The PHYSIOLOGIC NATURE OF SLEEP

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Imperial College Press

This book provides a broad introduction to the fascinating subject of sleep, a behavioral state in which human beings spend a third of their life span, and a topic which interests not only the specialist but also the layperson. Everybody knows that well-being also depends on undisturbed, normal sleep.

The Physiologic Nature of Sleep is self-contained in presentation. It may be used as an advanced textbook by graduate students and even ambitious undergraduates in biology, medicine and psychology. It is also suitable for the expert hypnologist who wishes to have an overview of some of the classic and fundamental achievements in sleep research. The explanations in the book are detailed enough to capture the interest of the curious reader, and complete enough to provide the necessary background material needed to go further into the subject and explore the research literature.

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The abstract painting on the front cover by Joaquín Torres García broadly represents the many aspects of the sleep-wake cycle, including the sun, the moon, man and woman, etc. Source: "Arte Universal," 1943. Museo Nacional de Artes Visuales, Monetvideo, Uruguay.

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Chapter 6

BRAIN IMAGING ON PASSING TO SLEEP

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Sleep deeply modifies the regulation of most physiological systems (Orem and Keeling, 1980). However, during sleep, no functional changes are more profound than in the central nervous system, for the very reason that the brain generates and maintains sleep and its alternation with wakefulness. The inescapable recurrence of sleep periods suggests that processes beneficial and necessary for normal brain function are taking place during sleep. A large part of sleep research is precisely to investigate these processes at the molecular, cellular, network, and systems levels. Despite this remarkable research effort, a comprehensive understanding of the functions of sleep remains elusive.

In humans, the characterisation of brain function is only possible through neurophysiological [e.g., electro-encephalography (EEG) and magneto-encephalography (MEG)] and hemodynamic [e.g., single-photon emission computed tomography (SPECT) and positron emission tomography (PET), functional magnetic resonance imaging (fMRI)] behavioural measurements. In this chapter, we provide an account of the functional neuroanatomy of non-rapid eye movement (NREM) and rapid-eye-movement (REM) sleep. Early studies showed that the distribution of brain activity is

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specific for each type of sleep, and differs from the waking pattern of brain activity. While the activity of subcortical structures is easily explained by the mechanisms which generate REM sleep and NREM sleep in animals, the distribution of the activity within the cortex remains harder to explain and its origin remains speculative.

Recently, a more dynamic characterisation of sleep has emerged. For instance, it was shown that cerebral responses in response to external auditory stimulations persist in NREM sleep. Likewise, regional brain function during sleep has been shown to be modulated by new experience acquired during previous wakefulness. The latter findings support the view that plastic brain changes are taking place during sleep. They suggest that sleep has a role in the behavioural adaptation to changing environmental conditions, thereby favouring the survival of the individual.

Regional Brain Activity during Human Sleep

NREM sleep (slow-wave sleep)

In mammals, the neuronal activity observed during NREM sleep oscillations (spindles, delta, and slow rhythms) is characterised by bursting patterns which alternate short bursts of firing with long periods of hyperpolarisation (Steriade and Amzica, 1998). The latter have a major impact on the regional blood flow, which on the average decreases in the areas where these oscillations are expressed. These decreases in blood flow and metabolism reflect more a change in the temporal patterns of neuronal activity (i.e., a bursting pattern) than an actual decrease in average neuronal firing rate. Accordingly, as compared to wakefulness, the average cerebral metabolism and blood flow begin to decrease in light (stage 2) NREM sleep (Madsen *et al.*, 1991a, 1992), and their nadir is observed in deep (stages 3 and 4) NREM sleep or slow-wave sleep (SWS) (Maquet *et al.*, 1990; Madsen *et al.*, 1991b) (Figure 1A).

The cascade of events which underpin the NREM sleep oscillations in the thalamo–neocortical networks is conditional upon a decreased firing in the activating structures of the brainstem tegmentum. In humans, the brainstem blood flow is decreased during light NREM sleep (Kajimura *et al.*, 1999) as during SWS (Braun *et al.*, 1997; Maquet *et al.*, 1997; Kajimura *et al.*, 1999). In light NREM sleep, the pontine tegmentum is specifically deactivated, whereas the mesencephalon seems to retain an activity which is not significantly different from wakefulness (Kajimura *et al.*, 1999). In SWS, both pontine and mesencephalic tegmenta are deactivated.

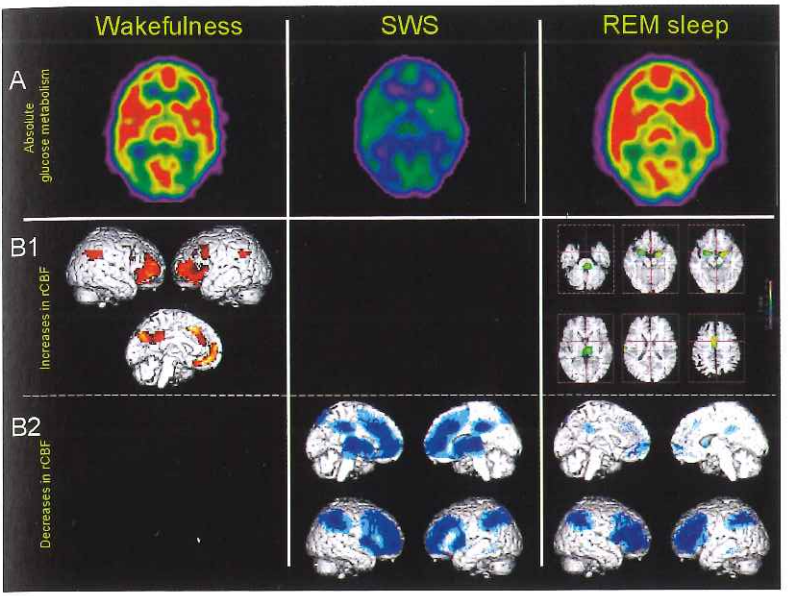

Figure 1. Glucose metabolism and regional cerebral blood flow (rCBF) during wakefulness (first column), deep NREM sleep (second column), and REM sleep (third column). (A) Cerebral glucose metabolism quantified in the same individual at 1-week interval, using fluorodeoxyglucose and PET. The three images are displayed at the same brain level using the same colour scale. There is a significant decrease in the average glucose metabolism during deep NREM sleep as compared to wakefulness. During REM sleep the glucose metabolism is as high as during wakefulness (Maquet *et al.*, 1990). (B1) Distribution of the highest regional brain activity, as assessed by CBF measurement using PET, during wakefulness and REM sleep. The most active regions during wakefulness are located in the polymodal associative cortices in the pre-frontal and parietal lobes (both on the medial wall and convexity) (Maquet, 2000). During REM sleep, the most active areas are located in the pontine tegmentum, the thalami, the amygdaloid complexes, and the anterior cingulate cortex (Maquet *et al.*, 1996). Other data (not shown) have shown a large activity in the occipital cortices, the insula, and the hippocampus (Braun *et al.*, 1997). (B2) Distribution of the lowest regional brain activity, as assessed by CBF measurement using PET, during NREM and REM sleep. In both sleep stages, the least active regions during wakefulness are located in the polymodal associative cortices in the pre-frontal and parietal lobes (convexity). During NREM sleep, the brainstem and thalami are also particularly deactivated.

The thalamus plays a central role in the generation of NREM sleep rhythms, due to the intrinsic properties of its neurons and to the intra-thalamic and thalamo–cortico–thalamic connectivity. Expectedly, in humans, the thalamus is deactivated during both light and deep NREM sleep (Braun *et al.*, 1997; Maquet *et al.*, 1997; Kajimura *et al.*, 1999), in

proportion to the power density in the spindle and delta frequency range (Hofle *et al.*, 1997), respectively.

The role of the cortex in the generation of NREM sleep oscillations is equally important and begins to be better understood (Steriade and Amzica, 1998). However, the respective contribution of the different parts of the neocortex in the generation of NREM sleep rhythms is still unknown at the microscopic level. In humans, the deactivation of the cortex is not homogeneous. When compared to wakefulness, the most deactivated areas are located in associative cortices of the frontal, parietal, and to a lesser extent temporal and insular lobes (Braun *et al.*, 1997; Maquet *et al.*, 1997; Andersson *et al.*, 1998; Kajimura *et al.*, 1999), while the primary cortices are the least deactivated.

Polymodal association cortices are the most active cerebral areas during wakefulness (Maquet, 2000). Because of this high waking activity, they might be more profoundly influenced by SWS rhythms than primary cortices (Maquet, 2000), local sleep intensity being homeostatically related to prior waking activity (Kattler *et al.*, 1994).

On the other hand, sleep is not a state of complete unresponsiveness to external stimuli. The first cortical relay areas for exteroceptive stimuli remain relatively active during NREM sleep. In cats involved for some time in an active visual task, neurons in the associative visual cortex can adopt a bursting pattern typical for the sleeping cortex and become less responsive to visual stimulation, while the primary visual areas maintain a normal response to visual inputs (Pigarev *et al.*, 1997). In humans, external stimuli can induce an autonomic or electrophysiological response, in particular after a relevant or meaningful stimulus presentation (Bonnet, 1982). Studies on event-related potentials (ERPs) have demonstrated that external information is efficiently processed during sleep. The brainstem auditory evoked potentials are not modulated by the vigilance state, but rather by the circadian variations of the body temperature, whereas the middle-latency evoked potentials are found to be reduced during deep sleep (Bastuji and García-Larrea, 1999). Long-latency components are also observed during sleep, but are modulated by the sleep stage. During NREM sleep (and especially in stage 2 sleep), ERPs correspond to K-complexes, which are differently affected by the characteristics of the stimulus, the early ones being more connected to the physical attributes of the stimulus and the latter ones to its intrinsic significance (Perrin *et al.*, 2000). Likewise, an fMRI study has shown that the presentation of auditory stimuli activates bilaterally the thalamus and the auditory cortex, during NREM sleep as

well as during wakefulness (Portas *et al.*, 2000). Furthermore, hearing one's own name (as compared to hearing a neutral pure tone) additionally activates the left amygdala and prefrontal (associative) cortex. These results suggest that the processing of external stimuli can go beyond the primary cortices during NREM sleep. The mechanisms by which salient stimuli can recruit associative cerebral areas during sleep remain unclear.

REM sleep (paradoxical sleep)

REM sleep is characterised by sustained neuronal activity (Steriade and McCarley, 1990; Jones, 1991) and, correspondingly, by high cerebral energy requirements (Maquet *et al.*, 1990) and blood flow (Madsen *et al.*, 1991c; Franzini, 1992). In this sleeping but working brain, some areas are more active than others; in contrast, other regions have lower than average regional activity.

Neuronal populations in the mesopontine tegmentum are the source of a major activating input to the thalamic nuclei during REM sleep (Steriade and McCarley, 1990). The thalamus forwards this activation to the entire forebrain. Accordingly, in humans, the activation of mesopontine tegmentum and thalamic nuclei has been systematically reported during REM sleep (Maquet *et al.*, 1996; Braun *et al.*, 1997; Nofzinger *et al.*, 1997).

In the forebrain, PET data showed that limbic and paralimbic areas (amygdala, hippocampal formation, anterior cingulate, orbito-frontal, and insular cortices) were among the most active areas in REM sleep (Figure 1B1). Temporal and occipital cortices were also shown to be very active (Braun *et al.*, 1997), although this result is less reproducible (Maquet *et al.*, 1996). In contrast, the prefrontal and parietal areas are relatively quiescent during REM sleep (Maquet *et al.*, 1996; Figure 1B1).

The functional connectivity between brain areas is modified during human REM sleep. The functional relationship between striate and extrastriate cortices, usually excitatory, is inverted during REM sleep (Braun *et al.*, 1998). Likewise, the functional relationship between the amygdala and the temporal and occipital cortices is different during REM sleep than during wakefulness or NREM sleep (Maquet and Phillips, 1998).

The reasons of these changes in the cortical activity patterns remain unclear. A change in neuromodulation might participate to a modification of the forebrain activity and responsiveness during REM sleep, as REM sleep is characterised by a prominent cholinergic tone and a decrease in noradrenergic and serotonergic modulation (Steriade and McCarley, 1990).

Unfortunately, at present, there is no report exploring how changes in the neuromodulation may affect the regional brain function during REM sleep.

The influence of pontine waves or ponto-geniculo-occipital (PGO) waves should also be considered. Several observations suggest that PGO waves also occur during human sleep. In epileptic patients, direct intra-cerebral recordings in the striate cortex showed mono-phasic or di-phasic potentials during REM sleep, isolated or in bursts (Salzarulo *et al.*, 1975). In normal subjects, surface EEG revealed transient occipital and/or parietal potentials time-locked to REMs (McCarley *et al.*, 1983). Source dipoles of MEG signal were localised in the brainstem, thalamus, hippocampus, and occipital cortex during REM sleep (Inoue *et al.*, 1999).

We also tried to get some evidence that activities like pontine or PGO waves exist in humans and result in a hemodynamic signal detectable by PET and cerebral blood flow (CBF) measurements. Since REMs during sleep have been shown to correlate with the occurrence of the so-called PGO waves in cats, we reasoned that the presence of such waves in humans implies that the neural activity of the brain regions from which PGO waves are the most easily recorded in animals (i.e., the dorsal meso-pontine tegmentum, the lateral geniculate bodies, and the occipital cortex) should be more tightly related to spontaneous ocular movements during REM sleep than during wakefulness. We confirmed this hypothesis by showing that the activity in the lateral geniculate body and the occipital cortex is related to REMs more closely during sleep than during wakefulness (Peigneux *et al.*, 2001b). These results support the assumption that pontine or PGO waves do exist in humans. This finding has important functional implications. In rats, the generator of the pontine waves, which has been located in the dorsal part of the subcoeruleus nucleus, projects to a set of brain areas shown to be active in human REM sleep: the occipital cortex, the entorhinal cortex, the hippocampus, the amygdala, as well as brainstem structures participating in the generation of REM sleep (Datta *et al.*, 1998). In cats, although most easily recorded in the pons (Jouvet, 1967), the lateral geniculate bodies (Mikiten *et al.*, 1961), and the occipital cortex (Mouret *et al.*, 1963), PGO waves are observed in many parts of the brain (Hobson, 1964), including limbic areas (amygdala, hippocampus, cingulate gyrus). Taken together, these various experimental elements warrant the hypothesis that activities similar to pontine or PGO waves play a prominent role in shaping the distribution of regional brain activity during REM sleep in humans. This finding is potentially important, for PGO waves have been implicated in various non-exclusive processes such as the alerting reaction to external

stimuli or internal signals (Bowker and Morrison, 1976), sensorimotor integration through the transmission of an efferent copy of ocular movements to the visual system (Callaway *et al.*, 1987), and facilitation of brain plasticity (Datta, 1999).

Finally, it is important to stress that these changes in regional brain activity may have a profound impact on other physiological systems. For instance, heart rate is conspicuously more variable during REM sleep than during wakefulness. We were recently able to show that the large variability in heart rate during REM sleep is specifically related to the activity in the amygdaloid complexes (Desseilles *et al.*, in preparation).

Experience-Dependent Changes in Functional Connectivity during Post-Training Sleep

Sleep is believed to participate in the consolidation of memory traces (Maquet, 2001; Peigneux *et al.*, 2001a). Although the processes of this consolidation remain unknown, the reactivation during sleep of neuronal ensembles activated during learning appears as a possible mechanism for the off-line memory processing. Such a reactivation has been reported in at least two experimental situations: in the rat hippocampus and cortex (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Kudrimoti *et al.*, 1999; Nadasdy *et al.*, 1999; Ribeiro *et al.*, 1999; Louie and Wilson, 2001; Lee and Wilson, 2002) and in the song area of young zebra finches (Dave and Margoliash, 2000). This suggests the generality of the reactivation in the processing of memory traces during sleep. In order to observe the reactivation of brain areas during post-training sleep in humans, we designed a multi-group experiment (Maquet *et al.*, 2000). Normal subjects were trained on a probabilistic serial reaction time (SRT) task. In this task, six permanent position markers are displayed on a computer screen 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 the subjects, the sequential structure of the material is manipulated by generating a 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 15% chance, on each trial, that the stimulus generated based on the grammar [grammatical (G) stimuli] is 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). A first group of subjects (group 1) were trained on the SRT task in the afternoon, then scanned during the post-training night, both during waking and during various sleep stages (i.e., SWS, stage 2, and REM sleep). A post-sleep training session verified that learning had occurred overnight. The analysis of PET data identified the brain areas that are more active in REM sleep than during resting wakefulness. To ensure that the post-training REM sleep regional CBF (rCBF) distribution differed from the pattern of "typical" REM sleep, a second group of subjects (group 2), not trained to the task, was similarly scanned at night, both when awake and during sleep. The analysis was aimed at detecting the brain areas that would be more active in trained than in non-trained subjects, during 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 third group of subjects (group 3) were scanned during wakefulness both while they were performing the SRT task and at rest. The comparison described the brain areas that are activated during the execution of the SRT task. And finally, a conjunction analysis identified the regions that would be both more active during REM sleep in the trained subjects (group 1) compared to the non-trained subjects (group 2) and activated during the execution of the task during waking (group 3), i.e., the regions reactivated in post-training REM sleep. Our results showed that the bilateral cuneus and the adjacent striate cortex, the mesencephalon and the left pre-motor cortex were both activated during the practice of the SRT task and during post-training REM sleep in subjects previously trained on the task, significantly more than in control subjects without prior training, suggesting a reactivation process which may have contributed to overnight performance improvement in the SRT task. In addition, we reasoned that, if the reactivated regions participate in the processing of memory traces during REM sleep, they should establish or reinforce functional connections between parts of the network activated during the task. Consequently, 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 pre-motor cortex was significantly more correlated with the activity of the pre-supplementary motor area (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). The demonstration of a differential functional connectivity during REM sleep between remote brain areas engaged in the practice of a previously experienced visuo-motor task gave further support to the hypothesis that memory traces are replayed in the cortical network and contribute to the optimisation of the performance. It should be stressed that, in this first experiment, our conclusions were limited by the fact that we could not specify whether the experience-dependent reactivation during REM sleep was related to the simple optimisation of a visuo-motor skill or to the high-order acquisition of the probabilistic structure of the learned material, or both. To test the hypothesis that the cerebral reactivation during post-training REM sleep reflects the reprocessing of high-order information about the sequential structure of the material to be learned, a new group of subjects (group 4) was scanned during sleep after practice on the same SRT task, but using a completely random sequence (Peigneux *et al.*, 2003; Figure 2). The experimental protocol was identical in all respects to the trained group in our original study (Maquet *et al.*, 2000), except for the absence of sequential rules. Therefore, post-training rCBF differences during REM sleep between the subjects trained to the probabilistic SRT or to its random version should be related specifically to the reprocessing of the high-order sequential information.

During post-training REM sleep, blood flow in the left and right cuneus increased more in subjects previously trained to a probabilistic sequence of stimuli than to a random one. Since both groups were exposed prior to sleep to identical SRT practice that differed only in the sequential structure of the stimuli, our result suggests that reactivation of neural activity in the cuneus during post-training REM sleep is not merely due to the acquisition of basic visuo-motor skills, but rather corresponds to the reprocessing of elaborated information about the sequential contingencies contained in the learned material. If the material does not contain any structure, as is the case in the random SRT task, post-training REM sleep reactivation does not occur, or at least to a significantly lesser extent. These results are reminiscent of previous experiments. At the behavioural level, increase in REM sleep duration was observed in rats following aversive

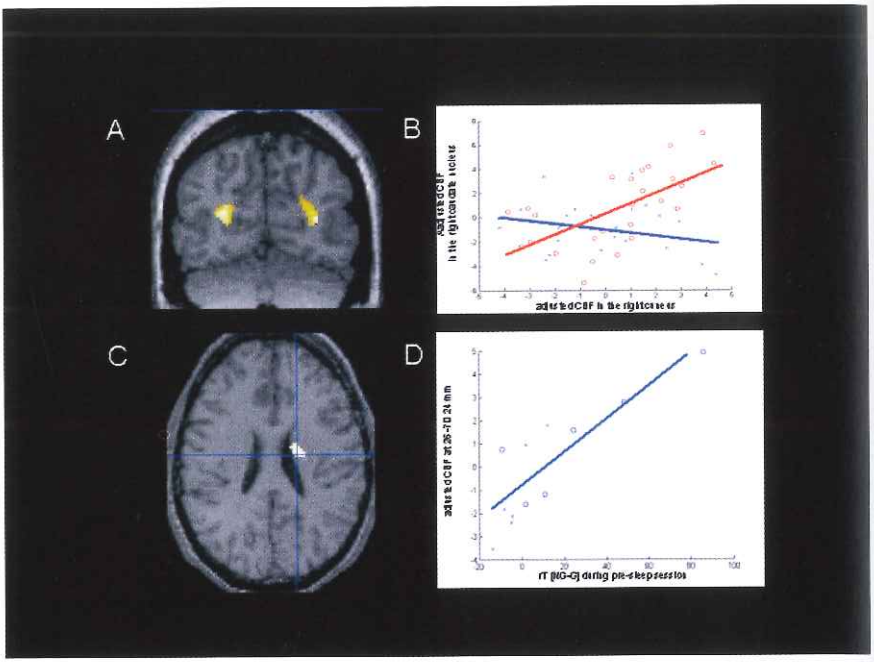

Figure 2. Probabilistic versus random serial reaction time task. (Data from Peigneux *et al.*, 2003.) (A) Statistical parametric maps of the brain regions that both activated during SRT practice (versus rest) and activated more during REM sleep (versus wakefulness) in the probabilistic rather than the random group, superimposed on the coronal section of a subject's normalised MRI at 68 mm behind the anterior commissure. The SPM is displayed at $p < 0.001$, uncorrected. (B) Plot of the regression of centred CBF in the right cuneus (32, −68, 12 mm) and right caudate nucleus (18, −12, 20 mm) during post-training REM sleep in subjects trained to the probabilistic SRT task (red circles) and subjects trained to the random SRT task (blue stars). (C) The right caudate nucleus, with which the right cuneus has a tighter functional connection in subjects trained to the probabilistic SRT task than in subjects trained to the random SRT task. A similar regression is observed between cuneus and caudate nucleus in the left hemisphere. The SPM is displayed at $p < 0.001$, uncorrected. (D) Regression of pre-sleep high-order performance on post-training REM sleep CBF (centred) in the right parieto-occipital fissure (coordinates 26, −70, 24 mm in standard anatomical space), in probabilistic SRT (circles) and random SRT (stars) subjects.

conditioning in which a tone is paired with a footshock, but not after pseudo-conditioning in which the tone and the footshock were not paired (Hennevin and Leconte, 1971).

Using a similar procedure at the systems level, tone-evoked responses were obtained in the medial geniculate nucleus (Hennevin *et al.*, 1993) during REM sleep after a conditioning procedure initiated at wake, but not after pseudo-conditioning. Likewise in humans, REM sleep percentage

increased after learning textbook passages, but only when they were meaningful (Verschoor, 1984). A similar situation occurred when the material to learn was so complex that its underlying structure cannot be extracted through practice. Consequently, during REM sleep, functional connections should be reinforced between the reactivated areas and cerebral structures specifically involved in sequence learning only after the practice of the probabilistic version of the task. Indeed, as compared to the practice of the random sequence, we observed that the cuneus establishes or reinforces functional connections with the caudate nucleus during REM sleep following probabilistic SRT practice. The cuneus, which participates in the processing of the probabilistic sequence both during SRT practice and during post-training REM sleep, has been shown to be activated during sequential information processing in the waking state (Schubotz and von Cramon, 2001). On the other hand, the striatum is known to play a main role in implicit sequence learning (Rauch *et al.*, 1995) and specifically in the encoding of the temporal context set by the previous stimulus in the probabilistic SRT task (Peigneux *et al.*, 2000). The finding that the strength of the functional connections between cuneus and striatum is increased during post-training REM sleep suggests the involvement of the basal ganglia in the off-line reprocessing of implicitly acquired high-order sequential information. Finally, a direct relationship between the pre-sleep learning performance and regional blood flow was found in the cuneus. In this region, the regional blood flow during post-training REM sleep is modulated by the level of high-order, but not low-order, learning attained prior to sleep. In other words, the neural activity recorded during REM sleep in brain areas already engaged in the learning process during wakefulness is related to the amount of high-order learning achieved prior to sleep. This latter result further supports the hypothesis that sleep is actively involved in the processing of recent memory traces.

Conclusions

As compared to wakefulness, segregated patterns of regional CBF activity are observed during NREM and REM sleep in humans. The cortical activity is not only influenced by the processes which lead to the generation of specific sleep patterns, but remains responsive to external stimuli. Moreover, the neural populations recently challenged by a new experience are reactivated and increase their functional connectivity during the post-training sleep episodes, suggesting the off-line processing of recent memory traces in sleep.

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