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MEMORY PROCESSING DURING SLEEP MECHANISMS AND EVIDENCE FROM NEUROIMAGING STUDIES

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A growing number of studies support the hypothesis that sleep participates in the off-line processing of recent memories. However, many determinants and outcomes of memory reprocessing during sleep remain to be identified. This review provides a summary description of the main behavioural, neurophysiological and hemodynamic features of sleep, with a special emphasis on sleep mechanisms deemed potentially important to support sleep-related brain plasticity and memory consolidation: PGO-waves, spindles and hippocampal rhythms. Next are presented brain imaging studies having demonstrated the re-expression and modulation of learning-related cerebral activity during post-training sleep in humans. As a whole, functional neuroimaging results nowadays suggest that learning-dependent modulations in cerebral activity during human sleep reflect the offline processing of recent memory traces, which eventually leads to the plastic changes underlying the subsequent improvement in performance.

Circulating blood in the cardiovascular system, respiring and sleeping have in common to be essential for the integrity and survival of most living organisms including humans. What makes unique the latter is that we have no certainty as to the function(s) supported by sleep, despite an increasing knowledge of its semiology, mechanisms and regulation. Nonetheless, the infinite repetition of sleep episodes, from the first to the last night of one's life, suggests that sleep houses a series of processes necessary for normal brain function. Among several non-exclusive proposals, the hypothesis that sleep is a favourable period for brain plasticity has received increasing attention in the last 25 years (Maquet, Smith, & Stickgold, 2003). We will deal here with the corollary hypothesis that brain plasticity during sleep participates in the off-line processes of learning and memory consolidation.

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Memory consolidation is defined as the time-dependent process that converts labile memory traces into more permanent and/or enhanced forms (McGaugh, 1966). Brain plasticity is the capacity of the brain to modify its structure and function along time (Kolb & Whishaw, 1998). In the sleep for memory hypothesis, the information acquired during wakefulness would be actively altered, restructured and strengthened during sleep. The ensuing robust memory trace would enduringly adjust the behavioural responses to the recent environmental changes thereby enlarging the organism's behavioural repertoire (Gaarder, 1966). These modifications should be observed simultaneously at the brain cellular and systems levels, providing a neural signature for memory-related cognitive processes during sleep. In humans, non–invasive neurophysiological (e.g., electroencephalography [EEG]) and hemodynamic (e.g., positron emission tomography [PET] or functional magnetic resonance imaging [fMRI]) measurement techniques offer unique opportunity to investigate the neural correlates of memory processing during normal sleep and wakefulness.

In this paper, we will provide a summary, non-exhaustive, description of the main behavioural, neurophysiological and hemodynamic features of sleep. A special emphasis will be set on a few sleep mechanisms deemed potentially important to support sleep-related brain plasticity and memory consolidation processes. Functional brain imaging studies having specifically investigated the role of sleep for memory consolidation will be then presented and discussed.

Behavioral and Polygraphic Descriptions of Sleep

During sleep periods, the organism adopts a recognizable relaxation posture, specific to the particular species and/or to the conditions of the environment, and responsiveness to external stimuli is decreased (see Perrin, this issue, for a discussion on sensory processing during sleep). This peculiar behaviour is regulated by a homeostatic process, whereby the deprivation of sleep subsequently leads to a sleep rebound. The homeostatic process maintains the duration and intensity of sleep within certain boundaries, and is complemented by the circadian rhythm, which determines the timing of the sleep/wake cycle according to internal (e.g., the suprachiasmatic biological clock) and external (e.g., the light-dark cycle) signalling systems (Borbely & Achermann, 1999). Circadian systems and their interaction with sleep-related cognitive processes are reviewed in Cajochen, Blatter and Wallach, this issue.

Sleep in homeotherms is not a unitary process however (Aserinsky & Kleitman, 1953), but is composed of two main stages. Identification of these stages goes beyond the behavioural description and requires electrophysio-

logical non-invasive measurements. One main stage of sleep is characterized by the presence of ocular saccades despite global muscular tonus abolition and is therefore often referred to as rapid eye movements (REM) sleep. The high-frequency, desynchronised, pattern of the EEG recording and the phasic activity of the eye muscles during REM sleep bear some resemblance to the awake state, which explains why it is also known as paradoxical sleep (Jouvet & Michel, 1959). Conversely, the other main stage of sleep is characterized by the EEG recording of slow synchronized oscillations of large amplitude, and is therefore called slow wave sleep (SWS). However, it is also denominated non REM (NREM) sleep because it can be decomposed into several sub-stages, mostly in humans (Rechtschaffen & Kales, 1968), in which case SWS corresponds to stages 3 and 4 of NREM sleep, characterized by the highest amount of slow oscillations in the delta range (1.5-4 Hz). Stage 2, the light stage of NREM sleep, is mostly characterized by K complexes and sleep spindles (i.e. waxing-and-waning oscillations within the 12-15 Hz [sigma] frequency range) in the EEG recording. A slow rhythm (<1 Hz) occurs both during light and deep NREM sleep, characterized respectively as the regular recurrence of spindles every 3-10 seconds or as slow waves below 1 Hz (Steriade & Amzica, 1998). Refinement in the categorization of NREM sleep stages, somehow arbitrary, varies amongst species. Subdivided into light and deep SWS in carnivores such as cats or dogs, only one NREM stage is usually defined in rats or mice. In healthy subjects, NREM invariably precedes REM sleep following an ultradian cycle (about 90-100 minutes in humans) all along the night. However, the distribution of stages is unequal: SWS is most abundant during the first half of the night in humans, up to 80% of the sleep time in this period, whereas the proportion of REM sleep dramatically increases in the second half of the night and alternates with stage 2 sleep.

Functional Neuroanatomy of Normal Human Sleep

A more refined characterization of sleep mechanisms at the cellular and system levels is not attainable through behavioural observation or surface electrophysiology. In animals, substantial information has been gained using, for instance, single or multiple intracerebral cellular recording, coupled or not with in-depth intracranial stimulations, gene expression measurement or pharmacological manipulations. In healthy humans however, most of these techniques are usually precluded for obvious ethical and technical reasons. In this perspective, the advent of non-invasive functional neuroimaging techniques has offered a suitable alternative to unravel a macroscopic description of the neuroanatomical bases of human sleep.

The functional neuroanatomy of normal human sleep has been mainly investigated using positron emission tomography (PET) and glucose metabolism or cerebral blood flow (CBF) determination. Possibilities and limitations of the techniques are discussed elsewhere (Maquet, 2000). Early studies have found that global cerebral glucose metabolism is decreased during NREM sleep (Buchsbaum et al., 1989; Maquet et al., 1990), especially during SWS (Maquet et al., 1990), but do not differ significantly from wakefulness during REM sleep (Buchsbaum et al., 1989; Maquet et al., 1990) or even during stage 2 of NREM sleep (Maquet et al., 1990), although admittedly tending to decrease in the latter condition (Maquet et al., 1992). However, further studies, reviewed hereafter, have demonstrated that some cortical regions are more activated or deactivated than others, which indicates that the neuronal activity is regionally modulated during sleep stages, rather than globally modified.

Non-REM (NREM) Sleep

In NREM sleep, as compared to wakefulness, CBF significantly decreases in a large set of cortical and subcortical regions. Studies having investigated the regional distribution of CBF during SWS using H215O with PET (Andersson et al., 1998; Braun et al., 1997; Hofle et al., 1997; Kajimura et al., 1999; Maquet et al., 1997) have shown that the most deactivated areas are located in the dorsal pons and mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain/hypothalamus, prefrontal cortex, anterior cingulate cortex, precuneus and in the mesial temporal lobe. Noticeably, we have found that a very similar pattern of brain regions is yielded when rCBF is correlated with delta EEG power in NREM sleep, including the ventromedial prefrontal cortex, the basal forebrain, the striatum, the anterior insula and the precuneus (Dang-Vu et al., submitted). However, in contrast to the results of a previous PET study investigating the brain correlates of delta activity (Hofle et al., 1997) but in which waking EEG activities were incorporated in the analysis of NREM sleep scans, no such correlation was found in the thalamus in our study. The absence of correlation between thalamic activity and delta power during human NREM sleep emphasizes the possible importance of an extra-thalamic, cortical, delta rhythm among the synchronous oscillations of NREM sleep (Steriade & Timofeev, 2003). Also, the association between delta power and the activity of the ventromedial prefrontal cortex could reflect homeostatic sleep regulation processes (Cajochen, Foy, & Dijk, 1999; Knoblauch, Krauchi, Renz, Wirz-Justice, & Cajochen, 2002) as well as hyperpolarization and synchronization mechanisms associated with cortical delta waves generation during NREM sleep (Steriade & Amzica, 1998).

Stage 2 sleep per se, as differentiated from SWS, has received less interest. The same study described above (Hofle et al., 1997) reported that spindle activity (i.e., maximal during stage 2) bears a negative relationship with the CBF level in the midline-medial thalamus. Finally, it is worth mentioning that regional increases in glucose utilization have been reported during NREM sleep, mostly stage 2, in a set of regions including the pontine reticular formation, the amygdala and the hippocampus (Nofzinger et al., 2002). These latter results, involving regions reputedly implied in brain plasticity and memory consolidation during sleep, await further confirmation.

Rapid-Eye-Movement (REM) Sleep

REM sleep is mostly characterized by rCBF increases in a cerebral network including the mesopontine tegmentum, thalamic nuclei, limbic areas (amygdaloid complexes, hippocampal formation, anterior cingulate cortex) and the temporo-occipital areas (Braun et al., 1997; Maquet et al., 1996). In addition, increases have been described in the supplementary motor area, premotor and superior parietal cortices (group 3 in Maquet et al., 2000). Regional decreases, in comparison to the awake resting state, are observed in the dorso-lateral prefrontal cortex, parietal cortex, as well as the posterior cingulate cortex and precuneus. Consistent results were found in an FDG-PET study (Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997).

Although the functional significance and the characterization of these regional patterns of activation/deactivation during REM sleep remain a picture in development, functional brain imaging techniques, and especially PET scanning, have greatly contributed to our understanding of the functional neuroanatomy of REM sleep. At the neurophysiological level, the respective roles of the pons in REM sleep generation and of the thalamic nuclei to dispatch to the cortex the activation arising from the pontine tegmentum were established in animals (Steriade, Contreras, Curro Dossi, & Nunez, 1993), but questions remained as to know if this activation was homogeneously or heterogeneously distributed to the cortex. PET results have clearly demonstrated that the distribution of the human telencephalic regional activity is definitely heterogeneous during REM sleep, in line with metabolic data in animals (e.g. Lydic et al., 1991; Ramm & Frost, 1986).

A prominent finding of PET sleep studies was the strong activation of the limbic system including the amygdala and hippocampus during human REM sleep (Maquet et al., 1996; Nofzinger et al., 1997). Indeed, amygdaloid complexes have numerous anatomical connections with the cortical brain areas activated during REM sleep in animals, but very few with the least active regions (Aggleton, 1992; Amaral & Price, 1984; Amaral, Price, Pitkänen, &

Carmichael, 1992), and the amygdala and/or hippocampal formation are especially critical structures for memory systems (Bechara et al., 1995). Hence, amygdaloid complexes are in a good position to modulate the activity of distant cortical areas and play a role in the putative brain plasticity/memory consolidation processes occurring during REM sleep (Maquet & Franck, 1997). In humans, the modulation hypothesis was reinforced using PET by the demonstration that functional interactions between amygdala and occipito-temporal areas differ in the context of REM sleep as compared to SWS or wakefulness (Maquet & Phillips, 1998). Note that one study failed to report increases in the hippocampal formation concomitant to amygdala activation (Braun et al., 1997), suggesting that REM sleep would be more characterized by an activation of the limbic system than by mere amygdalar hyperactivity (Maquet, 2000). This would be consistent with the finding that total suppression of REM sleep (albeit concomitant with large SWS decreases in this study) prior to conditioning impairs hippocampus-mediated contextual learning but not amygdala-mediated cued learning in rats (Ruskin, Liu, Dunn, Bazan, & LaHoste, 2004). Also, memory formation is prevented by functional inactivation of the amygdala before, but not after, auditory fear conditioning (Wilensky, Schafe, & LeDoux, 1999), which suggests that synaptic activity in the amygdala is necessary during memory acquisition, but does not per se affect consolidation. The hypothesis that elevated hippocampal activity is specifically linked to memory consolidation during REM sleep should also be reconciled with that recent report suggesting that glucose utilization likewise increases from waking in hippocampus and amygdala during NREM sleep (Nofzinger et al., 2002).

Sleep-Dependent Mechanisms of Brain Plasticity and Memory Consolidation

As shown above, sleep stages can be characterized at the behavioural, electrophysiological functional and neuroanatomical levels. In this section, we will focus on specific mechanisms viewed as particularly important to support sleep-stages related processes of brain plasticity and memory consolidation: PGO waves, sleep spindles and hippocampal rhythms.

PGO Waves

In animals, a further distinguishing feature of REM sleep is the recording of ponto-geniculo-occipital (PGO) waves (Mouret, Jeannerod, & Jouvet, 1963), i.e. prominent phasic bioelectrical potentials, closely related to rapid

eye movements, that occur in isolation or in bursts during the transition from NREM to REM sleep or during REM sleep itself (Callaway, Lydic, Baghdoyan, & Hobson, 1987; Datta, 1999). Although observed from many parts of the animal brain (Hobson, 1964), PGO waves are recorded the most easily in the pons (Jouvet & Michel 1959), the lateral geniculate bodies (Mikiten, Niebyl, & Hendley, 1961) and the occipital cortex (Mouret et al., 1963), hence their name. PGO waves seem to represent a fundamental process of REM sleep in animals. Abolition of PGO waves in kittens leads to a maturational deficit in lateral geniculate bodies (Davenne & Adrien, 1984), additive to the maturational impairment following visual deprivation (Shaffery, Roffwarg, Speciale, & Marks, 1999), suggesting a significant role for PGO waves in central nervous system maturation.

Most importantly, PGO waves might participate in learning and memory consolidation processes in adults. Indeed, P-wave (i.e., the pontine component of PGO-type waves recorded in rats) density not only substantially increases after aversive conditioning in rats (Datta, 1999), but the percentage of changes in P-wave density between REM sleep episodes was shown proportional to the improvement of task performance between sessions (Datta, 2000). Moreover, carbachol microinjection into the phasic P-wave generator induces an increase of P-wave density during REM sleep, coupled with enhanced performance improvement on a two-way active avoidance learning task (Mavanji & Datta, 2003). Conversely, carbachol-induced activation of the P-wave generator could eliminate the learning impairment produced by post-training REM sleep deprivation (Datta, Mavanji, Ulloor, & Patterson, 2004). Hence, it suggests that the activation of the P-wave generator during REM sleep represents a natural physiological process of memory (Pavlides & Ribeiro, 2003), possibly through the synchronization of fast oscillations that would convey experience-dependent information in thalamo-cortical and intra-cortical circuits (Amzica, Neckelmann, & Steriade, 1997; Amzica & Steriade, 1996).

In humans, it is likely that the rapid eye movements observed during REM sleep are generated by mechanisms similar or identical to PGO waves in animals. In epileptic patients, direct intracerebral recordings in the striate cortex have shown monophasic and diphasic potentials during REM sleep (Salzarulo, Lairy, Bancaud, & Munari, 1975). In normal subjects, surface EEG evidenced transient occipital and/or parietal potentials time-locked to rapid eye movements (McCarley, Winkelman, & Duffy, 1983) and source dipoles of magnetoencephalography (MEG) signal have been localized in the brainstem, thalamus, hippocampus and occipital cortex during REM sleep (Inoué, Saha, & Musha, 1999). Still, a definitive proof for the existence of PGO waves in humans would necessitate in-situ electrophysiological recordings that specify their site of origin, demonstrate their propagation in the cere-

brum and their pharmacological reactivity, which is obviously precluded in healthy subjects. Therefore, non-invasive functional neuroimaging techniques represent a suitable approach to unravel the existence of PGO waves in humans. Using cerebral blood flow (CBF) determination with PET in normal sleepers, we demonstrated that regional cerebral activity in the lateral geniculate bodies and the occipital cortex is closely related to the production of spontaneous rapid eye movements during REM sleep, more than during wakefulness (Peigneux, Laureys, Fuchs et al., 2001). It suggests that processes similar to PGO waves, responsible for rapid eye movements generation, exist in humans. Unlike in animals however, a direct demonstration of the association between PGO activity and memory consolidation during REM sleep is still awaited. Nonetheless, the hypothesis is supported by studies showing an increase in the density of rapid eye movements during REM sleep following procedural learning (Smith, 2001a) and intensive learning periods (Smith & Lapp, 1991), or a correlation between retention levels after learning a Morse code and the frequency of rapid eye movements during post-training REM sleep (Mandai, Guerrien, Sockeel, Dujardin, & Leconte, 1989).

Sleep Spindles

Sleep spindles are a prominent feature of slow wave sleep, prevailing during stage 2. The neurophysiological mechanisms of spindle generation involves thalamic and corticothalamic networks, but their definitive functional meaning still remains to be elucidated (De Gennaro & Ferrara, 2003). Functional neuroimaging studies using the PET technique have shown a relative CBF decrease in the human thalamus during stage 2 sleep and SWS (Braun et al., 1997; Kajimura et al., 1999; Maquet et al., 1997), in proportion to the power density in the spindle-related sigma frequency range (Hofle et al., 1997). Recent works outline a possible role of spindles, and their organized activity driven by slow oscillations, as an essential feature of synaptic plasticity and memory processes during sleep (Steriade, 2000; Steriade & Timofeev, 2003). In this perspective, spindle oscillations in the thalamocortical system during stage 2 sleep might open molecular gates to plasticity in pyramidal neurons. In a subsequent phase of SWS the alternation of slow waves and fast oscillations could iteratively "recall" and "store" information primed in neural assemblies, providing a substrate for memory consolidation (Sejnowski & Destexhe, 2000).

Accordingly, several studies have evidenced experience- and/or use-dependent modifications of spindle activity during sleep. In humans, prolonged periods of auditory stimulation during wakefulness (Cantero, Atienza, Salas, & Dominguez-Marin, 2002) or sustained exploration in a vir-

tual maze, independently of its complexity (Meier-Koll, Bussman, Schmidt, & Neuschwander, 1999), increases spectral power within the sigma frequency range during subsequent NREM sleep. Most importantly, the density of sleep spindles is enhanced following training on a declarative learning task and correlates with recall performance both before and after sleep (Gais, Molle, Helms, & Born, 2002; see also Gais and Born, this issue), suggesting an association between the hippocampal-neocortical system of declarative long-term memory and the thalamocortical networks responsible for spindles generation. The result is in line with the hypothesis that coactivation and transfer between hippocampal and neocortical pathways is important for the process of memory consolidation, during which memories are gradually translated from short-term hippocampal to longer-term neocortical stores (Siapas & Wilson, 1998; Sirota, Csicsvari, Buhl, & Buzsaki, 2003).

However, other studies suggest that spindles and stage 2 sleep might participate in the consolidation of other types of memory processes (see Smith, Aubrey and Peters, this issue, for a proposed model). Marked increases in sleep spindle activity have been reported after a procedural motor memory task, that correlate with performance improvement (Fogel, Jacob, & Smith, 2001). Sigma activity and spindle counts also correlate positively with Full Scale Intelligence Quotients (IQ) and with the Performance IQ subscale, but not with Verbal IQ subscale (Nader & Smith, 2001), pleading for a relationship between a higher level of spindle activity and a greater ability to perform tasks which require perceptual, analytical and reasoning abilities. These results suggest that spindles could be an indicator of current level of aptitude for learning certain types of material.

Hippocampal Rhythms

The theta rhythm (i.e., regular sinusoidal oscillations in the frequency range of 4-7 Hz recorded in the hippocampal EEG) constitutes a prominent signature of REM sleep in mammals, albeit its presence and characteristics in humans is still discussed (Bodizs, Szucs, & Halasz, 2001; Uchida, Maehara, Hirai, Okubo, & Shimizu, 2001). Still, it is also found in the awake state during various ecologically-relevant species-specific behaviours, suggesting that theta waves are involved in the acquisition and processing of particularly meaningful environmental information (Winson, 1990; cited in Pavlides & Ribeiro, 2003). Hence, theta represents the “on-line” state of the hippocampus, believed to be critical for temporal coding/decoding of active neuronal ensembles and the modification of synaptic weights (Buzsaki, 2002). On the other hand, population synchrony of pyramidal cells is maximal during quiet wakefulness and SWS associated with sharp waves (i.e.,

sharp waves of SWS are the consequence of synchronous discharge of bursting CA3 pyramidal neurons) and fast ripples (140-200 Hz). For various reasons, sharp waves and ripples during SWS constitute a good candidate to induce neuronal plasticity (for a detailed account see Buzsaki et al., 2003). Hence, both REM sleep/active wake theta activity and SWS/quiet wakefulness sharp waves and ripples could contribute to brain plasticity. From this point however, contrasted theories have been put forward to explain the implication of these phenomena in sleep-related memory consolidation processes.

In its original version (Buzsaki, 1989), the two-stage model of memory formation hypothesizes that it is SWS that is critical for the consolidation of recently learned information. According to this model, during learning, associated with active waking and theta rhythmic activity in the hippocampus, the neocortical information activates the entorhinal input, which will cause synaptic changes to occur in the hippocampal CA3 system. In the subsequent non-theta state (i.e., SWS or – maybe — quiet wakefulness), the previously activated neurons are reactivated during sharp waves bursts, and the memory representation transiently stored in the CA3 region can be transferred to neocortical targets for the long-term. Hence, there is a reversal in the direction of the hippocampo-neocortical dialogue between active learning during wakefulness, in which information flow near the hippocampus, and consolidation of learned information during SWS through transfer of the hippocampal content to the neocortex (Buzsaki, 1996, 1998). This model fits well with behavioural and pharmacological studies having shown SWS-dependent consolidation of declarative memories in man (Gais & Born, 2004; Plihal & Born, 1999; Plihal, Pietrowsky, & Born, 1999; see also Gais and Born, this issue). Also, it may account for the finding of a recent PET sleep study showing experience-dependent reactivation of hippocampal activity during SWS, but not REM sleep, following spatial/declarative learning in a virtual town (Peigneux, Laureys, Perrin et al., 2003). The effect of quiet wakefulness on memory consolidation is less documented, although an early study reported that forced activity (as compared to immobility) is detrimental to the retention of a simple avoidance task in the cockroach (Minami & Dallenbach, 1946).

One parallel hypothesis is that elaboration of memory traces acquired during the waking period requires two sequential steps taking place during SWS and eventually during REM sleep (Giuditta, 1984; Giuditta et al., 1995; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). Here, the memory consolidation in the hippocampus would result from interplay during sleep stages between the sharp waves/ripples of SWS and theta/gamma oscillations during REM sleep. In this perspective, since the rCBF deactivation of the hippocampal system during NREM sleep is thought to reflect local slow syn-

chronous oscillations possibly implicated in "off-line" reactivation of memory traces (McClelland, 1994; Stickgold, 1998), the rCBF increase in the hippocampal formation during REM sleep could represent the continuation of the processes initiated during SWS. Evidence in support of this hypothesis derives from studies having shown that discharge patterns in the place cells of the rat hippocampus, which fires when the animal occupies a specific position in space, are re-expressed during subsequent SWS (Wilson & McNaughton, 1994), in relative conjunction with sleep spindles, i.e. another neocortical rhythmic event linked to brain plasticity (Siapas & Wilson, 1998). Eventually hippocampal neurons were found during REM sleep to replay the sequence of spatial activity that had been experienced on an expanded timescale of tens of seconds to minutes, and the general patterns of theta rhythmic modulation of population response that reflect the state of locomotion of the animal were also recapitulated (Louie & Wilson, 2001).

Neuronal Replay and Memory Consolidation During Human Sleep

Reactivation studies described here above suggest the neuronal replay of previous experience during sleep. Hence, post-training sleep activity in brain areas involved during the learning episode could represent the neural signature of memory-related cognitive processes. Reactivations have been initially reported in two main experimental situations, in the rat hippocampus and cortex following exposure to a spatial environment (Kudrimoti, Barnes, & McNaughton, 1999; Lee & Wilson, 2002; Louie & Wilson, 2001; Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999; Pavlides & Winson, 1989; Ribeiro, Goyal, Mello, & Pavlides, 1999; Wilson & McNaughton, 1994) and in the song area of young zebra finches (Dave & Margoliash, 2000). It is now established that spatiotemporal patterns of neuronal ensemble activity produced by tactile or visual exploration of novel objects recurred for up to 48 h in the cerebral cortex, hippocampus, putamen, and thalamus, especially during SWS, suggesting that persistent experience-dependent neuronal reverberation is a general property of multiple forebrain structures (Ribeiro et al., 2004). Although data suggest the generality of the reactivation in the processing of memory traces during sleep, it must be noticed that it has never been shown in these studies that experience-dependent modifications in neuronal populations during sleep are associated to any noticeable change in the animal's subsequent behaviour (Maquet, 2001; Peigneux, Laureys, Delbeuck, & Maquet, 2001). Therefore, the behavioural relevance of these sleep-dependent cellular processes for memory systems remains to be shown.

Similar evidences for experience-dependent reactivation in the processing of memory traces during human sleep are unfortunately slim for the present

time. A series of experiments was conducted by the authors to observe the reactivation of brain areas during post-training sleep in humans (Laureys et al., 2001; Maquet et al., 2000; Peigneux, Laureys, Fuchs et al., 2003; Peigneux, Laureys, Perrin et al., 2003).

In a first PET experiment (Maquet et al., 2000), we determined the variations in regional cerebral blood flow (rCBF) in three groups of normal subjects under different conditions. The first group (A) was scanned while trained to the probabilistic serial reaction time (SRT) task (Cleeremans & McClelland, 1991), a paradigm of implicit sequence learning. In this task, participants simply have to press as fast and as accurately as possible on the key corresponding to the spatial location of a dot appearing on the computer screen; the next stimulus is then displayed at another location. Unknown to participants, the succession of stimuli follows a sequential pattern based on a highly complex probabilistic finite-state grammar. The analysis of PET data in group A provided a list of the brain areas that are activated during the execution of the SRT task, as compared to rest. A second group (B) was similarly trained on the SRT task in the afternoon, then scanned during the post training night, both during waking and in various sleep stages (i.e., SWS, stage 2 and REM sleep). A post-sleep SRT 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 after practice of the SRT task. To ensure that post-training REM sleep rCBF distribution differed from the pattern of "typical" REM sleep, a third group (C), not trained to the task, was scanned at night in the same conditions. The final analysis aimed to identify those regions that would be both more active during REM sleep (versus resting wakefulness) in the trained subjects compared to the non-trained subjects and activated during the execution of the SRT task. Results showed that the bilateral cuneus and adjacent striate cortex, mesencephalon and left premotor cortex, already activated during the practice of the SRT task, were activated during post-training REM sleep in subjects previously trained on the task, significantly more than in control subjects sleeping without prior training (Maquet et al., 2000). In addition, among these reactivated regions, the rCBF in the left premotor cortex was significantly more correlated with the activity of the pre-SMA and posterior parietal cortex (PPC) during post-training REM sleep than during "typical" REM sleep (Laureys et al., 2001). Since PPC et pre-SMA are important structures in sequence learning, these data further suggested that sequential memory traces are replayed in the cortical network during REM sleep.

In a next step, we aimed to determine the type of memory traces reprocessed during REM sleep (Peigneux, Laureys, Fuchs et al., 2003). Indeed, behavioural data yielded evidence for an overnight improvement both in measures of simple visuo-motor skill optimisation (i.e., global improve-

ment in reaction time [RTs]) and estimates of the high-order acquisition of the probabilistic sequential structure of the learned material (i.e., faster RTs for items that follow the probabilistic sequential rules than for the 15% interspersed items that violate these rules). Hence, we could not specify whether experience-dependent reactivation during REM sleep were related to low- or high-order components of sequence learning, or both. The simplest way to test the hypothesis that cerebral reactivation during post-training REM sleep reflected the reprocessing of high-order sequential information was to scan a new group (D) during sleep after practice on the same SRT task, but using a completely random sequence. Hence, the low-level visuo-motor skill component would not differ between groups B and D, and higher rCBF increases during REM sleep after probabilistic SRT than during REM sleep after random SRT should be related specifically to the reprocessing of the high-order sequential information. Such probabilistic-specific activation during post-training REM sleep was found in the left and right cuneus, suggesting that reactivation in these areas corresponds to the reprocessing of elaborated information about the sequential contingencies contained in the learned material. Moreover, we failed to detect any significant reactivation during post-random SRT training, suggesting that simple visuo-motor optimisation on the SRT task is not sufficient to elicit rCBF changes during post-training REM sleep. We also found that functional connections are reinforced between the reactivated cuneus and the caudate nucleus of the striatum during REM sleep after probabilistic SRT, as compared to REM sleep after random SRT. The finding that the strength of the functional connections between cuneus and striatum, know to be specifically involved in probabilistic sequence learning during wakefulness (Peigneux et al., 2000), 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, in the reactivated cuneus, regional blood flow during post-training REM sleep in brain areas already engaged in the learning process during wakefulness was correlated to the amount of high-order learning achieved prior to sleep (Peigneux, Laureys, Fuchs et al., 2003).

An important suggestion conveyed by these results is that the processing of recent memories during post-training sleep does not seem to be initiated unless the material to be learned is structured. 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 at least to a significantly lesser extent. These results are in keeping with previous animal experiments showing an increase in REM sleep duration (Bramham, Maho, & Laroche, 1994) or evoked responses in the medial geniculate nucleus (Hennevin, Maho, Hars, & Dutrieux, 1993) and in the hippocampus (Maho, Hennevin, Hars, & Poincheval, 1991) during REM sleep after a conditioning procedure initiated

at wake, but not after pseudo-conditioning. Likewise in humans, REM sleep percentage increases after learning textbook passages, but only when they are meaningful (Verschoor & Holdstock, 1984), or when complexity of a virtual maze allow subjects to learn their way and form a cognitive map (Meier-Koll et al., 1999).

At this point, it should be reminded that neither memory nor sleep are unitary phenomena. Long-term memories belong to multiple memory systems, categorized in two main types: fact-and-event episodic, declarative memories, and implicit, non-declarative memories (Squire, 1992; Tulving, 1987), and the respective role of REM and NREM sleep stages in the consolidation of different types of memories is still unsettled (Peigneux, Laureys, Delbeuck et al., 2001; Smith, 2001b). Probabilistic SRT is predominantly an implicit learning task, and our data show that cortical areas engaged in the implicit acquisition of procedural memories are reactivated during post-training REM sleep, but not SWS or Stage 2 sleep (Maquet et al., 2000; Peigneux, Laureys, Fuchs et al., 2003). Conversely, we have recently reported a reactivation of the (para)hippocampal system during post-training SWS and stage 2 sleep, but not REM sleep, following intensive topographical/episodic learning in a virtual town. Most importantly, the amount of hippocampal activity during SWS in trained subjects was proportional to their overnight improvement in performance (Peigneux, Laureys, Perrin et al., 2003). These results fit with behavioural data suggesting that NREM sleep and REM sleep differentially modulate the consolidation of declarative and non-declarative memories, respectively (i.e., the dual process hypothesis; Plihal & Born, 1997, 1999; Smith, 1995). However, it should be kept in mind that other data indicate that the ordered succession of NREM sleep and REM sleep is necessary for the consolidation of memory traces, whatever the memory system (i.e., the double step hypothesis; Gais, Plihal, Wagner, & Born, 2000; Giuditta et al., 1995; Stickgold et al., 2000). These hypotheses should not be viewed as mutually exclusive and deserve further investigation.

Sleep Deprivation and Memory-Related Modifications in Cerebral Activity

The observation of experience-dependent reactivations during post-training sleep in non-sleep deprived humans remains a challenge, since subjects are required to sleep an entire night on the bed of the PET scanner. Technical difficulties related to on-line EEG measurement in powerful magnetic fields, added to the important noise produced by sequence acquisition, make things even more difficult in fMRI scanners. However, other strategies have been devised to evidence the cerebral bases of memory processing during sleep.

Indeed, reactivation studies rely on the assumption that post-training sleep processes will favour plastic brain changes and consolidation of memories, which eventually lead to performance improvement on the next days. It seems therefore logical to assume that sleep deprivation should hamper these processes, with the consequences that (1) memory performance will be diminished on the next days, as compared to sleeping subjects, and that (2) the cerebral organization underlying consolidated memories will be altered in sleep-deprived subjects. The methodological advantage is that both consequences can be assessed during wakefulness after sleep or sleep deprivation outside of the scanner. Using this strategy, Maquet, Schwartz, Passingham, and Frith (2003) devised an fMRI study in which subjects were trained to a procedural memory pursuit task, then either sleep-deprived or allowed to sleep on the following night. Three days later, all subjects were scanned with fMRI while practicing the pursuit task on new and previously learned trajectories. Two intervening nights of sleep were allowed both for sleeping and sleep-deprived groups to ensure a similar arousal state at retest. Behavioural results indicated that performance gain on retest was significantly reduced in subjects deprived of 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 (SEF) and in the right dentate nucleus (DN). Most importantly, an effect of sleep deprivation was found in the right superior temporal sulcus (STS), which was more active for the learned than the new trajectory, and significantly more in subjects allowed to sleep on the first post-training night than in subjects deprived of sleep during this night. In addition, activity in the dentate nucleus was more tightly correlated to the STS, and the supplementary eye field (SEF) to the frontal eye field (FEF), for the learned than for the new trajectory, significantly more in subjects who slept during the first post-training night. These results show that sleep deprivation on the first post-training night both prevent performance improvement and alter cerebral connectivity on the long-term.

According to the authors, these data suggest that the performance on the pursuit task depends on the subject's capacity to build up an internal model of the trajectory in order to program the appropriate pursuit eye movements, which will become optimal as the prediction made by the internal model improves. The building of the internal model and the more accurate control of the eye movements are suggested by the increased functional coupling between the DN and the STS and between the SEF and the FEF, respectively, but only in those subjects who slept during the first post-training night. Sleep deprivation during this night disturbs the slow processes that lead to the acquisition of this procedural skill and hampers the related changes in connectivity that is usually reinforced in subjects allowed to sleep the night after training.

Conclusions

During the last decade, functional brain imaging techniques have demonstrated the re-expression and modulation of learning-related cerebral activity during post-training sleep in man and in animals, supporting the hypothesis that sleep participates in the off-line processing of recent memories. These studies furthermore suggest that (1) post-training sleep modifications are not merely the consequence of extended pre-sleep practice, but are crucially contingent upon the underlying cognitive content of the task, (2) that experience-dependent modifications of regional cerebral activity can be found during distinctive sleep stages according to specific memory types, and (3) that experience-dependent modifications engage specific networks of learning-related brain areas, (4) whose efficiency and connectivity is disrupted by post-training sleep deprivation. Finally, (5) these post-training sleep reactivations relate to performance improvement. Therefore, functional neuroimaging results nowadays suggest that learning-dependent modulations in cerebral activity during human sleep reflect the offline processing of recent memory traces, which eventually leads to the plastic changes underlying the subsequent improvement in performance. Further studies should concentrate on the identification of the precise mechanisms underlying plastic changes and memory consolidation processes during the sleep-wake cycle.

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