep. Indeed, increases of activity within the striatum have previously been related to the acquisition of wrist movement sequences (19–21) per se, as well as the learning of MSL, as opposed to the mere increase in speed of finger movements (22). Moreover, such increase in striatal activity has also been seen following motor memory consolidation when sleep (10), or a 24-h delay including sleep is present after initial learning (23). Altogether, these findings suggest that

authors reported that the corticocerebellar and corticostriatal systems known to be involved in the acquisition phase of motor skills interact early on during wakefulness after subjects have been trained on a MSL task. Although conjectural, a similar interplay between these two neuronal systems might explain the behavioral savings seen on the MA task after a 12-h delay during daytime. As it is, our experimental design does not allow us to test this hypothesis directly, but it is possible that the cerebellar activation seen in the retest session corresponds to the end result of an interaction between these systems, a supposition that is consistent with Doyon's model of cerebral plasticity associated with motor skill learning (7, 8).

Finally, why are some motor learning processes dependent on sleep for consolidation to occur, whereas others are not? One possible answer to that question relies on the difference in the acquisition mechanisms necessitated between our two motor tasks. Indeed, MSL was based upon explicit mnemonic processes as the subject had prior declarative knowledge of the sequence, whereas learning during MA was implicit in nature. Indeed it has been suggested that an explicit strategy for MA would be counterproductive (32). Such dissociation has previously revealed sleep effect differences in the consolidation of motor sequences (33, 34), and could thus explain the results reported above on the basis of our versions of the MSL and MA tasks. Furthermore, considering that "replay mechanisms" are critical for memory consolidation to take place, this suggests that time alone would permit implicit information acquired during MA practice to be replayed and consolidated, as it could be done in parallel to our everyday conscious activities. By contrast, replay of motor sequence representations acquired through explicit mechanisms could interfere with our thought processing during daytime, and thus requiring sleep for a reorganization of the neural network involved in MSL. Alternatively, another possible answer to the sleep/no-sleep issue in motor memory consolidation comes from our own results, which suggest that such effects could be due to differences in neural networks supporting these mnemonic functions. Processes dependent on the striatum would rely on sleep, whereas others dependent upon the cerebellum would rely on daytime alone. Although probable, however, such a working hypothesis awaits further experimental investigation.

Methods

Subjects. Forty-eight young healthy subjects (mean age 23.0 y, 32 women) participated in the present study. They were divided into four groups: MSL night/sleep ($n = 13$; mean age 23 y, eight women), MSL day/awake ($n = 11$; mean age 24 y, six women), MA night/sleep ($n = 12$; mean age 22 y, nine women), and MA day/awake ($n = 12$; mean age 25 y, nine women). Additional details on the specifications for the participants' selection can be found in *SI Methods*. They gave their written informed consent to participate in the study. The project was approved by the Regroupement Neuroimagerie/Québec Ethics Committee at the Montreal Geriatric Institute.

Experimental Design. To compare the effects of sleep and passage of time on the consolidation of both motor sequence and motor adaptation tasks, and to identify the neural correlates mediating the consolidation process of each type of motor skill, between-subject (night/sleep–day/awake) and within-subject conditions (test and delayed retest) were implemented. In the night/sleep group, subjects were first trained in the evening (9:00 PM approximately) on one of the two motor tasks in a mock scanner and reached asymptotic performance. Following this training session, subjects were moved to the MRI room and scanned using a blocked design paradigm while executing the recently learned task. They then slept in the laboratory while polysomnographies (PSGs) were acquired (data not reported here) and participants were scanned the following morning 12 h after (9:00 AM approximately) in a retest session. In the day/awake group, subjects were trained around 9:00 AM in the simulator and scanned after. They were then required to spend 12 h in the laboratory under supervision (during which they could only read or watch television) and were retested in a second scanning session around 9:00 PM (Fig. 1A).

Behavioral Paradigms. Motor sequence learning task. A modified version of the finger tapping task (35) with a fixed number of sequences per block was used to control for the number of movements executed during the training and scanning sessions. The sequence 4-1-3-2-4 (1 being the index) was explicitly known to the subjects from the start and was executed with the nondominant hand using an MRI-compatible response box (custom made key pad) (Fig. 1B). The training, immediate posttraining (test), and delayed retest sessions consisted of eight blocks of 20 sequences each. Once the training was completed, subjects entered the MRI room. All experimental blocks started with a 2.5-s instruction where the word "sequence" appeared in the middle of the screen, followed by a green square indicating that subjects could start producing the known sequence as fast and accurately as possible. After having completed 20 sequences, the color of the square changed to red to indicate the beginning of a 15-s rest period. TpS and the number of correct sequences were recorded for each block.

Motor adaptation task. A version of an eight-target tracking task (2) was used to measure motor adaptation (Fig. 1B). In this task, subjects are required to manipulate a joystick with their dominant hand, to move a cursor positioned at the center of the screen to one of eight targets (separated by 45°) following an elliptical trajectory. Contrary to the MSL task, the dominant hand was chosen here to be able to compare our results to those from the motor adaptation literature, and because the results of the two tasks were never compared directly. The experimental task consisted of a "reversed mode," where the relation between movements with the joystick and direction of the cursor were inverted by 180° on each trial. The training was done in the MR simulator room and consisted of 10 blocks of 64 trials to make sure that all subjects had reached asymptotic performance. Once lying down in the scanner with the joystick apparatus on their stomach, subjects could then watch the projection of the instructions and targets to be reached displayed on the screen via the inverted mirrors. During the immediate posttraining test and delayed retest sessions, subjects were required to complete four runs comprising three blocks of 16 trials each. Each block of trials was followed by a 32-s "perceptual" condition where subjects were simply asked to observe (without making movements) the ideal elliptical trajectories that they needed to execute for reaching each target in the previous block of trials. Each trial began with a white circle (0.75 cm in diameter) in the middle of the screen followed by the appearance of a small green-square cursor superimposed on top of the starting point. The target represented by a red square (1.5 cm large) was displayed 10 cm away from the starting point, and an elliptical line (0.5 cm in thickness; 2.5 cm of radius) joining the starting point and the target were both displayed at the same time. Targets appeared randomly within the eight target locations, constituting one cycle. Subjects were instructed to reach the target as fast and accurately as possible within a time limit of 2,900 ms and to stay on the target for 100 ms. If subjects reached the target on time, the color of the red square changed to green, whereas if subjects had not reached the target on time, the target disappeared and the trial was considered an error. (Please see *SI Methods* for further information on the behavioral data analysis approaches.)

MRI Acquisition and Analysis. Brain imaging data were obtained with a 3T scanner (Magnetom Trio, Siemens AG), equipped with an eight-channel head coil. A high resolution anatomical T1-weighted scan was acquired for each subject (voxel size = $1 \times 1 \times 1 \text{ mm}^3$; TR = 23 ms, TE = 2.98 ms, FA = 90°; FOV = $256 \times 240 \text{ mm}^2$; matrix 256×256 ; 176 slices). Functional T2*-weighted images were also acquired using a gradient echo-planar sequence sensitive BOLD signal (voxel size = $3.75 \times 3.75 \times 5 \text{ mm}^3$; TR = 2.5 s for MSL (28 volumes) and 3.2 s for MA tasks (28 volumes); TE = 30 ms; FA = 90°; FOV = $240 \times 240 \text{ mm}^2$, matrix size = 64×64 ; 28 slices). A different TR was used for scanning subjects in the two tasks to equate the number of volumes acquired in each block of trials. Data were analyzed with SPM 2 software (<http://www.fil.ion.ucl.ac.uk/spm/software>). Preprocessing steps included the realignment, coregistration of functional and anatomical images, slice timing correction, spatial normalization into the MNI-152 stereotaxic space, and smoothing using a Gaussian kernel of 6 mm full-width at half maximum (FWHM). Consistent with the behavioral analyses, fMRI analyses for the MSL task comprised only the functional volumes obtained in the last five blocks of the immediate posttraining test and the first five blocks of the retest. By contrast, all of the volumes were included in the analyses of the MA task.

Statistics were derived on the basis of the general linear model. First, an intraindividual analysis tested the effects of interest, using linear contrasts convolved with a standard canonical hemodynamic response function (HRF), generating statistical parametric maps. Movement parameters derived from realignment of the functional volumes were not included as it is not recommended when using a block design and manual responses (36). Linear contrasts estimated the main effects of either the MSL or MA task, relative

to its respective baseline, as well as the main effect of sleep (night_{delayed retest} > night_{immediate posttraining}) or passage of time (day/awake_{delayed retest} > day/awake_{immediate posttraining}). For both tasks, the baseline consisted of their respective rest period. The statistical images obtained at the individual level were then entered into a random-effects model. Participants were put in their respective groups (night/sleep and day/awake), and these were modeled as two distinct regressors of interest. For both tasks, commonalities between the day/awake and night/sleep groups during the immediate posttraining test were assessed by a global conjunction analysis revealing activity levels that were jointly significant in the two groups (night/sleep_{immediate} ∩ day/awake_{immediate}). We also assessed whether there were common changes between the night/sleep and day/awake groups in both test and retest sessions using another conjunction analysis based on the results of the delayed retest > immediate posttraining test contrast (night/sleep_{delayed} > immediate ∩ day/awake_{delayed} > immediate). Similarly, for both tasks, we assessed group × session interactions (night/sleep_{delayed} > immediate > day/awake_{delayed} > immediate) to assess any specific effect of sleep as opposed to the simple passage of time on motor memory consolidation of both motor tasks. To further assess the relationship between brain regions of the motor

network and the behavioral reflection of consolidation, multiple regression analyses were carried out on the interaction and the conjunction contrast analyses for the MSL and MA tasks, respectively. The gain in Tps was used as the predictor for the MSL task, whereas the amount of savings served as the predictor for the MA task. All activation maps reported below are displayed at $P < 0.001$ to better display the extent of the activity. Results that were significant at $P \leq 0.05$ after false discovery rate (FDR) correction (37) for the whole brain volume are also reported in Table 1, and Tables S1 and S2. Because we formulated strong a priori hypotheses, we then used small volume correction (svc, radius = 10 mm) for a structure of interest in which correction over the whole brain volume was too strict (cerebellum, 28, -74, -18 mm; ref. 38). In that case, we used familywise error (FWE) correction as it is known to better control for false positives than FDR (39).

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