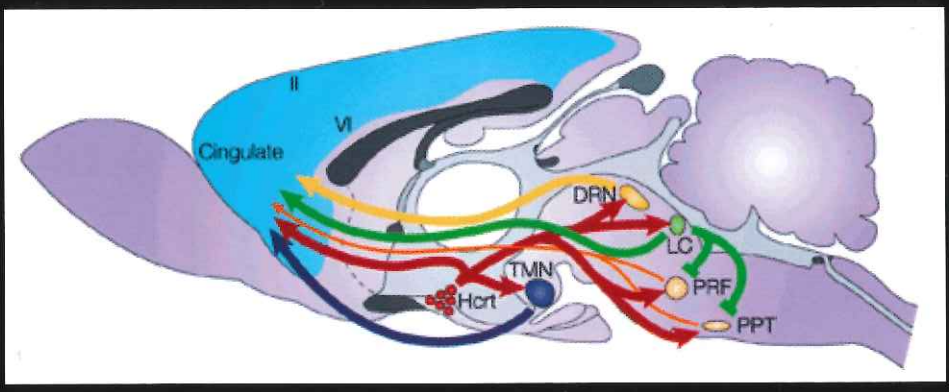
CRC PRESS

SLEEP
CIRCUITS AND FUNCTIONS



Edited by
Pierre-Hervé Luppi

FRONTIERS IN NEUROSCIENCE

Neuroscience

SLEEP CIRCUITS AND FUNCTIONS

As new biomedical technologies advance our understanding of sleep, a wave of developments in sleep research and the emergence of new technologies offer hope and help for a good night's sleep.

Sleep: Circuits and Functions discusses the major discoveries related to the circuits responsible for slow wave sleep (SWS) and rapid eye movement (REM) sleep, narcolepsy, and the possible role of sleep in memory and developmental processes. World-renowned researcher Pierre-Hervé Luppi and a panel of expert contributors highlight recent advances in sleep research obtained by means of promising technologies. New data obtained by differential gene expression analysis, transgenic mice, and functional imaging is presented, as well as the latest theoretical concepts on the mechanisms regulating sleep.

Features

- Focuses on the neuronal networks responsible for the sleep-waking cycle and the functions of sleep
- Includes changes in gene expression in the cortex and hippocampus induced by waking and sleep
- Discusses genes regulating the sleep-waking states, their circadian and ultradian distribution
- Presents recent advances in sleep research including new approaches and technologies

Updating our knowledge of the most recent strides made in sleep research, this comprehensive book also identifies future research opportunities in this growing field.

CRC PRESS
www.crcpress.com

1519
ISBN 0-8493-1519-0
90000
9 780849 315190

13 Cerebral Functional Segregation and Integration during Human Sleep

Pierre Maquet, Fabien Perrin, Steven Laureys, Tahn Dang-Vu, Martin Desseilles, Mélanie Boly, and Philippe Peigneux

CONTENTS

INTRODUCTION

A comprehensive understanding of human brain function requires the characterization of both cerebral segregation and connectivity.[1] Functional segregation pertains to the involvement of certain cerebral areas and networks in specific cerebral functions. For instance, Broca's and Wernicke's areas are known to participate in language. On the other hand, functional integration reflects how different regions interact to mediate a specific function. At the level of macroscopic systems, functional neuroimaging using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) can probe *in vivo* the segregation and integration of the human brain function during sleep and wakefulness.

0-8493-1519-0/05/$0.00+$1.50

Early studies described the functional anatomy of normal human sleep. They showed that the distribution of brain activity was specific for each type of sleep and differed from the waking pattern of brain activity. While the activity of subcortical structures was easily explained by the mechanisms that generate rapid eye movement (REM) sleep and non-REM (NREM) sleep in animals, the distribution of the activity within the cortex was harder to explain and its origin remains speculative.

In order to better understand how cortical function is organized during sleep, regional cerebral responses have been explored in three different situations:

1. In response to external auditory stimulations in NREM sleep
2. In response to the internal activation due to putative PGO activity in humans during REM sleep
3. In relation to previous waking experience

This chapter reviews these three issues after a short account of the functional neuroanatomy of NREM and REM sleep.

TWO SLEEP TYPES, TWO DIFFERENT DISTRIBUTIONS OF REGIONAL BRAIN ACTIVITY

NREM Sleep

In mammals the neuronal activity observed during NREM sleep oscillations (spindles and slow rhythms) is characterized by bursting patterns that alternate short bursts of firing with long periods of hyperpolarization.[2] The latter have a major impact on the regional blood flow, which on the average decreases in the areas where these oscillations are expressed. Accordingly the average cerebral metabolism and blood flow begin to decrease in light (stage 2) NREM sleep,[3,4] and their nadir is observed in deep (stage 3 and 4) NREM sleep or slow-wave sleep (SWS).[5,6]

The cascade of events that 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[7] as during SWS.[7–9] In light NREM sleep, the pontine tegmentum is specifically deactivated, whereas the mesencephalon seems to retain an activity that is not significantly different from wakefulness.[7] In SWS both pontine and mesencephalic tegmenta are deactivated.

The thalamus plays a central role in the generation of NREM sleep rhythms due to the intrinsic properties of its neurones and to the intrathalamic and thalamo-cortico-thalamic connectivity. In humans the thalamus is deactivated during both light and deep NREM sleep[7–9] in proportion to the power density in the spindle and delta frequency range,[10] respectively.

The role of the cortex in the generation of NREM sleep oscillations is equally important and begins to be better understood,[2] but the respective contribution of the different parts of the neocortex in NREM sleep rhythms generation is still unknown at the microscopic level. In humans the deactivation of the cortex is not homogeneous. The most deactivated areas are located in associative cortices of the frontal,

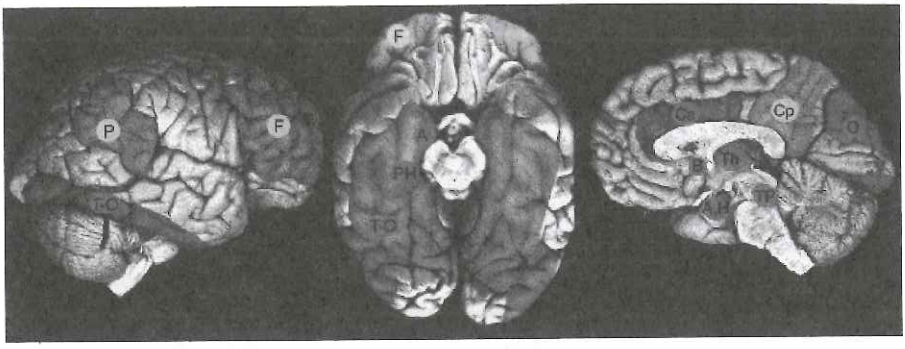


FIGURE 13.1 (See color insert following page 108.) Functional neuroimaging of REM sleep. Schematic representation of the relative increases and decreases in neural activity associated with REM sleep. Left panel: lateral view; middle panel: ventral view; right panel: medial view. A, H = amygdala and hypothalamus; B = basal forebrain; Ca = anterior cingulate gyrus; Cp = posterior cingulate gyrus and precuneus; F = prefrontal cortex; M = motor cortex; P = parietal supramarginal cortex; PH = parahippocampic gyrus; PT = pontine tegmentum; O = occipital-lateral cortex; Th = thalamus; T-O = temporo-occipital extrastriate cortex.(Adapted from Schwartz, S. and Maquet, P., Sleep imaging and the neuro-psychological assessment of dreams, *Trends Cogn. Sci.*, 6, 23, 2002.)

parietal — And to a lesser extent temporal and insular lobes[7–9,11] — while the primary cortices are the least deactivated. This observation suggests that the first cortical relay areas for exteroceptive stimuli remain relatively active during SWS. Although attractive, this hypothesis is challenged by another interpretation of the data. It should be emphasized that polymodal association cortices are the most active cerebral areas during wakefulness. Because of this high waking activity, they might be more profoundly influenced by SWS rhythms than primary cortices.[12] This suggestion supports the view that sleep intensity is targeted disproportionately to areas of the brain intensely used during prior waking.[13] Accordingly, in cats involved for some time in an active visual task, neurones 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.[14]

REM Sleep

In mammals neuronal populations in the mesopontine tegmentum are the source of a major activating input to the thalamic nuclei during REM sleep.[15] The thalamus forwards this activation to the entire forebrain. In humans the activation of mesopontine tegmentum and thalamic nuclei has been systematically reported during REM sleep[8,16,17] (Figure 13.1). 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. Temporal and occipital cortices were also shown to be very active,[8] although this result is less reproducible.[16]

The functional integration is modified during human REM sleep. The functional relationship between striate and extrastriate cortices, usually excitatory, is inverted during REM sleep.[18] Likewise, the functional relationship between the amygdala

and the temporal and occipital cortices is different during REM sleep than during wakefulness or SWS.[19] The reasons for these changes in the cerebral activity patterns remain unclear. One possibility is that the brainstem structures influence the forebrain activity in a regionally specific way through aminergic modulation or direct excitatory activities such as pontine waves.

BRAIN RESPONSES TO EXTERNAL STIMULI DURING SLEEP

Sleep is not a state of complete unresponsiveness to external stimuli. Although animal studies have suggested a decreased processing of sensory information during sleep,[20] human behavioral and physiological studies have shown that stimuli can be integrated even into the sleeper's mental or oneiric activity.[21] External stimuli can also induce an autonomic or electrophysiological response, in particular after a relevant stimulus presentation.[22] Event-related potentials (ERPs) studies 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.[23]

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 stimulus physical attributes and the latter ones to its intrinsic significance.[24] In contrast during REM sleep, the morphology of long-latency components was very comparable to that observed in wakefulness. Notably it has been shown that N100, mismatch negativity (MMN), P300, and N400 could be recorded during this sleep stage. This implies that during PS, subjects may automatically detect stimulus occurrence and discernible changes in environment,[25] may discriminate a deviant tones[26,27] as well as her or his own first name[28] and may detect the presence of a linguistic incongruence.[29,30]

As indicated earlier, the preserved capacity to evaluate salient stimulus features during SWS might be related to the relative preservation of cerebral activity in unimodal sensory cortical regions.[7,8] Accordingly the presentation of auditory stimuli activates bilaterally the thalamus and the auditory cortex during NREM sleep as well as during wakefulness;[31] however 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.

BRAIN RESPONSES TO INTERNAL STIMULI DURING SLEEP: DOES THE PGO ACTIVITY EXIST IN HUMANS?

Ponto-geniculo-occipital (PGO) waves are prominent phasic bioelectrical potentials that occur in isolation or in bursts just before and during REM sleep.[32] In several

mammal species, including nonhuman primates, PGO waves seem to represent a fundamental process of REM sleep, at least in its phasic aspects.[33] PGO waves are closely related to the generation of ocular saccades,[34] therefore during REM sleep saccades might be also generated in humans by mechanisms similar to PGO waves in cats.[35–37] This hypothesis implies that the neural activity of the brain regions from which PGO are the most easily recorded in cats (i.e., the mesopontine tegmentum,[38] the lateral geniculate bodies,[39] and the occipital cortex[32]) should be more closely related to spontaneous ocular movements during REM sleep than during wakefulness.

According to this prediction, regional blood flow changes in the lateral geniculate bodies and in the striate cortex are significantly more correlated to ocular movement density during REM sleep than during wakefulness (Figure 13.2).[40] Hence cerebral mechanisms for spontaneous ocular movement generation differ during REM sleep and during wakefulness in humans, and brain regions known to be involved in the generation of PGO waves in animals are involved in this phenomenon.

This finding is potentially important because PGO waves have been implicated in various nonexclusive processes, such as the alerting reaction to external stimuli or internal signals,[41] sensorimotor integration through the transmission of an efferent copy of ocular movements to the visual system,[33] and facilitation of brain plasticity.[42]

EXPERIENCE-DEPENDENT CHANGES IN FUNCTIONAL CONNECTIVITY DURING POST-TRAINING SLEEP

Sleep is believed to participate in the consolidation of memory traces.[43,44] 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[45–50] and in the song area of young zebra finches.[51] 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.[52] A first group of subjects (group 1) were trained on a probabilistic serial reaction time (SRT) task* in the afternoon,

* 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 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 stimuli; G) is replaced by a nongrammatical (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 2 to 3 previous trials at most.[53]

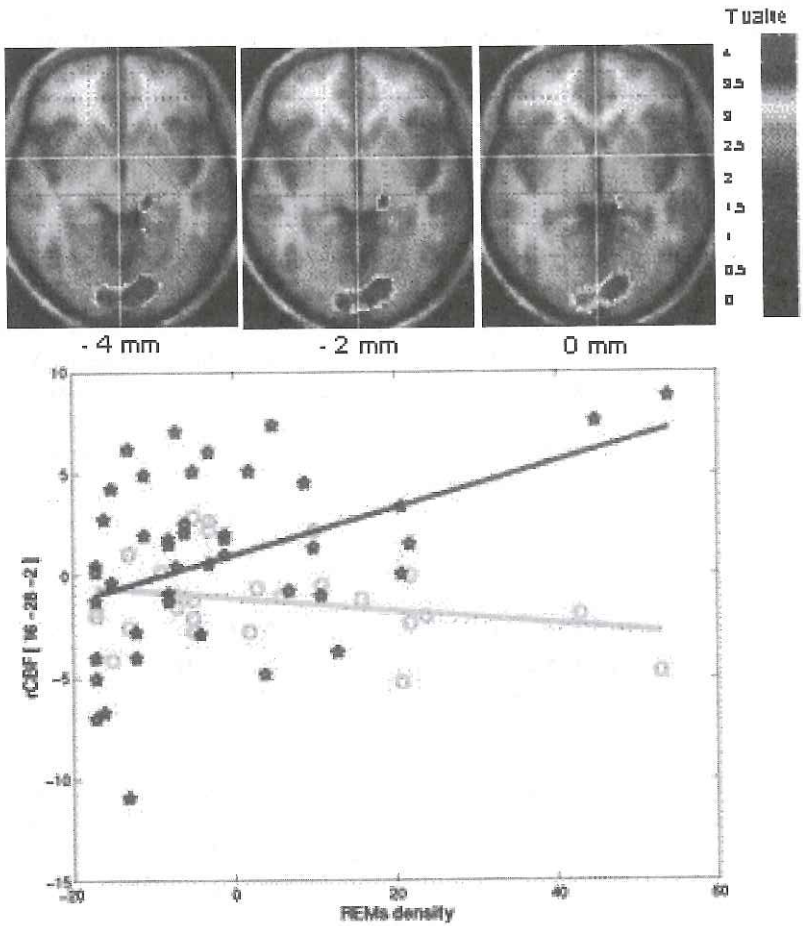


FIGURE 13.2 (See color insert.) Cerebral areas more active responding proportionally more in relation to saccades during REM sleep than during wakefulness. Upper panel: transverse sections from –4 mm to 0 mm from the bi-commissural plane. The functional data are displayed at $p < 0.001$ uncorrected, superimposed on the average MRI of the subjects, coregistered to the same reference space. Bottom panel: plot of the regional adjusted CBF (arbitrary units) in the right geniculate body in relation to the rapid eye movement (REMs) counts. The geniculate CBF is correlated to the rapid eye movement counts more during REM sleep (in red) than during wakefulness (in green). (Adapted from Peigneux, P. et al., Generation of rapid eye movements during paradoxical sleep in humans, *Neuroimage*, 14, 701, 2001.)

then scanned during the post-training night, both during waking and in various sleep stages (i.e., SWS, stage 2, and REM sleep). A postsleep training session verified that learning had occurred overnight. 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 rCBF distribution differed from the pattern of typical REM sleep, a second group of subjects (group 2), 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 than in nontrained subjects and 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.

A conjunction analysis identified the regions that would be both more active during REM sleep in the trained subjects (group 1) compared to the nontrained 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 (Figure 13.3) showed that the bilateral cuneus and the adjacent striate cortex, the mesencephalon, and the left premotor 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 that 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 nontrained 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[54] (Figure 13.3). 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 contributes to the optimization 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 optimization 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.[55] The experimental protocol was identical in all respects to the trained group in our original study,[52] except for the absence of sequential rules. Therefore post-training regional cerebral blood flow differences during REM sleep between the subjects trained respectively to the probabilistic SRT or to its random version should be related specifically to the reprocessing of the high-order sequential information.

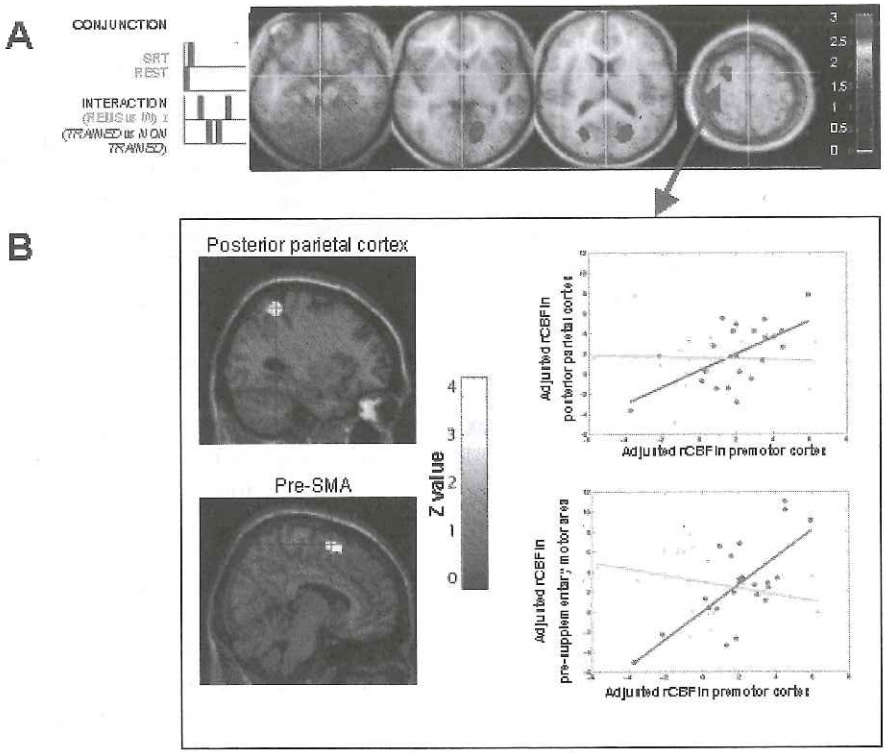


FIGURE 13.3 (See color insert.) Experience-dependent reactivations during human REM sleep. **(A)** Brain regions that are both activated in subjects scanned while performing the task during wakefulness and more active in trained than in nontrained subjects scanned during REM sleep. The SPM is displayed thresholded at $P < 0.001$ (uncorrected). (Data from Maquet, P. et al., Experience-dependent changes in cerebral activation during human REM sleep, *Nat. Neurosci.*, 3, 831, 2000. Reproduced with permission from *Nature Neuroscience.*) **(B)** Significant group (trained versus nontrained) by left premotor rCBF interaction in the posterior parietal cortex (upper image) and the supplementary motor area (lower image). The red arrow in panel *A* indicates the left premotor cortex. The SPM is displayed at $P < 0.001$ (uncorrected). On the right-hand side, plots of the adjusted and centered rCBF of the left premotor cortex (abscissa) and, respectively, the posterior parietal cortex and the supplementary motor area (ordinate). The functional relationships between these two areas are significantly different in trained subjects (red) than in nontrained subjects (green). (Adapted from Laureys, S, et al., Experience-dependent changes in cerebral functional connectivity during human rapid eye movement sleep, *Neuroscience*, 105, 521, 2001.)

During post-training REM sleep, blood flow in left and right cuneus increased more in subjects previously trained to a probabilistic sequence of stimuli than to a random one (Figure 13.3 **B**). Because 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 it 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 it is the case in the random SRT task, post-training REM sleep reactivation does not occur, or it occurs at a significantly lesser extent. These results are reminiscent of previous experiments. At the behavioral level, increase in REM sleep duration was observed in rats following aversive conditioning in which a tone is paired with a foot-shock, but not after pseudo-conditioning in which the tone and the foot-shock were not paired.[56] Using a similar procedure at the systems level, tone-evoked responses were obtained in the medial geniculate nucleus[57] 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.[58] A similar situation occurred when the material to learn was so complex that its underlying structure could not 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. 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 (Figure 13.3 **C**). The cuneus, which participates in the processing of the probabilistic sequence both during SRT practice and post-training REM sleep, has been shown to be activated during sequential information processing in the waking state.[59] On the other hand, the striatum is known to play a main role in implicit sequence learning[60] and specifically in the encoding of the temporal context set by the previous stimulus in the probabilistic SRT task.[61] 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 (Figure 13.3 **D**) in the off-line reprocessing of implicitly acquired high-order sequential information.

Finally, a direct relationship between the presleep 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 (Figure 13.3 **E**). 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.

CONCLUSION

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 that 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 con-

nectivity during the post-training sleep episodes, suggesting the off-line processing of recent memory traces in sleep.

ACKNOWLEDGMENTS

The work summarized in this paper was supported by the Fonds National de la Recherche Scientifique – Belgique (FNRS), the Fondation Médicale Reine Elisabeth, the Research Fund of ULg, PAI/IAP Interuniversity Pole of Attraction P4/22, and the Welcome Trust. PM and SL are supported by the FNRS.

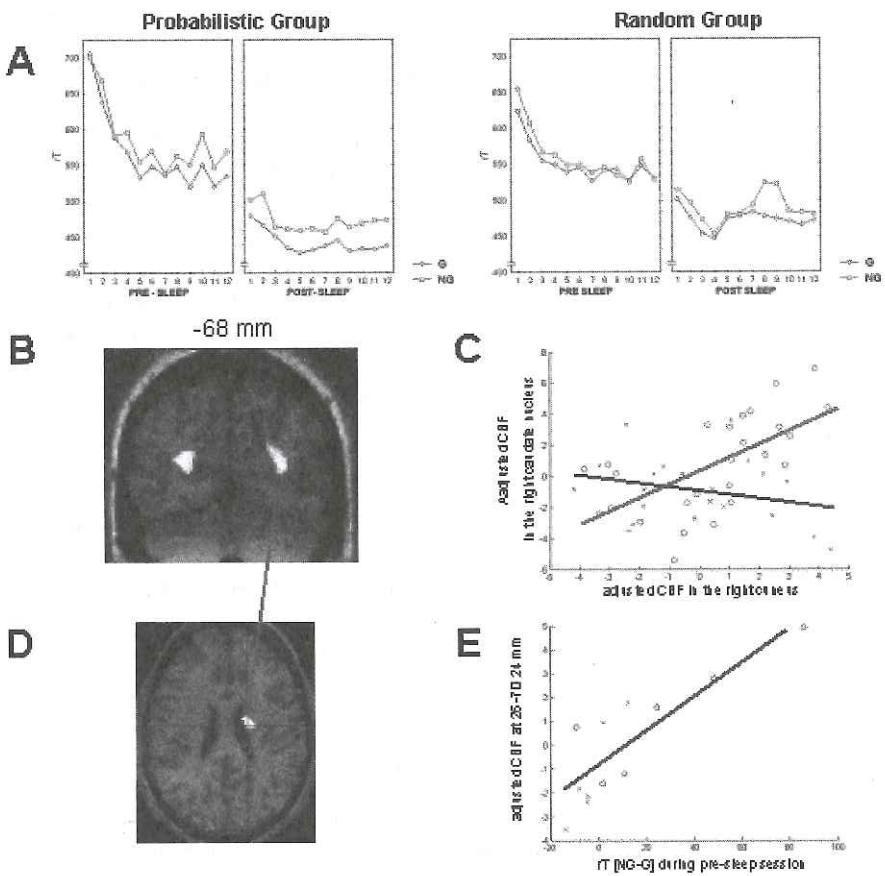


FIGURE 13.4 (See color insert.)

REFERENCES

1. Friston, K.J., Imaging neuroscience: principles or maps? *Proc. Natl. Acad. Sci. USA*, 95, 796, 1998.
2. Steriade, M. and Amzica, F., Coalescence of sleep rhythms and their chronology in corticothalamic networks, *Sleep Research Online*, 1, 1, 1998.
3. Madsen, P.L. et al., Cerebral oxygen metabolism and cerebral blood flow in man during light sleep (stage 2), *Brain Res.*, 557, 217, 1991.
4. Maquet, P. et al., Cerebral glucose utilization during stage 2 sleep in man, *Brain Res.*, 571, 149, 1992.
5. Madsen, P.L. et al., Cerebral O_2 metabolism and cerebral blood flow in humans during deep and rapid-eye-movement sleep, *J. Appl. Physiol.*, 70, 2597, 1991.
6. Maquet, P. et al., Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method, *Brain Res.*, 513, 136, 1990.
7. Kajimura, N. et al., Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep, *J. Neurosci.*, 19, 10065, 1999.
8. Braun, A.R. et al., Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study, *Brain*, 120, 1173, 1997.
9. Maquet, P. et al., Functional neuroanatomy of human slow wave sleep, *J. Neurosci.*, 17, 2807, 1997.

FIGURE 13.4 **(See facing page.)** Probabilistic versus random serial reaction time task. Data from Peigneux, P. et al., Learned material content and acquisition level modulate cerebral reactivations during post-training REM sleep (submitted). **(A)** Average reaction times (and standard errors) per block for grammatical (*G*; red lines) and nongrammatical (NG; blue lines) stimuli during pre- and postsleep sessions in Probabilistic (left-hand side) and Random (right-hand side) groups. Subjects in the Random Group were exposed to the random sequence in presleep sessions and to the probabilistic sequence in blocks 1–20 of postsleep sessions. In contrast to the subjects in group 1 (trained to the probabilistic sequence, left panel), reaction times for G and NG stimuli do not differ during the presleep training session for the subjects of group 4 (trained to the random sequence, right panel). **(B)** Statistical parametric maps of the brain regions that both activated during SRT practice (versus rest) and activated more during REM sleep (versus wakefulness) in Probabilistic rather than Random group, superimposed on the coronal section of a subject's normalized MRI at 68 and 70 mm behind the anterior commissure. The SPM is displayed at $p < 0.001$, uncorrected. **(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)** 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). **(E)** Regression of presleep 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.

10. Hofle, N. et al., Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans, *J. Neurosci.*, 17, 4800, 1997.
11. Andersson, J.L. et al., Brain networks affected by synchronized sleep visualized by positron emission tomography, *J. Cereb. Blood. Flow. Metab.*, 18, 701, 1998.
12. Maquet, P., Functional neuroimaging of normal human sleep by positron emission tomography, *J. Sleep. Res.*, 9, 207, 2000.
13. Krueger, J. et al., Sleep Modulation of the Expression of Plasticity Markers, in *Sleep and Brain Plasticity*, Maquet, P., C., Smith, and Stickgold, R., Eds., 2003, Oxford University Press, Oxford, (in press).
14. Pigarev, I.N., Nothdurft, H.C., and S. Kastner, Evidence for asynchronous development of sleep in cortical areas, *Neuroreport*, 8, 2557, 1997.
15. Steriade, M. and McCarley, R.W., *Brainstem Control of Wakefulness and Sleep*, 1990, Plenum Press, New York, p. 499.
16. Maquet, P. et al., Functional neuroanatomy of human rapid-eye-movement sleep and dreaming, *Nature*, 383, 163, 1996.
17. Nofzinger, E.A. et al., Forebrain activation in REM sleep: an FDG PET study, *Brain Res.*, 770, 192, 1997.
18. Braun, A.R. et al., Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep, *Science*, 279, 291, 1998.
19. Maquet, P. and Phillips, C., Functional brain imaging of human sleep, *J. Sleep Res.*, 7, 42, 1998.
20. Pompeiano, O., Mechanisms of sensory-motor integration during sleep, *Progr. Physiol. Psychol.*, 3, 1, 1970.
21. Burton, S.A., Harsh, J.R., and Badia, P., Cognitive activity in sleep and responsiveness to external stimuli, *Sleep*, 11, 61, 1988.
22. Bonnet, M., Performance during sleep, in *Biological Rythms, Sleep, and Performance*, W. Webb, Ed., 1982, John Wiley & Sons, Chichester, p. 205.
23. Bastuji, H. and García-Larrea, L., Evoked potentials as a tool for the investigation of human sleep, *Sleep Medicine Rev.*, 3, 23, 1999.
24. Perrin, F. et al., Functional dissociation of the early and late portions of human K-complexes, *Neuroreport*, 11, 1637, 2000.
25. Atienza, M., Cantero, J.L., and Escera, C., Auditory information processing during human sleep as revealed by event-related brain potentials, *Clin. Neurophysiol.*, 112, 2031, 2001.
26. Bastuji, H. et al., Brain processing of stimulus deviance during slow-wave and paradoxical sleep: a study of human auditory evoked responses using the oddball paradigm, *J. Clin. Neurophysiol.*, 12, 155, 1995.
27. Niiyama, Y. et al., Endogenous components of event-related potential appearing during NREM stage 1 and REM sleep in man, *Intl. J. Psychophysiol.*, 17, 165, 1994.
28. Perrin, F. et al., A differential brain response to the subject's own name persists during sleep, *Clin. Neurophysiol.*, 110, 2153, 1999.
29. Brualla, J. et al., Auditory event-related potentials to semantic priming during sleep, *Electroencephalogr. Clin. Neurophysiol.*, 108, 283, 1998.
30. Perrin, F., Bastuji, H., and Garcia-Larrea, L., Detection of verbal discordances during sleep, *Neuroreport*, 13, 1345, 2002.
31. Portas, C.M. et al., Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans, *Neuron*, 28, 991, 2000.
32. Mouret, J., Jeannerod, M., and Jouvet, M., L'activité électrique du système visuel au cours de la phase paradoxale du sommeil chez le chat, *J. Physiol. (Paris)*, 55, 305, 1963.

33. Callaway, C.W. et al., Pontogeniculooccipital waves: spontaneous visual system activity during rapid eye movement sleep, *Cell Mol. Neurobiol.*, 7, 105, 1987.
34. Datta, S., PGO wave generation: mechanism and functional significance, in *Rapid Eye Movement Sleep*, Mallick, B.N. and Inoue, S., Eds., 1999, Narosa Publishing House, New Delhi, p. 91.
35. Inoué, S., Saha, U.K., and Musha, T., Spatio-temporal ristribution of neuronal activities and REM sleep, *in Rapid-Eye-Movement Sleep*, B.N. Mallick and S. Inoue, Eds., 1999, Narosa Publishing, New Delhi, p. 214.
36. McCarley, R.W., Winkelman, J.W., and Duffy, F.H., Human cerebral potentials associated with REM sleep rapid eye movements: links to PGO waves and waking potentials, *Brain Res.*, 274, 359, 1983.
37. Salzarulo, P. et al., Direct depth recording of the striate cortex during REM sleep in man: are there PGO potentials? *EEG Clin. Neurophysiol.*, 38, 199, 1975.
38. Jouvet, M. and Michel, F., Corrélations électromyographiques du sommeil chez le Chat décortiqué et mésencéphalique chronique, *C.R. Soc. Biol. (Paris)*, 153, 422, 1959.
39. Mikiten, T.H., Niebyl, P.H., and Hendley, C.D., EEG desynchronization during behavioral sleep associated with spike discharges from the thalamus of the cat, *Fed. Proc.*, 20, 327, 1961.
40. Peigneux, P. et al., Generation of rapid eye movements during paradoxical sleep in humans, *Neuroimage*, 14, 701, 2001.
41. Bowker, R.M. and Morrison, A.R., The startle relfex and PGO spikes, *Brain Res.*, 102, 185, 1976.
42. Datta, S., A physiological substrate for sleep dependent memory processing, *Sleep Research Online*, 2, 23, 1999.
43. Peigneux, P. et al., Sleeping brain, learning brain, the role of sleep for memory systems, *Neuroreport*, 12, A111, 2001.
44. Maquet, P., The role of sleep in learning and memory, *Science*, 294, 1048, 2001.
45. Kudrimoti, H.S., C.A., Barnes, and McNaughton, B.L., Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics, *J. Neurosci.*, 19, 4090, 1999.
46. Lee, A.K. and Wilson, M.A., Memory of sequential experience in the hippocampus during slow wave sleep, *Neuron*, 36, 1183, 2002.
47. Louie, K. and Wilson, M.A., Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep, *Neuron*, 29, 145, 2001.
48. Nadasdy, Z. et al., Replay and time compression of recurring spike sequences in the hippocampus, *J. Neurosci.*, 19, 9497, 1999.
49. Pavlides, C. and Winson, J., Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes, *J. Neurosci.*, 9, 2907, 1989.
50. Wilson, M.A. and McNaughton, B.L., Reactivation of hippocampal ensemble memories during sleep, *Science*, 265, 676, 1994.
51. Dave, A.S. and Margoliash, D., Song replay during sleep and computational rules for sensorimotor vocal learning, *Science*, 290, 812, 2000.
52. Maquet, P. et al., Experience-dependent changes in cerebral activation during human REM sleep, *Nat. Neurosci.*, 3, 831, 2000.
53. Cleeremans, A. and McClelland, J.L., Learning the structure of event sequences, *J. Exp. Psychol. General*, 120, 235, 1991.
54. Laureys, S, et al., Experience-dependent changes in cerebral functional connectivity during human rapid eye movement sleep, *Neuroscience*, 105, 521, 2001.

55. Peigneux, P. et al., Learned material content and acquisition level modulate cerebral reactivations during post-training REM sleep (submitted).
56. Hennevin, E. and Leconte, P., The function of paradoxical sleep: facts and theories, *Annee. Psychol.*, 71, 489–519, 1971.
57. Hennevin, E. et al., Learning-induced plasticity in the medial geniculate nucleus is expressed during paradoxical sleep, *Behav. Neurosci.*, 107, 1018, 1993.
58. Verschoor, G. and Verschoor, H.T.L., REM bursts and REM sleep following visual and auditory learning, *S. Afr. J. Psychol.*, 14, 69, 1984.
59. Schubotz, R.I. and von Cramon, D.Y., Interval and ordinal properties of sequences are associated with distinct premotor areas, *Cerebral Cortex*, 11, 210, 2001.
60. Rauch, S. et al., A PET investigation of implicit and explicit sequence learning, *Human Brain Mapping*, 3, 271, 1995.
61. Peigneux, P. et al., Striatum forever, despite sequence learning variability: a random effect analysis of PET data, *Human Brain Mapping*, 10, 179, 2000.
62. Schwartz, S. and Maquet, P., Sleep imaging and the neuro-psychological assessment of dreams, *Trends Cogn. Sci.*, 6, 23, 2002.