# Fonctions du sommeil

# Memory processing during human sleep as assessed by functional neuroimaging

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## SUMMARY

Sleep is believed to participate in memory consolidation, possibly through off-line processing of recent memory traces. In this paper, we summarize functional neuroimaging data testing this hypothesis. First, sleep deprivation disrupts the processing of recent memory traces and hampers the changes in functional segregation and connectivity which underpin the gain in performance usually observed in subjects allowed to sleep on the first post-training night.

Second, experience-dependent changes in regional brain activity occur during post-training sleep. These changes are shown to be related to the processing of high-level material and to be modulated by the amount of learning achieved during the training session. These changes do not involve isolated brain areas but entire macroscopic cerebral networks. These data suggest a role for sleep in the processing of recent memory traces.

**Évaluation du traitement de la mémoire pendant le sommeil par neuroimagerie fonctionnelle.**
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## RÉSUMÉ

Il se pourrait que le sommeil intervienne dans le traitement des traces mnésiques fraîches, en particulier dans leur consolidation. Dans cet article, nous résumons l'apport de la neuroimagerie fonctionnelle dans l'évaluation de cette hypothèse chez l'homme. Ainsi, nous montrons que la privation de sommeil empêche les modifications de ségrégation et d'intégration fonctionnelles qui suivent l'apprentissage d'une tâche et qui, en règle, accompagnent l'amélioration de la performance à cette tâche. Nous montrons par ailleurs que l'activité cérébrale régionale durant le sommeil dépend de l'expérience acquise au préalable par le sujet à l'éveil. L'ensemble de ces résultats sont en faveur de l'hypothèse testée.

## INTRODUCTION

Sleep is believed to participate in memory consolidation, possibly through off-line processing of recent memory traces. Accordingly, regional brain function during sleep, far from being fixed and stereotyped, is modulated by the individual experience acquired during the previous waking period (for review, see Maquet, 2001). Two kinds of experiments are described below. The first study shows that sleep deprivation during the first post-training night hampers the changes in regional brain segregation and integration that usually underpin the gain in performance in subjects allowed to sleep on this particular night. The second type of studies demonstrates changes in brain activity and functional connectivity during the post-training sleep, in relation to learning. These results provide the first experimental evidence in humans for a link between learning, as measured by behavioural methods, and the activity of neuronal populations during sleep.

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## INFLUENCE OF SLEEP
## VERSUS SLEEP DEPRIVATION
## ON RECENT MEMORY TRACES

In a functional magnetic resonance imaging (fMRI) study (Maquet et al., 2003), we compared learning-dependent changes in regional brain activity after sleep or sleep deprivation using a pursuit task (PT). We trained the participants on a particular version of the PT (Frith, 1973) in which the target trajectory was predictable on the horizontal but not on the vertical axis. Half of the subjects were totally sleep deprived during the first post-training night. Three days later, during a fMRI scanning session, they were exposed to the previously learned trajectory and also to a new one in which the predictable axis was vertical. This experimental design allowed for the assessment of the effects of learning on brain activity, using within-subject comparisons between learned and new conditions.

Our objective was to provide evidence that sleep deprivation disrupts the slow processes that lead to memory consolidation. In contrast to others (e.g., Drummond et al., 2000), we were not aiming to characterize the immediate effect of sleep deprivation on human performance or cognition. This is the reason why we adopted an experimental protocol where both sleeping and sleep deprived subjects were retested after at least two complete nights of sleep, i.e. in a state of arousal that was similar across the two groups, and between the training and retest sessions (Stickgold et al., 2000).

Behaviourally, the time on target was used as the metric of subjects'performance. The time on target was comparable for the two groups during the scanning session, irrespective of the trajectory. The time on target was larger for the learned trajectory than for the new one in both groups. However, the difference in time on target was significantly larger in the group of subjects who slept than in the subjects who were sleep deprived on the first post-training night. These results suggest that performance gain is maximal only in subjects allowed to sleep on the first post-training night.

The analysis of fMRI data showed a significant effect of learning (irrespective of the group) in the left supplementary eye field and in the right dentate nucleus. The group by trajectory interaction was significant in the right superior temporal sulcus (STS). This suggests that STS is more active for the learned than the new trajectory, and more so in subjects allowed to sleep on the first post-training night than in subjects deprived of sleep during this night. Interestingly, the functional connectivity of the dentate nucleus and the supplementary eye field was different in the two groups of subjects. The dentate nucleus was more closely linked to the STS, and the supplementary eye field to the frontal eye field for the learned than for the new trajectory, and more so in subjects who slept during the first post-training night.

Taken together, these data suggest that the performance on the PT heavily relies on the subject's capacity to learn

the motion patterns of the trajectory in order to program the optimal pursuit eye movements. Indeed, interactions between temporal cortex and the cerebellum as well as between the FEF and the SEF are both implicated in conventional pursuit eye movement pathways (Krauzlis and Stone, 1999). More to our point, the data suggest that sleep deprivation during the first post-training night disturbs the slow processes that lead to the acquisition of this procedural skill and hampers the related changes in connectivity that are usually reinforced in subjects allowed to sleep on the first post-training night.

## EXPERIENCE-DEPENDENT
## CEREBRAL REACTIVATIONS
## DURING HUMAN REM SLEEP

If sleep plays a role in memory trace processing, changes in activity should be observed during post-training sleep in the neuronal populations involved in the learning of a particular task. In this positron emission tomography (PET) study, we trained subjects to an implicit learning task, the probabilistic serial reaction time task, which allowed both a quantitative measure of implicit learning and massive training of the participants without any ceiling effect (Cleeremans and McClelland, 1991). In this task, participants face a computer screen where six permanent position markers are displayed above six spatially compatible response keys. On each trial, a black circle appears below one of the position markers, and the task consists of pressing as fast and as accurately as possible on the corresponding key. The next stimulus is displayed at another location after a 200 ms response-stimulus interval. Unknown to participants, the sequential structure of the material was manipulated by generating series of stimuli based on a probabilistic finite-state grammar that defines legal transitions between successive trials. To assess learning of the probabilistic rules of the grammar, there is a 15p. cent chance, on each trial, that the stimulus generated based on the grammar (grammatical stimuli, G) was replaced by a non-grammatical (NG), random stimulus. Assuming that response preparation is facilitated by high predictability, predictable G stimuli should thus elicit faster responses than NG stimuli, but only if the context in which stimuli may occur has been encoded by participants. In this task, contextual sensitivity emerges through practice as a gradually increasing difference between the reaction times (RTs) elicited by G and NG stimuli occurring in specific contexts set by two to three previous trials at most (Cleeremans and McClelland, 1991).

In order to observe the reactivation of brain areas during post-training sleep, we designed a multi-group experiment (Maquet et al., 2000). A first group of subjects (group 1) were scanned during wakefulness both while they were performing the SRT task and at rest. The comparison provided a list of the brain areas that are activated during the execution of the SRT task. A second group of subjects (group 2) were trained on the task in the afternoon, then scanned

during the post training night, both during waking and in various sleep stages (i.e., SWS, stade 2 and REM sleep). A post-sleep training session verified that learning had occurred overnight. Here, the analysis of PET data identified the brain areas more active in REM sleep than during resting wakefulness. To ensure that the post-training REM sleep regional cerebral blood flow (rCBF) distribution differed from the pattern of "typical" REM sleep, a third group of subjects (group 3), not trained to the task, were similarly scanned at night, both awake and during sleep. The analysis was aimed at detecting the brain areas that would be more active in trained *vs* non trained subjects, and in REM sleep as compared to resting wakefulness. And finally, to formally test that these brain regions, possibly reactivated during REM sleep, would be among the structures that had been engaged by executing and learning the task, a conjunction analysis was performed. This analysis identified those regions that would be *both* more active during REM sleep in the trained subjects (group 2) compared to the non-trained subjects (group 3) *and* activated during the execution of the task during waking (group 1). Our results showed that the cuneus and adjacent striate cortex (bilaterally), mesencephalon and left premotor cortex were both (1) activated during the practice of the SRT task and (2) during post-training REM sleep in subjects previously trained on the task (significantly more than in control subjects without prior training), suggesting a re-activation process which may have contributed to overnight performance improvement in the SRT task.

These reactivated areas participate in macroscopic cerebral networks. In consequence, during post-training sleep, they should establish or reinforce functional connections between parts of the network activated during the task. Such connections should be stronger, and the synaptic trafficking between network components more intense during post-training REM sleep than during the "typical" REM sleep of non trained subjects. Accordingly, we found that among the reactivated regions, the rCBF in the left premotor cortex was significantly more correlated with the activity of the pre-SMA and posterior parietal cortex during post-training REM sleep than during REM sleep in subjects

without any prior experience with the task (Laureys *et al.*, 2001).

## CONCLUSIONS

Functional neuroimaging during post-training sleep provides direct evidence for experience-dependent changes in regional brain activity. These changes are likely to be task-dependent. They were shown to be related to the processing of high-level material and to be modulated by the amount of learning achieved during the training session. These changes do not involve isolated brain areas but entire macroscopic cerebral networks. In contrast, sleep deprivation disrupts the processing of recent memory traces and hampers the changes in functional connectivity which underpin the gain in performance usually observed in subjects allowed to sleep on the first post-training night.

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