CHAPTER 8

Neural Correlates of Human Sleep and Sleep-Dependent Memory Processing

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INTRODUCTION

The brain is able to generate three distinct functional modes that are associated with specific neural firing patterns, oscillatory modes, and neuromodulatory contexts: wakefulness, non- rapid-eye-movement (NREM) sleep, and REM sleep. The mechanisms underlying these vigilance states are known with increasing detail through neurophysiological and molecular studies conducted in animals. Sleep being conserved across species, similar mechanisms should also underlie the organization of human brain function during sleep and wakefulness. The characterization of human brain function during sleep thus appears as an important step in the translational effort that aims at understanding the mechanisms underlying human sleep. Unfortunately, the access to human brain function is limited. With the exception of depth recordings in selected patients with brain disorders (e.g., intractable epilepsy or Parkinson disease), functional neuroimaging techniques provide the most straightforward access to regional human brain function at a macroscopic level. Various imaging techniques are available. Some techniques measure slow metabolic or hemodynamic signals at spatial resolution of a few millimeters: single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). In contrast, electroencephalography (EEG) and magnetoencephalography (MEG) follow electromagnetic signals sampled at high temporal resolution but with a limited spatial resolution. These various techniques provide complementary views of human brain function and a comprehensive characterization of human sleep ultimately requires their integration with the mechanistic data revealed by animal research.

Sleep and Brain Activity
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This chapter focuses on the modifications of brain activity reported during normal human sleep. First, we focus on the changes in regional cerebral metabolism and hemodynamics during NREM and REM sleep. In particular, we describe novel data combining EEG and fMRI recordings, which characterize changes in brain activity associated with slow waves and spindles, as well as the modification in functional brain connectivity during NREM sleep. Then we review the influence of previous waking experience on brain activity during sleep, and discuss the implication of sleep in memory consolidation.

NREM SLEEP

During NREM sleep, neuronal activity is organized by a slow rhythm (<1 Hz). Intracellular recordings showed that the neuronal membrane potential alternates between a depolarized state, associated with sustained firing, and a hyperpolarized phase, during which most neurons remain silent (Steriade, Nunez, & Amzica, 1993b). These variations in membrane potential occur locally in close synchrony within large neural populations, which therefore alternate between activated ("ON" state) and quiet periods ("OFF" state) (Vyazovskiy et al., 2009). EEG slow waves recorded on the scalp occur in synchrony with these neural events, the peak negativity being considered as corresponding to the neural "OFF" state (Molle, Marshall, Gais, & Born, 2002). On scalp EEG in humans, slow waves predominate over frontal areas and appear as traveling waves: each single wave is initiated at a definite cortical site and propagates following a given trajectory on the scalp (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004).

The slow oscillation temporally organizes other sleep rhythms such as spindles or hippocampal sharp waves and ripples. Spindles result from cyclic inhibition of thalamocortical neurons by reticular thalamic neurons. Post-inhibitory rebound spike bursts in thalamocortical cells entrain cortical populations in spindle oscillations (Steriade & McCarley, 2005). Corticothalamic neurons in turn synchronize thalamic spindling activity (Contreras, Destexhe, Sejnowski, & Steriade, 1996). Spindles preferentially occur during the neuronal "UP" state (Steriade, Nunez, & Amzica, 1993a) or in humans, during the positive phase of the EEG slow waves (Molle et al., 2002). In humans, two kinds of spindles are observed on EEG recordings (De Gennaro & Ferrara, 2003). Slow spindles (typically <13 Hz) predominate over frontal areas, whereas fast spindles (typically >13 Hz) prevail over centroparietal regions. The two spindles types have been associated with several functional differences (De Gennaro & Ferrara, 2003).

The hippocampal activity during NREM sleep is characterized by sharp waves and ripples, which are synchronous to the cortical slow oscillation (Clemens et al., 2007; Isomura et al., 2006; Ji & Wilson, 2007; Molle, Yeshenko, Marshall, Sara, & Born, 2006), although it is not yet clear which oscillation is driving the other (Molle & Born, 2009; Tononi, Massimini, & Riedner, 2006).

Global Changes in Brain Energy Metabolism

On average, neural firing activity is decreased during NREM sleep, relative to wakefulness or REM sleep (Vyazovskiy et al., 2009). Accordingly, measures of brain energy metabolism by tracer techniques showed that it is decreased in NREM sleep, relative to wakefulness, in cats (Ramm & Frost, 1983, 1986), monkeys (Kennedy et al., 1982) and humans (Buchsbaum et al., 1989; Madsen, Schmidt, Wildschiodtz, et al., 1991; Maquet et al., 1990). These early data have been reviewed elsewhere (Madsen & Vorstrup, 1991; Maquet, 2000). Quantitatively, cerebral glucose metabolic rates are 11% lower in stage 2 sleep (Maquet et al., 1992) and about 40% lower in deep NREM sleep (Buchsbaum et al., 1989; Maquet et al., 1990), relative to resting wakefulness. Likewise, cerebral oxygen utilization decreases by 5% (Madsen, Schmidt, Holm et al., 1991) to 7% (Takahashi, 1989) during light NREM sleep and by 25% in deep NREM sleep (Madsen, Schmidt, Wildschiodtz et al., 1991), as compared to resting wakefulness. Cerebral blood flow measurements showed the same general decrease in NREM sleep in humans (Braun et al., 1997; Kajimura et al., 1999; Madsen, Schmidt, Wildschiodtz, et al., 1991; Takahashi, 1989). In deep NREM sleep, the most deactivated areas were located in the dorsal pons and mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain/hypothalamus, mesial frontal areas, and the precuneus (Andersson et al., 1998; Braun et al., 1997; Kajimura et al., 1999; Maquet et al., 1997). Regional decreases in blood flow in the brainstem, thalamus, and basal forebrain were interpreted as the diminished activity of activating structures maintaining wakefulness. The decreases in cortical blood flow were considered as identifying the areas where the slow oscillation consistently drives the activity of a large fraction of the local neural population. In keeping with this interpretation, blood flow in the medial prefrontal cortex was also inversely proportional to the EEG power in the delta frequency band (1.5–4 Hz), suggesting that local blood flow decreases as the synchronization of neural firing increases in this area (Dang-Vu et al., 2005). Tracer techniques like 2-deoxyglucose autoradiography in animals (Sokoloff, 1981), or positron emission tomography

in humans (Phelps & Mazziotta, 1985) require long uptake periods (in the order of one to tens of minutes), several order of magnitude larger than the dynamics of neural activity during slow oscillation. In this respect, they can be thought of as estimating the average metabolic consequences of the alternating "ON" and "OFF" states.

Neural Correlates of Spindles and Slow Waves

These decreased average metabolic demands should by no means suggest that NREM sleep is a resting period for the brain; the slow oscillation is associated with substantial neural activity. Accordingly, with the advent of simultaneous recordings of functional magnetic resonance imaging and EEG signals, it became possible to characterize consistent changes in regional brain activity associated with the NREM sleep neural transients such as slow waves or spindles.

In contrast to EEG recordings, which insisted upon the variability between slow waves (Massimini et al., 2004), EEG/fMRI data identified the regions that are systematically recruited when a slow wave is recorded on the EEG. During NREM sleep, significant *increases* in activity were associated with slow waves in several cortical areas including inferior frontal, medial prefrontal, precuneus, and posterior cingulate cortex (Dang-Vu et al., 2008). These results were confirmed by reconstruction of electric sources of slow waves, as recorded by high-density EEG: slow waves were consistently associated with currents in the medial frontal gyrus, the inferior frontal gyrus, the anterior cingulate, the precuneus, and the posterior cingulate cortex (Murphy et al., 2009). This peculiar response pattern that primarily involves the medial aspect of the frontal, cingulate, and parietal cortices is thought to reflect the propagation of slow waves through major connectivity pathways of the human brain (Hagmann et al., 2008).

In addition, EEG/fMRI data further showed that the largest slow waves (>140 μV) were associated with significant activity in the parahippocampal gyrus, cerebellum, and pontine tegmentum (Dang-Vu et al., 2008). This finding indicates that slow waves reflect the synchronous firing of distributed cortical populations but also recruit mesiotemporal cortex and subcortical structures. In keeping with this view, depth recording in epileptic patients showed that gamma oscillations, a major determinant of fMRI signal (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), are recorded in synchrony with cortical slow oscillation at approximately the same time in many different cortical areas, the most prominent source being the parahippocampal gyrus (Le Van Quyen et al., 2010). The recruitment

of the pons was unexpected, because the slow oscillation is interrupted by the stimulation of brainstem structures promoting wakefulness (Steriade, Amzica, & Nunez, 1993). However, there is now evidence that some brainstem populations involved in sleep/wake regulation fire in synchrony with the cortical slow oscillation (Eschenko, Magri, Panzeri, & Sara, 2012; Mena-Segovia, Sims, Magill, & Bolam, 2008). Collectively, EEG/fMRI data show that slow waves are associated with a transient increase in activity, not only in a distributed set of highly connected cortical areas but also in mesiotemporal regions and even in brainstem structures.

EEG/fMRI data also showed that spindles were associated with increased activity in the thalami, anterior cingulate, insular, and superior temporal cortices (Schabus et al., 2007). In addition, fast spindles recruited a set of cortical regions involved in sensorimotor processing (precentral and postcentral gyri, supplementary motor area, and neighboring midcingulate cortex), as well as the mesial frontal cortex and hippocampus. In contrast, slow spindles were associated with increased activity in the superior frontal gyrus (Schabus et al., 2007). These results were consistent with EEG source reconstruction reporting a spindle source in medial prefrontal cortex for slow spindles, and in the precuneus for fast spindles (Anderer et al., 2001). Moreover, EEG/fMRI data further showed that functional connectivity between the hippocampal formation and the neocortical regions recruited by fast spindles was increased in light NREM sleep, during which spindles predominate, relative to wakefulness (Andrade et al., 2011). These results suggest that fast spindles are associated with a synchronous activity in distributed hippocampocortical circuits, a condition suspected to favor exchange of information within these networks.

However, there seems to be more than two spindle types in humans. MEG recordings in humans identified multiple asynchronous neural generators during sleep spindles (Dehghani, Cash, Rossetti, Chen, & Halgren, 2010), a finding recently corroborated by intracerebral recordings in epileptic patients (Nir et al., 2011). Why MEG identifies multiples spindle sources is currently not fully understood. It was suggested that MEG preferentially recruit the recruitment of the focal core thalamocortical system, whereas EEG would be more sensitive to the distributed matrix thalamic system (Dehghani et al., 2010). In this view, the functional impact of spindles on information processing during sleep might imply multiple thalamocortical loops, in addition to the set of brain areas recruited by the two spindle classes identified on scalp EEG recordings.

In summary, EEG/fMRI data identified regional brain responses consistently associated with slow waves and spindles. Both slow waves and

spindles result in increased activity in a distributed set of cortical and subcortical areas, suggesting that these oscillations transiently synchronize large-scale brain networks and potentially affect information processing during sleep. These consistent regionally specific response patterns complement the characterization of their variability illustrated by electrophysiological recordings. It is also worth observing that the description of the neural correlates of human NREM sleep rhythms is still fragmentary and other oscillations remain to be fully characterized. For instance, preliminary results showed that infraslow EEG oscillations (<0.1 Hz) during NREM sleep appear to be associated with activity increases in subcortical structures and negative responses in the cortex (Picchioni et al., 2011).

Functional Connectivity

Interactions between neural populations or, at the macroscopic level, between brain areas constitute a fundamental aspect of brain function. Functional connectivity is usually assessed by temporal covariations of activity between brain areas (Friston, Frith, Liddle, & Frackowiak, 1993). During resting wakefulness, spontaneous fluctuations of regional brain activity occur simultaneously in several distributed sets of brain areas. Several such functional networks are reliably identified across subjects (Damoiseaux et al., 2006). One of these networks is composed of brain areas that are consistently more active during resting wakefulness than when the subject is engaged in a cognitive task (Raichle et al., 2001). This network, which is usually referred to as the default mode network, includes medial anterior areas (medial prefrontal cortex, anterior cingulate cortex) and posterior regions (precuneus, posterior cingulate cortex, inferior parietal lobule).

During light NREM sleep, functional connectivity does not change in primary sensory areas and in the default mode network, relative to wakefulness (Larson-Prior et al., 2009). The connectivity between the intraparietal sulcus and frontal eye fields, two regions involved in attention, is even increased (Larson-Prior et al., 2009). In contrast, during deep NREM sleep, the connectivity between frontal and posterior components of the default mode network significantly decreases (Horovitz et al., 2009). These findings are consistent with a comprehensive analysis of functional connectivity using graph theory, which showed that changes in functional connectivity were specific to sleep stages (Spoormaker et al., 2010). Thalamocortical connectivity was significantly reduced at the transition from wakefulness to light NREM sleep. In contrast, the connectivity between cortical areas was maintained or even increased during light sleep, but broke down during

deep NREM sleep. The reduction in corticocortical connectivity was more pronounced for long than short connections, which resulted in increased local clustering in deep NREM sleep. Although the functional significance of these changes in functional connectivity are not yet fully understood, they imply that information processing during deep NREM sleep substantially differs from wakefulness. The results suggest that brain function during deep NREM sleep is organized in multiple segregated functional systems, a pattern which echoes the local expression of slow waves and spindles.

REM SLEEP

REM sleep is characterized by tonic features that persist throughout REM sleep, such as fast, low amplitude EEG oscillations, muscle atonia or, in animals, rhythmic hippocampal theta rhythm. It is also associated with phasic features, that occur episodically, such as rapid eye movements, muscle twitches, autonomous instability or, in animals, pontine waves.

REM sleep is associated with an intense neuronal activity, similar to waking levels (Steriade & McCarley, 2005). Accordingly, brain glucose metabolism (Maquet et al., 1990) and oxygen utilization (Madsen, Schmidt, Wildschiodtz et al., 1991) are elevated during REM sleep and reach levels comparable to wakefulness. However, the spatial distribution of brain activity during REM sleep and wakefulness differ considerably. Cerebral blood flow measurements using PET characterized the distribution of regional brain activity during REM sleep. In keeping with animal data (Lydic et al., 1991; Ramm & Frost, 1986), REM sleep was associated with a high activity in the brainstem and thalamic nuclei as well as in limbic and paralimbic areas: the amygdala, the hippocampal formation, and the anterior cingulate, orbitofrontal, and insular cortices (Braun et al., 1997; Maquet et al., 1996; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997). Temporal and occipital cortices (Braun et al., 1997) as well as motor and premotor areas (Maquet et al., 2000) were also shown to be very active during human REM sleep. These activity increases contrasted with the relative quiescence of the associative frontal and parietal cortices (Braun et al., 1997; Maquet et al., 1996; Maquet et al., 2005).

Functional brain connectivity is also modified during REM sleep. For instance, REM sleep was associated with selective activation of extrastriate visual cortices, which was correlated with decreases in the striate cortex (Braun et al., 1998). Likewise, the functional relationship between the amygdala and the temporal and occipital cortices was enhanced during REM sleep relative to wakefulness or NREM sleep (Maquet & Phillips, 1998).

The mechanisms explaining this peculiar distribution of cortical activity are not yet fully understood. They might be intimately related to the activity of brain structures that generate REM sleep. For instance, the precoeruleus area in rat, a pontine REM-on area, projects to the medial septum and might influence hippocampal theta EEG during REM sleep (Lu, Sherman, Devor, & Saper, 2006). Changes in neuromodulation, predominantly cholinergic during REM sleep (Steriade & McCarley, 2005), could also participate in modifying the distribution of forebrain activity although to our knowledge, this suggestion has not been experimentally tested.

The neural correlates of phasic REM sleep have seldom been investigated in humans. Several observations suggest the presence of pontine waves during human REM sleep. Intracerebral recordings in the striate cortex of epileptic patients showed monophasic or diphasic potentials during REM sleep, appearing in isolation or in bursts (Salzarulo, Lairy, Bancaud, & Munari, 1975). Phasic potentials suggestive of PGO waves were also recorded from the pedunculopontine nucleus (Lim et al., 2007) and subthalamic nucleus (Fernandez-Mendoza et al., 2009) in patients with Parkinson disease before and during REM sleep. In normal subjects, the evidence is naturally more speculative. Transient occipital and/or parietal potentials time-locked to rapid eye movements were observed on EEG recordings in normal volunteers during REM sleep (McCarley, Winkelman, & Duffy, 1983). MEG recordings revealed similar potentials during REM sleep and their magnetic source was localized in the brainstem, thalamus, hippocampus, and occipital cortex (Inoué, Saha, & Musha, 1999). The sequence of activation of these magnetic sources suggested that the activation of the frontal eye field and the pons precedes the recruitment of limbic and paralimbic areas (orbitofrontal cortex, amygdala, parahippocampal gyrus) (Ioannides et al., 2004). Using PET and cerebral blood flow measurements, it was shown that the activity in the right geniculate body and the primary occipital cortex increases in proportion to the density of eye movements to a larger extent during REM sleep than during wakefulness (Peigneux et al., 2001), a result confirmed by fMRI studies (Hong et al., 2009; Miyauchi, Misaki, Kan, Fukunaga, & Koike, 2009; Wehrle et al., 2005).

The variability of respiratory and heart rates is another phasic aspect of REM sleep. A preliminary PET study showed that the variability of heart rate was more tightly correlated with the activity in the extended amygdala during REM sleep than during wakefulness (Desseilles et al., 2006). In addition, the functional connectivity between the amygdala and

the insular cortex, a region involved in cardiovascular regulation during wakefulness (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000), was weaker during REM sleep than during wakefulness. These results suggest a functional reorganization of central cardiovascular regulation during REM sleep that deserves further investigation.

FUNCTIONAL NEUROIMAGING OF MEMORY PROCESSING DURING SLEEP

Due to his permanent interaction with the environment, the individual continuously acquires new memories. Initially labile, these representations are further processed and transformed into more stable ones, which are progressively incorporated into long-term memories. This process, which is referred to as memory consolidation, involves changes in brain structure and function at both synaptic and systems levels. Sleep was shown to actively promote memory consolidation. It is associated with improved retention of declarative memories (Gais, Lucas, & Born, 2006) and enhanced performance in procedural learning tasks (Gais, Plihal, Wagner, & Born, 2000; Stickgold, James, & Hobson, 2000; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). It also renders memories more resistant to interference (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). The mechanisms underlying sleep-dependent memory consolidation are currently conceived within two conceptual frameworks. The first one suggests that sleep locally and ubiquitously maintains synaptic homeostasis; the second assumes that sleep promotes the systems-level reorganization of memories within hippocampo-neocortical networks.

Sleep and Synaptic Homeostasis

This theory claims that wakefulness is associated with a net increase in synaptic strength in the brain, which would become energetically unsustainable in the long term (Tononi & Cirelli, 2003, 2006). Due to this progressive synaptic potentiation, sleep pressure would increase monotonically in the brain with time spent awake, or more precisely, in proportion to neural activity accrued locally during wakefulness. During NREM sleep, slow waves would be associated with a gradual downscaling of the average brain synaptic strength to a baseline level, a process beneficial for learning and memory because it ultimately increases the signal-to-noise ratio related to the learned material. In support of this hypothesis, a local increase in slow wave activity (SWA) is locally enhanced following increased neural

activity during waking: vibratory stimulation of the hand (Kattler, Dijk, & Borbely, 1994), training to a visuomotor adaptation task (Huber, Ghilardi, Massimini, & Tononi, 2004), transcranial magnetic stimulation of the motor cortex (Huber, Esser, et al., 2007), or after spike timing-dependent activity is elicited during waking by transcranial paired associative stimulation (Huber et al., 2008). In contrast, arm immobilization results in a decrease in SWA over controlateral sensorimotor areas during subsequent NREM sleep (Huber et al., 2006).

This hypothesis is currently supported by a number of animal data. Slow wave activity increases in rats exposed to enriched environment in relation to release of BDNF (brain-derived neurotrophic factor), a neurotrophin involved in synaptic potentiation (Huber, Tononi, & Cirelli, 2007). At the cellular level, multiunit recordings showed that the mean firing rate in the cerebral cortex increases after periods of wakefulness and decreases after periods of sleep, consistent with a net change in synaptic strength (Vyazovskiy et al., 2009). Changes in firing patterns in NREM sleep correlate with changes in slow-wave activity (Vyazovskiy et al., 2009). The slope and amplitude of cortical evoked responses, taken as markers of local synaptic strength, increase after wakefulness and decrease after sleep in proportion to changes in SWA (Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008). The level of several molecular markers of synaptic potentiation are elevated in the cortex after a period of wakefulness and low after sleep, consistent with synaptic potentiation during wakefulness and depression during sleep (Vyazovskiy et al., 2008). Finally, there is evidence in flies that synapse size or number increases after a few hours of wake and decreases during sleep (Bushey, Tononi, & Cirelli, 2011).

Sleep-Dependent Systems-Level Consolidation of Hippocampal-Dependent Memories

Organisms are continuously exposed to novel pieces of information and have to flexibly retain this new information while preserving the knowledge, concepts, and skills gradually forged by earlier experience. To resolve this conflict, it has been assumed that the brain resorts to complementary learning systems with different dynamics (Marr, 1970, 1971; McClelland, McNaughton, & O'Reilly, 1995). On the one hand, novel information would quickly induce substantial changes in synaptic strength in the hippocampus. By contrast, in the cortex, it would result in limited synaptic changes that would not be sufficient to allow for the reliable reinstatement of the specific response pattern associated with a recent memory. Multiple

repetitions of similar phases of information processing would be necessary for synaptic changes to accumulate thereby gradually reinforcing this novel representation and integrating it into the corpus of long-term representations stored predominantly in the cortex. Spontaneously reinstatements of hippocampal and neocortical activity associated with newly encoded representations would participate in this process and progressively strengthen corticocortical connections, which eventually buttress long-term memories (Marr, 1970, 1971; McClelland et al., 1995). These so-called "reactivations" can occur both during wakefulness and sleep. However, sleep appears as a particularly favorable period for memory reactivation, since the brain is less responsive than during wakefulness to environmental stimuli, which might potentially interfere with the learned material.

Reactivations have indeed been observed at the cellular level during both NREM and REM sleep in rodents. Neural firing patterns recorded during wakefulness are spontaneously repeated during sleep in the hippocampus (e.g., Louie & Wilson, 2001; Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999), which coincide with sharp waves and ripples (Kudrimoti, Barnes, & McNaughton, 1999). The selective elimination of hippocampal ripples during post-training consolidation periods impairs spatial memory tasks (Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009). Replay of neural firing patterns is also observed in various brain structures such as the neocortex (Ji & Wilson, 2007; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009; Ribeiro et al., 2004), or the striatum (Pennartz et al., 2004). Importantly, during NREM sleep, reactivations in the neocortex appear in close temporal synchrony with hippocampal sharp waves (Ji & Wilson, 2007; Peyrache et al., 2009), within 100 ms after the hippocampal cells (Wierzynski, Lubenov, Gu, & Siapas, 2009). In particular, the interactions between the hippocampus and the medial prefrontal cortex seem to play a key role in memory consolidation of hippocampal-dependent memories. The medial prefrontal cortex shows compressed replays of neural activity patterns during sleep (Euston, Tatsuno, & McNaughton, 2007), which coincide with hippocampal sharp waves and are selectively induced by the acquisition of novel information (Peyrache et al., 2009). Collectively, these findings illustrate learning-dependent hippocampo-neocortical interactions during post-training sleep, consistent with the hypothesis of a systems-level memory consolidation.

Some results suggest that at the macroscopic brain systems level, similar reactivations occur during NREM sleep in humans. After the exploration of a virtual tridimensional maze, the activity is enhanced during NREM

sleep in occipital, parietal, and mesiotemporal areas (Peigneux et al., 2004). Moreover, the increase in hippocampal activity is linearly related to the individual gain in the ability to navigate in the maze the next day, suggesting that the changes in hippocampal activity during NREMS relates to the offline processing of topographical memory. No such reactivation was observed during REM sleep. In order to experimentally induce learning-related reactivations, olfactory cues were associated with the encoding of object locations during a source memory task. Reexposure to conditioned cues during NREM sleep improved memory retention and increased hippocampal activity, as assessed by fMRI (Rasch, Buchel, Gais, & Born, 2007). Again, conditioned cues were ineffective if delivered during REM sleep or wakefulness. Finally, reactivating memories by conditioned cues during NREM sleep not only is associated with significant hippocampal and neocortical responses, but it also increases their subsequent resistance to interference (Diekelmann, Buchel, Born, & Rasch, 2011). These findings support the view that the hippocampal activity during NREM sleep results in a strengthening and stabilization of recent memories.

Conversely, hindering the offline memory processing by sleep deprivation modifies the neural correlates of subsequent retrieval. In a within-subject cross-over design, recall of word-pair associates was assessed using fMRI 48 hours after encoding (Gais et al., 2007). In one condition, sleep was allowed in as usual during the two post-encoding nights. In the other condition, the volunteers were totally sleep deprived on the first post-encoding night. Hippocampal responses were significantly larger during recall of words learned before sleep than before sleep deprivation. In addition, sleep enhanced the functional connectivity between the hippocampus and the mPFC during recall. Six months later, memory recall more strongly recruited the medial prefrontal and occipital cortex for words that were encoded before sleep than before sleep deprivation. These results confirm earlier experiments in humans showing that over the course of three months, hippocampal activity during memory retrieval gradually decreases whereas activity in a ventral medial prefrontal region increases (Takashima et al., 2006). However, they further show that sleep after encoding leads to a long-lasting reorganization in memories in the cortex. Sleep deprivation had similar effects on emotional memory, although the recruitment of mesial prefrontal cortex could be observed as early as 72 hours after encoding. In a between-subjects design, episodic recognition of emotional and neutral stimuli was tested 72 hours after encoding, with or without total sleep deprivation during the first post-encoding night (Sterpenich et al.,

2007). Successful recollection of emotional stimuli elicited larger responses in the hippocampus and the medial prefrontal cortex in the sleep group than in the sleep deprived group. In addition, the functional connectivity between hippocampus and medial prefrontal cortex was enhanced during recollection of emotional items after sleep. Six months later, recollection was associated with significantly larger responses in subjects allowed to sleep than in sleep-deprived subjects, in a set of cortical areas, including the medial prefrontal cortex, the precuneus, and the occipital cortex (Sterpenich et al., 2009). Moreover, the functional connectivity was enhanced between the medial prefrontal cortex and the precuneus. These results confirm that sleep during the first night after encoding profoundly influences the long-term organization of memories in cortical networks.

In sum, NREM sleep is associated with a strengthening of memories that become resistant to interference. Functional neuroimaging in humans shows that hippocampal activity increases during post-training NREM sleep, suggesting that the hippocampus, and its interactions with cortical areas, takes part in memory consolidation. When these processes are disturbed by sleep deprivation, responses at retrieval are altered in the hippocampus and, in the long term, in cortical networks which involve the medial prefrontal cortex.

Early Memory Structuring during Encoding

Given the central role of the hippocampus in the consolidation of declarative memories, one may wonder if the hippocampal activity during encoding is a critical factor in making a memory trace susceptible to sleep-dependent consolidation. Some functional neuroimaging data support this view. In a study testing the effect of directed forgetting, volunteers were asked to learn a series of words (Rauchs et al., 2011). Each word was followed by an instruction indicating whether the item was to be remembered (TBR item) or forgotten (TBF item). During the following night, half of the volunteers were allowed to sleep whereas the others were totally sleep deprived. Three days after encoding, memory for TBR and TBF items was probed using a recognition task during which subjects had to categorize each word presented as previously learned or not. The key finding was a larger response in the hippocampus during encoding of TBR items that were later remembered compared with TBR items that were ultimately forgotten. No such difference was detected for the TBF items indicating that the hippocampal recruitment during encoding identified memories that would be ultimately consolidated. In addition,

the increase in hippocampal response was observed only in the volunteers allowed to sleep and not in the sleep deprived group, indicating that memory consolidation was sleep-dependent. These findings suggest that the recruitment of the hippocampus during encoding foreshadows subsequent sleep-dependent memory consolidation.

Sleep-Dependent Consolidation of Procedural Motor Memories

Sleep promotes the consolidation of motor memories. In particular, during motor sequence learning sleep has been associated with spontaneous gains in performance (Walker et al., 2002) and increased resistance to interference (Korman et al., 2007). The neural correlates of this sleep-dependent motor consolidation have not yet been systematically characterized.

The activity during REM sleep after motor sequence learning is enhanced in various brain areas (Maquet et al., 2000). Normal volunteers were trained to a probabilistic serial reaction task. In this task, participants have to press as fast and as accurately as possible on the key corresponding to a stimulus appearing at one out of six possible screen positions. Unknown to subjects, the sequence of stimulus positions was generated by a probabilistic finite-state grammar. In comparison to control volunteers who were not trained to the task, the activity in premotor and occipital cortices, thalamus, and upper brainstem was increased during REM sleep in trained participants. In addition, the functional connectivity between premotor cortex and posterior parietal cortex and presupplementary motor area was also enhanced during REM sleep after training (Laureys et al., 2001). These changes in regional activity during REM sleep were observed only if the learned material was structured by hidden rules imposed by the probabilistic grammar and not when it was random, suggesting that they were related to the processing of the underlying higher-order sequential structure (Peigneux et al., 2003).

Other attempts to assess the effects of sleep on procedural motor learning characterized the neural correlates of the finger tapping task. In this task, volunteers have to repeat an explicitly known five-element finger sequence as rapidly and as accurately as possible with their nondominant hand. In two studies, volunteers were either trained in the morning or in the evening, and tested 12 hours later, in the morning (after sleep) or in the evening, after an equivalent period of wakefulness. Increased responses were observed at retest after sleep in the ventral striatum (Debas et al., 2010), or in the right primary motor cortex, medial prefrontal lobe,

hippocampus. and left cerebellum (Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). In another study, volunteers were scanned during initial training and 2 days later, at retesting, with either sleep or sleep deprivation during the first post-training night (Fischer, Nitschke, Melchert, Erdmann, & Born, 2005). In these conditions, sleep was associated with reduced brain responses in prefrontal, premotor, and primary motor cortical areas. The reasons for these discrepancies are unclear but they probably arise from differences in experimental design (day/evening versus sleep/sleep deprivation), which might be associated with different levels of local sleep pressure. They might also characterize the evolution of motor memory trace at different stages of their consolidation.

The detailed mechanisms underlying sleep-dependent consolidation of motor memories are still unsettled. Behavioral evidence indicates that it might vary according to different experimental factors. For instance, the consolidation of dynamic visuomotor adaptation would differ from sequence learning (Debas et al., 2010); implicit and explicit learning would result in different time courses of consolidation (Robertson, Pascual-Leone, & Press, 2004); and the complexity of the learned material might influence memory consolidation (Kuriyama, Stickgold, & Walker, 2004). Likewise, procedural motor memory has been associated to various aspects of sleep: sleep in the second half of the night (Plihal & Born, 1997), sleep spindles (Fogel & Smith, 2006; Morin et al., 2008), or REM sleep (Fogel, Smith, & Cote, 2007). Both synaptic (Huber et al., 2004) and system-level consolidation (Debas et al., 2010) have been involved in motor memory consolidation. Further research is obviously required to gain a thorough understanding of motor memory consolidation during sleep.

CONCLUSIONS

Over the years, functional neuroimaging has revealed several important aspects of human sleep. After demonstrating the profound differences in brain energy metabolism and hemodynamics between wakefulness and sleep, functional data have showed the dynamic fluctuations of regional brain activity resulting from sleep-specific oscillations. Slow waves and spindles have been shown to result in transient synchronous activity in distributed brain areas. These activity patterns certainly constrain the way the brain processes information during sleep. This was also suggested by profound changes in functional integration taking place across brain areas during sleep. Finally, functional neuroimaging has shown the significant influence of waking experience on regional brain

function during sleep. During NREM sleep, data are consistent with both a ubiquitous use-dependent increase in slow oscillation but also with a reorganization of declarative memories within hippocampal-neocortical circuits.

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