

Sleep and Sleep States: PET Activation Patterns

T T Dang-Vu and M Desseilles, University of Liege and Centre Hospitalier Universitaire, Liege, Belgium
P Peigneux, University of Liege, Liege, Belgium
S Laureys and P Maquet, University of Liege and Centre Hospitalier Universitaire, Liege, Belgium

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Introduction

Positron emission tomography (PET) shows the distribution in the body (or in the brain, in the context of neuroimaging) of compounds labeled with positron-emitting isotopes. In the field of sleep research, two compounds have mainly been used to assess the global and regional cerebral activity during the different sleep stages: [^{18}F]fluorodeoxyglucose, which is a marker of glucose metabolism, and oxygen-15-labeled water (H_2^{15}O), which is an indirect marker of blood flow. In the framework of sleep research, PET images are acquired in combination with simultaneous recordings of brain electrical activity by electroencephalography for sleep staging. After data transformation and inter-individual standardization, statistical procedures allow the comparison of regional cerebral activity between two conditions (e.g., a specific sleep stage and wakefulness) or the examination of correlation patterns between regional activity distribution in a specific condition and measurements of relevant physiological events (e.g., sleep oscillations within a specific sleep stage). The resulting functional brain maps have contributed important information about human sleep physiology, assessed in the light of animal experimental data. Sleep functions have also been investigated with this technique. In particular, a role for sleep in learning and memory has been evidenced using PET recording during posttraining sleep associated with behavioral measurements.

Sleep Stages and Sleep Oscillations

PET studies have shown that global and regional patterns of brain activity during wakefulness are remarkably different from those obtained during sleep (i.e., rapid eye movement (REM) sleep and non-REM sleep).

Non-Rapid Eye Movement Sleep

Non-REM sleep is a state of synchronization of the electroencephalogram (EEG), along with the production of specific oscillations within thalamo-cortical networks: spindles, delta waves, and slow oscillations.

When compared to wakefulness and REM sleep, non-REM sleep is characterized by a decrease in global cerebral blood flow and regional cerebral blood flow (rCBF). The largest decreases in rCBF are observed in a set of subcortical and cortical areas, including the dorsal pons, mesencephalon, thalami, basal ganglia, basal forebrain, prefrontal cortex, anterior cingulate cortex, and precuneus (Figure 1(b)).

A lower activity in the brain stem and thalamus was expected from animal data of non-REM sleep-generation mechanisms; a decreased firing rate in the brain stem induces the sequential alternation of long hyperpolarization and short depolarization patterns in thalamic neurons, which leads to the formation of non-REM sleep rhythms (spindles, delta oscillations, and slow) among thalamocortical networks. Due to the low time resolution of the PET technique (i.e., one scan is the activity averaged over a period of time ranging from 40 to 90 s) and because the hemodynamic influences of hyperpolarization predominate over those of depolarization phases, brain areas where non-REM sleep rhythms are most expressed appear deactivated in PET studies.

At the cortical level, the pattern of deactivation is not homogeneously distributed. Indeed, the least active areas in non-REM sleep are located in associative cortices, especially the ventromedial prefrontal cortex (VMPF), which includes the orbitofrontal and anterior cingulate cortices. The VMPF is also one of the most active brain areas during the awake resting state and is involved in important cognitive processes such as action monitoring and decision making. In contrast, the primary cortices were the least deactivated cortical areas during non-REM sleep. This specific segregation of cortical activity remains poorly understood, although some hypotheses have been proposed, for instance, (1) that associative areas might be more profoundly influenced by non-REM sleep rhythms than primary cortices because they are the most active cerebral areas during wakefulness and (2) that sleep intensity is homeostatically related to prior waking activity at the regional level.

The precuneus is another cortical area that displays a reduced activity during non-REM sleep in PET studies. It is a region particularly active in wakefulness, during which it is involved in visual mental imagery processes, explicit memory retrieval, and consciousness. The precuneus is also deactivated during other states of decreased consciousness such as pharmacological sedation, hypnotic states, and vegetative states. The role of the precuneus during sleep still remains unclear. Its decreased activity during

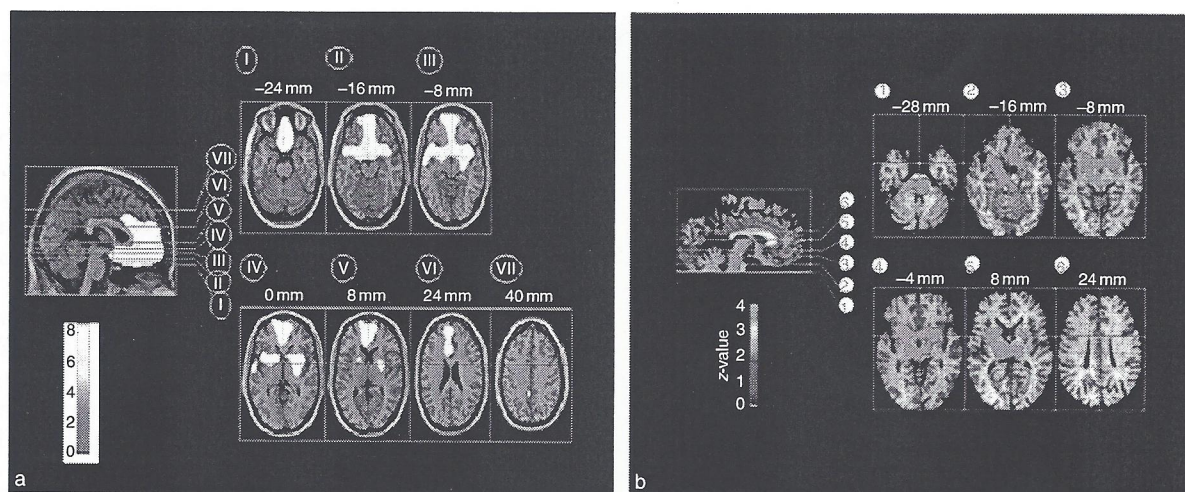


Figure 1 Functional neuroanatomy of normal human non-REM sleep, as assessed by $H_2^{15}O$ PET: (a) brain areas in which rCBF decreases as a function of delta power during non-REM sleep (stages 2–4); (b) brain areas in which rCBF decreases during non-REM sleep as compared to wakefulness and REM sleep. In (a), image sections are displayed on different levels of the z-axis, as indicated at the top of each picture. The color scale indicates the range of z-values for the activated voxels, superimposed on a canonical T1-weighted MRI image. Displayed voxels are significant at $p < 0.05$ after correction for multiple comparisons. Note that different analyses (correlation (a) vs. subtraction (b)) gave rise to strikingly similar results in terms of the regional blood flow distribution. MRI, magnetic resonance imaging; PET, positron emission tomography; rCBF, regional cerebral blood flow; REM, rapid eye movement. Adapted from Maquet P, Degueldre C, Delfiore G, et al. (1997) Functional neuroanatomy of human slow wave sleep. *Journal of Neuroscience* 17(8): 2807–2812. Copyright 1997 by the Society for Neuroscience.

non-REM sleep might reflect a homeostatic compensation of a high waking activity.

The basal forebrain and the basal ganglia (mostly the striatum) have also been found to be consistently deactivated during non-REM sleep in PET sleep studies. The basal forebrain is a functionally and structurally heterogeneous structure in which a majority of neurons is involved in cortical activation during wakefulness and REM sleep. Its deactivation during non-REM sleep may therefore reflect a lower activity of these arousal-promoting neurons. The role of the basal ganglia, and especially the striatum, in sleep regulation remains speculative, however. Two hypotheses have been put forward. First, the striatum receives massive afferent inputs from the frontal cortex and the thalamus, which are also deactivated during non-REM sleep. These structures are most likely to participate to the formation of non-REM sleep rhythms by oscillating synchronously between long phases of hyperpolarization and bursts of discharges. Due to the fronto- and thalamo-striatal connections, basal ganglia neurons may likewise oscillate following these non-REM sleep-rhythm sequential patterns and, thus, appear deactivated at the macroscopic level. According to the second proposal, the striatum may also send projections to the pedunculopontine tegmental nucleus (PPT) in the brain stem and induce the disinhibition of this activating structure, subsequently leading to

cortical arousal during wakefulness. In this perspective, the decreasing activity in the striatum during non-REM sleep may be related to a reduced propensity to arousal as well.

PET studies have not merely compared the activity between non-REM sleep and other stages of sleep or wakefulness. Another way to describe brain activity during this sleep stage was to search for the neural correlates of non-REM sleep oscillations (spindles and delta waves) by looking for brain areas in which rCBF values correlate with the EEG activity of interest (i.e., power density in the sigma or delta frequency band). Using this approach, spindle activity (12–15 Hz) has been shown to correlate negatively with rCBF in the thalamus, meaning that the higher the power density within the spindle frequency range on EEG recordings, the lower the thalamic activity. This result is in line with spindle-generation mechanisms in mammals, which are dominated by the cyclic repetition of hyperpolarization and spike bursts in the thalamic neurons. Delta activity (1.5–4 Hz) correlates negatively with rCBF in the VMPE, basal forebrain, striatum, and precuneus (Figure 1(a)). The resulting map is very similar to the brain map of the regions less activated during non-REM sleep compared to REM sleep and wakefulness (Figure 1(b)), which emphasizes the notion that delta activity is a prominent feature of non-REM sleep. A major difference,

however, is the absence of significant correlation between delta and thalamus activity, whereas the thalamus is markedly deactivated during non-REM sleep compared to other sleep stages or wakefulness. This discrepancy can be explained taking into account that two types of delta activity have been described in animals: a stereotyped delta rhythm, whose generation depends on intrinsic properties of thalamocortical neurons, and a cortical polymorphous delta rhythm, which persists after extensive thalamectomy. Therefore, the delta correlation map might preferentially reflect the brain areas involved in the generation of cortical delta waves during non-REM sleep. The physiology of these cortically generated delta oscillations, and their relationship with the slow rhythm, is still poorly understood.

It should be emphasized here that deactivation patterns found with PET studies do not imply that these brain areas remain idle during non-REM sleep. As already stated, non-REM sleep oscillations are produced by the recurrent and sequential alternation of hyperpolarization and depolarization phases in the thalamic and cortical neurons. The latter are characterized by bursts of neuronal firing temporally organized by the non-REM sleep slow oscillation. PET is insensitive to these bursts because it averages brain activity over long periods, during which the effects on regional brain function of prolonged hyperpolarization periods exceed those of shorter depolarization phases. This issue should be addressed in future studies using techniques with higher spatial and temporal resolution, such as combined EEG-functional magnetic resonance imaging (fMRI), that will provide activation patterns closer to the genuine non-REM sleep physiology, dominated by synchronous and low-frequency oscillations.

Rapid Eye Movement Sleep

REM sleep is characterized by a desynchronized EEG with high-frequency, low-amplitude activity, a major muscle atonia, spontaneous rapid eye movements, and an intense oneiric mentation. In contrast to non-REM sleep, PET studies showed that the global cerebral blood flow during REM sleep is sustained to a level comparable to wakefulness. At the regional level, several brain areas even display a higher rCBF during REM sleep compared to wakefulness and/or non-REM sleep: the pontine tegmentum, thalamus, amygdala, hippocampus, anterior cingulate cortex, temporal-occipital areas, and the basal forebrain. Conversely, regional decreases in activity are also found during REM sleep, in the dorsolateral prefrontal cortex (DLPF), posterior cingulate gyrus, precuneus, and inferior parietal cortex (Figure 2).

Activation of the pontine tegmentum, thalamic nuclei, and basal forebrain is in agreement with REM sleep-generation mechanisms in animals. REM sleep is generated by cholinergic processes arising from brain stem structures, located in the pedunculopontine tegmentum and laterodorsal tegmentum, which mediate widespread cortical activation via a dorsal pathway innervating the thalamus and a ventral pathway innervating the basal forebrain.

Consistent activations during REM sleep are also found in limbic and paralimbic structures, including the amygdaloid complexes, hippocampal formation, and anterior cingulate cortex. There is evidence that the amygdala plays a role in REM sleep modulation. For instance, carbachol (cholinergic agonist) injections in the central nucleus of amygdaloid complexes enhance REM sleep duration, and a shift from non-REM sleep to REM sleep is observed in rats after serotonin injection into the amygdala. The amygdala also appears to modulate important physiological features of REM sleep. For example, recent PET data suggest that the large variability in heart rate during REM sleep could be explained by a prominent influence of the amygdaloid complexes. Both amygdala and hippocampal formation are also critical for memory systems and may thus participate in the processing of memory traces during REM sleep.

PET studies showed higher rCBF values in temporal-occipital areas during REM sleep compared to wakefulness. These areas include the inferior temporal cortex and the fusiform gyrus, which are extrastriate cortices belonging to the ventral visual stream. Functional interactions between the primary visual cortex (striate cortex) and the extrastriate cortex during REM sleep were also assessed in a PET study. This study showed that extrastriate cortex activation is significantly correlated with striate cortex deactivation during REM sleep, whereas their activities are positively correlated during wakefulness. This result has been interpreted as supporting the hypothesis that REM sleep allows internal information processing (between extrastriate areas and their paralimbic projections, both activated during REM sleep) in a closed system dissociated from interactions with the environment (via striate cortex and prefrontal cortex, both deactivated during REM sleep).

Regional deactivations during REM sleep are mostly located in the DLPF (inferior and middle frontal gyrus), precuneus, posterior cingulate cortex, and a part of the parietal cortex (temporal-parietal region and inferior parietal lobule). In contrast, the activity in the superior parietal lobe and in the superior and medial prefrontal cortex is similar to waking level. The reasons of these cortical deactivations are still unclear. Animal data show that the cortical areas less



spontaneous eye movements and rCBF in the occipital cortex and lateral geniculate bodies of the thalamus, supporting the hypothesis that PGO-like activities are present during REM sleep in humans as well as in animals.

Neuroimaging and Dreams

Dreaming is experienced every night by many humans as multisensory mental representations occurring spontaneously during sleep, often organized in a narrative manner. Dreams are more often associated with REM sleep (dream reports are present in 90% of the episodes in subjects awakened during a REM sleep period). Dream during REM sleep is classically considered the canonical dream with several characteristics: hallucinoid imagery, narrative structure, bizarreness, hyperemotionality, delusional acceptance, and deficient memory of its content. Dream reports are usually less organized, poorer, and shorter during non-REM sleep.

At the neuroimaging level, it has been proposed that the PET activation patterns during REM sleep might be interpreted in the light of dreams. Indeed, brain functional segregation during REM sleep, as already described, may account for several typical dreaming features (Figure 2). We present a few examples here.

Dream reports differentially involve the sensory modalities. Visual components are nearly always present, auditory components are present in 40–60% of dreams, movement and tactile sensations are present in 15–30%, and smell and taste components are present in less than 1%. The activation of the associative posterior (temporal–occipital) cortices may be related to these perceptual aspects of dreams, consistently dominated by visual and auditory elements. Accordingly, a cessation of visual dream imagery was reported in some patients with temporal–occipital lesions.

Dream content is also characterized by the prominence of emotions especially negative emotions such as fear and anxiety. Responses to threatening stimuli or stressful situations are known to be modulated by the amygdala during wakefulness. The high limbic, and especially amygdalar, activity during REM sleep may therefore underpin the emotional intensity occurring during dreams. Moreover, PET data have shown functional interactions between the amygdala and temporal–occipital cortices during REM sleep, and fMRI studies during wakefulness have found positive relationships between the emotional intensity of visual stimuli and both amygdalar and inferotemporal cortex activity. Together, these data suggest that emotional experience during dreams may engage

specific brain networks encompassing the amygdala and temporal–occipital cortices rather than a single brain area.

The bizarreness of dream reports is another recurrent hallmark. The cortical patterns of hypoactivity during REM sleep may contribute to these aspects. Indeed, the prefrontal regions deactivated during REM sleep overlap with the areas involved in the selection of stimulus–response associations according to contextual signals, past events, and internal goals. The decreased activity of prefrontal regions consequently impairs the efficiency of this integrative system during REM sleep. This may, for instance, account for the inability of the dreamer to integrate information of a whole episode, leading to an oneiric content in which characters, times, and places are fused, incongruous, and discontinuous. It may also explain the decrease in volitional control and the dreamer's failure to organize mental representation toward a well-identified internal goal. Prefrontal inactivity during REM sleep may, then, explain why the dreamer is unable to control the flow of dream events.

These hypoactive areas also encompass frontal areas participating in the processing of episodic memory, that is, the ability to encode and recollect personally experienced events set in a particular spatiotemporal context. Prefrontal areas are involved in the monitoring of episodic memory retrieval by checking the accuracy and completeness of the processed information. The impairment of these areas during REM sleep might explain why, although 65% of dream reports contain residues of recent waking activity, only 1.4% of them are considered to represent a replay of full memory episodes. During dreams, episodic elements might be reactivated in a fragmented fashion, but the deactivation of the prefrontal cortex prevents the various details of past events from being integrated into an identifiable life episode. Impairment in these areas might also explain the well-known amnesia on awakening that prevents most people from accurately remembering the events experienced during the dream episode.

Overall, PET studies have brought interesting hypotheses about human dream organization. However, these assumptions remain largely speculative and partial, especially because combined dream and functional imaging data are still very sparse. In future studies, the use of scales to quantify and categorize the dream narrative in terms of different perceptual, emotional, or bizarre elements should provide crucial explanatory variables to model neuroimaging data. This combination of systematic neuropsychological assessments of dreams with neuroimaging data might greatly improve our insight into dreaming mechanisms by bringing genuine functional maps of the dreaming brain.

Sleep and Memory

The idea that sleep is involved in the processing of information that should be memorized dates back to the theory of memory consolidation a century ago. Consolidation here refers to the processing of memory traces during which the traces may be reactivated, analyzed, and gradually incorporated into long-term memory. In addition to anecdotal similarities between brain areas activated in canonical maps of normal human sleep and learning-related areas, other PET studies have supported a role for sleep in learning and memory. These studies suggest that neuronal activity patterns observed during a learning episode are reinstated during posttraining sleep. These reactivations allow for the adaptation of intercellular connection strengths between the elements of the network and the incorporation of the new experience into long-term memory. Both REM sleep and non-REM sleep are differentially involved in these processes.

During REM sleep, but not during non-REM sleep, the premotor and visual cortical areas engaged in the implicit learning of a procedural motor task are reactivated in subjects previously trained, compared to non-trained subjects. Such reactivations do not occur if the subjects are trained in a random version of the same task, showing that processing during sleep is not merely due to intense task exposure but rather relies on the sequential content of the material. These data speak for the reprocessing during REM sleep of procedural memory traces acquired during previous wakefulness.

During non-REM sleep, but not during REM sleep, the hippocampal areas activated during a spatial learning task are reactivated in subjects previously trained, compared to nontrained subjects. This result suggests a reprocessing during non-REM sleep of recent spatial memory traces acquired during previous wakefulness. Moreover, this study demonstrated a significant correlation between rCBF increases in the hippocampal areas during non-REM sleep and an overnight gain in behavioral performance, supporting the hypothesis that this offline reprocessing is related to plastic changes underlying a subsequent improvement in performance.

PET studies have thus contributed to a large amount of evidence supporting a role of sleep in learning and memory. These results are in agreement with behavioral data suggesting that REM sleep and non-REM sleep differentially modulate the consolidation of procedural and spatial/episodic memories, respectively, in the model called the dual process hypothesis. However, other behavioral data support, and brain-imaging results do not oppose to, the sequential hypothesis, in which the ordered succession of

non-REM sleep and REM sleep are necessary for the consolidation of memory traces, whatever the memory system. Furthermore, memory systems and mechanisms are complex and heterogeneous, and it remains unclear whether sleep influences all memory systems. Behavioral data already suggest that not all memories need sleep to consolidate. More studies are needed to refine the characterization of the precise contribution of each sleep stage in the processing of the different categories of memory traces.

Conclusion and Perspectives

PET studies have contributed to the understanding of human sleep neurophysiology by describing the functional neuroanatomy of sleep stages, by proposing brain correlates of dreaming features, and by showing cerebral reactivations during sleep of regions involved in prior learning. Yet our knowledge about normal human sleep remains fragmentary. These seminal studies only pave the way for future works that will benefit from the development of multimodal techniques such as combined EEG-fMRI. This neuroimaging method is technically more challenging in sleep studies, but it also has a number of advantages, including better spatial and temporal resolutions. This should help in describing more accurately the dynamics of brain activity throughout the sleep-wake cycle and especially in relation to the sleep physiological events, such as sleep oscillations. Future studies should also continue to characterize the specific extent of sleep's contribution to the learning and memory processes, which remains a topic of intense debates. There is no doubt that functional neuroimaging studies bring us significant insights into sleep functions (e.g., the relationships between sleep and brain plasticity) and sleep physiology, which is a prerequisite to the investigation of sleep disorders.

See also: Autonomic Dysregulation During REM Sleep; Dream Function; Electroencephalography (EEG); Positron Emission Tomography (PET); Sleep Mentation in REM and NREM: A Neurocognitive Perspective; Sleep Research and Sleep Medicine in Historical Perspective; Sleep Architecture; Sleep Oscillations and PGO Waves; Sleep Oscillations; Sleep-Dependent Memory Processing; The AIM Model of Dreaming, Sleeping, and Waking Consciousness.

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