Neuroimaging Studies of Sleep and Memory in Humans

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Abstract Human brain dynamics are nowadays routinely explored at the macroscopic level using a wide variety of non-invasive neuroimaging techniques, including single photon emission computed tomography (SPECT) and positron emission tomography (PET), near infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI). In the past decades, the application of brain imaging methods to the study of sleep raised a renewed interest for the field, especially in the domain of neuroscience. Indeed, these studies enabled researchers to characterize the functional neuroanatomy of sleep stages and identify the neural correlates of phasic and tonic sleep mechanisms. Furthermore, they provided the scientific community with tools to address the crucial question of brain plasticity processes during human sleep, the role of sleep-related plasticity for memory consolidation, and how sleep and the lack of post-training sleep impacts brain functioning in the neural networks underlying memory-related cognitive processes. This chapter reviews the contributions of neuroimaging to our understanding of the functional neuroanatomy of sleep and sleep stages, and discusses how sleep contributes to the long-term consolidation of recently acquired memories in light of contemporary neural models for memory consolidation during sleep.

Keywords Sleep · Memory · Neuroimaging · Human · Sleep deprivation · Learning · Memory consolidation · Brain plasticity · Behaviour · Function of sleep · REM · NREM · SWS

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1 Functional Neuroanatomy of Sleep and Sleep Stages

Early positron emission tomography (PET) sleep studies were mostly conducted using the [18F]-fluorodeoxyglucose (FDG) tracer, now widely used in clinical settings. These studies revealed a striking diminution of global cerebral glucose metabolism during non-rapid eye movement (NREM) sleep (Buchsbaum et al. 1989; Maquet et al. 1990), especially during the slow wave sleep (SWS) phase (Maquet et al. 1990). Global cerebral glucose metabolism showed only small decreases during the light stage 2 of NREM sleep (Maquet et al. 1992), and most importantly was shown *not* to differ from wakefulness during the rapid eye movement (REM) sleep phase (Buchsbaum et al. 1989; Maquet et al. 1990). At the regional, local cerebral level, glucose consumption was shown to decrease in the thalamus during SWS (Buchsbaum et al. 1989; Maquet et al. 1990, 1992). However, the use of FDG whose radioactivity decays in the scale of hours does not allow repeated measurements within a same night, is not temporally precise enough to focus on one sleep stage in particular and is lacking power for an

accurate description of the brain areas involved in the mechanisms subtending the promotion and the maintenance of sleep. Hence, although the FDG-PET technique remains in use for the investigation of the neuroanatomy of some sleep-related disorders (for reviews see e.g. Maquet 2005; Nofzinger 2004; Desseilles et al. 2011) and even normal sleep (e.g. Buchsbaum et al. 2001; Nofzinger et al. 1997), inferences that can be drawn from these studies are constrained by technical limitations. One advantage, however, of the long half-life ($\sim$120 min) of this compound is that it allows for the injection of the tracer while the participant is still lying in his own bed during a sleep episode of interest, and the subject can be transferred to the scanner for acquisition at some time later, thus minimizing discomfort and allowing for longer periods of sleep (e.g. Nofzinger et al. 1998). Similar advantages and limitations apply to the single photon emission computed tomography (SPECT) technique, which was used to demonstrate sleep-related cerebral activity patterns associated with sleep disorders behaviours. For instance, this approach revealed a dissociation between the activation of thalamocingulate pathways and the persisting deactivation of other thalamocortical arousal systems during sleepwalking (Bassetti et al. 2000), or increased perfusion in the supplementary motor area during a REM sleep behaviour attack (Dauvilliers et al. 2011).

1.1 Non-Rapid Eye Movement Sleep

Further improvements in high-resolution PET scanners, the introduction of iterative regional cerebral blood flow (rCBF) measurements (especially using the $H_2{}^{15}O$ infusion technique) and the development of more powerful statistical methods have been critical determinants to allow a reliable delineation of the functional neuroanatomy of normal sleep stages in humans (for a critical methodological discussion, see Maquet 2000). Using the $H_2{}^{15}O$ technique, several studies (Andersson et al. 1998; Braun et al. 1997; Hofle et al. 1997; Kajimura et al. 1999; Maquet et al. 1997) showed that those areas in which cerebral blood flow (CBF) significantly decreases during SWS as compared to wakefulness and REM sleep are located in a distributed cerebral network including the dorsal pons and mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain/hypothalamus, prefrontal cortex, anterior cingulate cortex, precuneus and the mesial temporal lobe. At the time scale of PET recordings, averaging neural activity over tens of seconds, the alternation of short bursts of synchronized neuronal activity with "silent" periods dominated by hyperpolarization during SWS (Steriade and Amzica 1998) actually results in a net decrease in the metabolic rate and consequently in regional CBF (Maquet 2000). Accordingly, EEG spectral power in the 0.5–4 Hz range during NREM sleep negatively correlates with rCBF in those brain areas in which CBF decreases during SWS (Fig. 1), including in the ventromedial prefrontal cortex, the basal forebrain, the striatum, the anterior insula and the precuneus (Dang-Vu et al. 2005). No correlation with thalamic activity was found in this latter study however, in contrast to a prior PET study where waking and

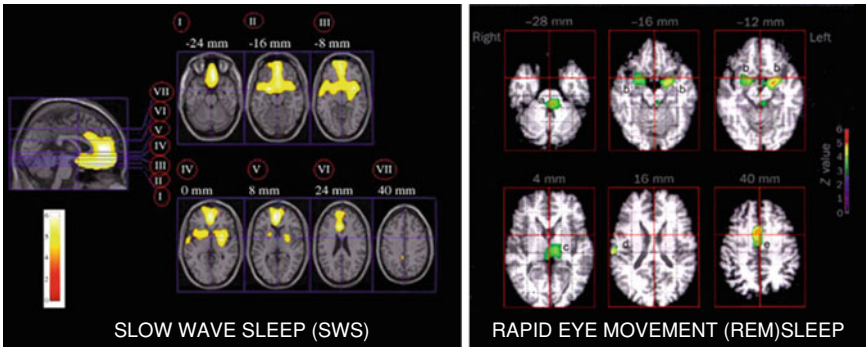

Fig. 1 Functional neuroanatomy of SWS and REM sleep. Brain sections showing brain areas where regional cerebral blood flow (rCBF) was negatively correlated with the density of slow oscillations (delta power) during SWS (*left panel*) or increased during REM sleep as compared to wakefulness (*right panel*). Adapted with permission from Dang-Vu et al. (2005) and Maquet et al. (1996)

NREM sleep scans were intermixed (Hofle et al. 1997). Hence the findings of Dang-Vu et al. (2005) support the proposal that extra-thalamic delta rhythms contribute to synchronous NREM sleep oscillations (Steriade 2003).

1.2 Rapid Eye Movements Sleep

In contrast to NREM sleep, REM sleep and wakefulness are characterized by sustained, desynchronized neuronal activity (Steriade and McCarley 1990) associated with high energy demands. Therefore, activity as measured using PET should be increased in brain regions actively involved in REM sleep as compared to NREM sleep, even above activity levels observed during wakefulness. Accordingly, regional patterns of activation have been observed during REM sleep using $H_2{}^{15}O$-PET (Braun et al. 1997; Maquet et al. 1996). These studies evidenced markedly increased rCBF in the mesopontine tegmentum, the thalamic nuclei, limbic (amygdaloid complexes, hippocampal formation, anterior cingulate cortex) and temporo-occipital areas (Fig. 1). Conversely, activity in the dorso-lateral prefrontal cortex, parietal cortex, as well as the posterior cingulate cortex and precuneus was reduced as compared to the awake resting-state. These results confirmed animal reports (e.g. Lydic et al. 1991) suggesting a heterogeneous and regionally specific distribution of telencephalic activity during REM sleep. Additionally, temporal correlations between neural activity in the amygdala and neuronal activity in the occipito-temporal areas during REM sleep suggested a modulation of these cortical areas by the limbic system (Maquet and Phillips 1998), which might participate in the mechanisms underlying dreaming activity (Schwartz and Maquet 2002) and emotional memory processing. $H_2{}^{15}O$ PET results also supported the hypothesis of the existence of ponto-geniculo-occipital

(PGO) waves in human (Peigneux et al. 2001). As evidenced in animal studies, PGO waves are responsible for the generation of REMs, and trigger cellular processes thought to favour brain plasticity during REM sleep (Datta 1999).

2 Transient and Oscillatory Processes in Sleep

Beyond regional patterns of sustained cerebral activity as evidenced by PET, functional magnetic resonance imaging (fMRI) has become a powerful tool for the description of the functional neuroanatomy of transient and oscillatory processes in sleep. fMRI, which records cerebral activity at the scale of the second, provides a more accurate temporal resolution than PET together with a good localizing power in the whole brain. A main disadvantage is the subject's discomfort in the scanner, due to elevated noise levels and the restricted space within the magnet. Nowadays, technical difficulties to get suitable EEG signal needed for the identification of sleep stages and characterization of sleep events in the fMRI environment are no longer an obstacle to research.

2.1 Stimulating the Brain to Understand the Neurophysiology of Sleep

Functional MRI studies initially focused on the cerebral correlates of auditory stimulations as a probe for the investigation of sleep neuroanatomy (Czisch et al. 2002, 2004; Kaufmann et al. 2006; Portas et al. 2000; Wehrle et al. 2007). The choice of auditory stimulations in sleep was mostly for practical and technical reasons, as it is rather easy to deliver sounds at non-awakening threshold in the context of the magnetic environment, as compared to e.g. tactile stimulations. Results of these studies mostly confirmed PET findings in terms of sleep stage-specific (Czisch et al. 2002, 2004; Kaufmann et al. 2006; Portas et al. 2000; Wehrle et al. 2007) and PGO-related (Kaufmann et al. 2006) activations patterns, further disclosing auditory reactivity differences in specific brain networks between phasic and tonic REM sleep episodes (Wehrle et al. 2007).

2.2 Endogenous Brain Stimulation: The up and down of Slow Oscillations and Spindles

Simultaneous EEG/fMRI recordings have enabled researchers to revisit the PET-based concept of SWS as a stage of brain quiescence, reputedly characterized by global and regional decreases of brain activity. Indeed, animal research taught us that cortico-thalamocortical loops are involved in the generation of EEG spindles

(11–15 Hz) and delta waves (0.5–4 Hz), which in turn are organized by cortically generated slow oscillations (<1 Hz; Steriade 2001), and that these rhythms (under the control of brainstem and forebrain modulatory systems) are combined within specific time windows corresponding to the depolarizing phase (up state) of the slow oscillations (Steriade 2005). Dang-Vu et al. (2008) used an endogenous event-related approach to investigate using fMRI the transient changes in regional cerebral activity specifically associated with slow waves (<1 Hz; >140 μV) and delta waves (0.5–4 Hz; 75–140 μV) during NREM sleep. That is, the events of interest were defined based on the participant's own neurophysiological activity, e.g. the rising slope of each slow wave during SWS, rather than on the occurrence of an externally delivered, exogenous stimulus (like for instance a sound). Using this approach, they found increased activity coincident with the active depolarized ("up") state of oscillations (as indexed by peak negativity in the EEG) in several cortical areas including the inferior frontal and medial prefrontal cortices, and the precuneus and posterior cingulate areas, both for slow and delta waves. Besides these commonalities, slow oscillations (<1 Hz) were associated with increased activity in the parahippocampal gyrus, the cerebellum and the brainstem, whereas delta waves were specifically associated with increased activity in frontal areas (Fig. 2). Another study found infraslow (<0.1 Hz) oscillations in the EEG band positively correlated with brain activity mostly in subcortical regions including cerebellum, thalamus, basal ganglia and hippocampus, whereas these infraslow oscillations negatively correlated with cortical activity (Picchioni et al. 2011). Additionally in the Dang-Vu et al. (2008) study, increased activity associated with slow oscillations was found in the midbrain and the pontine tegmentum, a region that includes critical structures involved in the regulation of sleep and wakefulness, and this activation encompassed the noradrenergic locus coeruleus (LC). In line with animal data (Eschenko et al. 2012), these findings suggest that pontine structures are active in phase with slow oscillations, possibly to allow the brain periodically restoring microwake-like activity patterns facilitating neuronal interactions (Dang-Vu et al. 2008). Hence, EEG/fMRI studies confirm that human NREM sleep genuinely is an active state during which phasic increases in brain activity are synchronized to slow oscillations.

Another endogenous event-related fMRI study showed that the occurrence of phasic sleep spindles during NREM sleep is associated with increased brain activity in a cortico-subcortical network including the thalamus, paralimbic areas, and superior temporal gyri (Schabus et al. 2007). Besides, activity in different thalamocortical networks was associated with fast (13–15 Hz) and slow (11–13 Hz) spindles. Indeed, whereas slow spindles were associated with activation of the superior temporal gyrus, fast spindles preferentially recruited hippocampal and sensorimotor cortical areas, further supporting the hypothesis that fast and slow spindles rely upon two functionally separated systems (Fig. 2). Another study similarly found increased spindle-related activity in the thalami, putamen, posterior cingulate, paracentral and temporal cortices, and an additional association between the occurrence of K-complexes and increased activity in the thalami, superior temporal and medial occipital, parietal and frontal areas (Caporro et al. 2012).

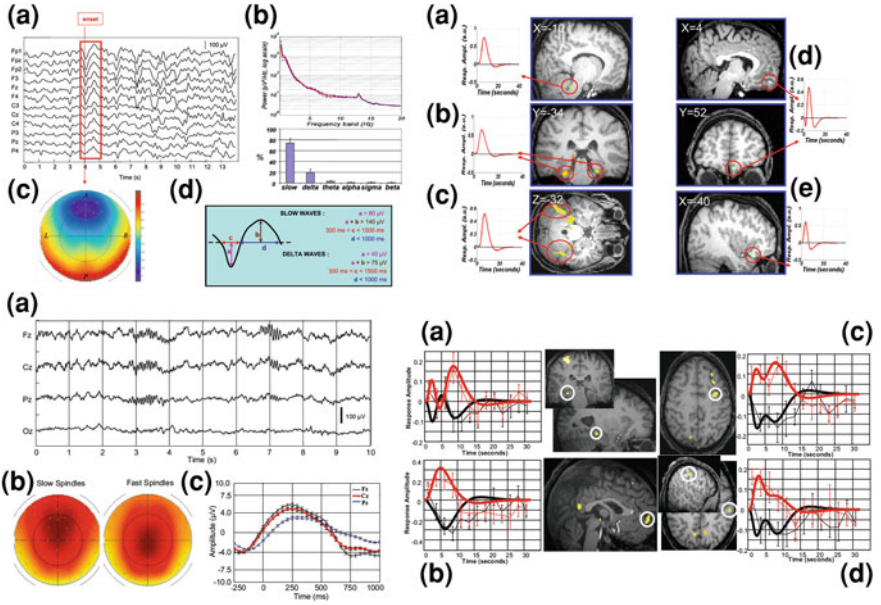

Fig. 2 Slow oscillations and spindles during NREM sleep investigated using endogenous event-related EEG-fMRI. *Left top* panel shows **a** detection of the onset of sleep EEG slow oscillations (peak negativity for sample wave framed in *red*); **b** EEG power spectrum; **c** topographical distribution of slow wave sleep epochs; and **d** criteria for separate detection of slow and delta waves. *Right top* panel shows brain regions specifically activated in relation to high amplitude slow waves (<1 Hz) (**a** Pontine tegmentum, **b** Parahippocampal gyrus, **c** Cerebellum) or in relation to delta waves (1–4 Hz) (**d** Medial prefrontal cortex, **e** Inferior frontal gyrus). Adapted with permission from Dang-Vu et al. 2008. *Left bottom* panel shows EEG characterization of sleep spindles with **a** representative spindles on a typical stage 2 sleep EEG recording after correction for fMRI-related artifacts; **b** topographical distribution of slow (11–13 Hz) and fast (13–15 Hz) spindles; and **c** EEG data (0.5–4 Hz) averaged with respect to the onset of all sleep spindles, showing that spindles start (time 0) on the depolarizing phase of the oscillation. *Right bottom* panel depicts differential fMRI activity (BOLD response) between fast and slow spindles. Larger brain responses for fast (*red*) than slow (*black*) spindles are revealed in the hippocampus (**a**), mesial prefrontal cortex (**b**), precentral gyrus (**c**), and postcentral gyrus (**d**). Side panels show the differential evolution of BOLD responses in fast and slow spindles. Adapted with permission from Schabus et al. 2007

2.3 *Endogenous Activity Modulates Brain Responsiveness to External Stimulation*

Both spindles and slow oscillations can modulate brain responsiveness to auditory stimulation during NREM sleep. Two studies showed persistent wake-like responses during NREM sleep except when spindles were present (Dang-Vu et al. 2011; Schabus et al. 2012) or stimulations occurred in the downward slope of the slow oscillation (Schabus et al. 2012), during which responses became less

consistent or even absent. Together with distinct N550 EEG responses to tones during sleep spindles (Schabus et al. 2012), this suggests that the brain is more responsive during the upward slope of the slow oscillation during deep NREM sleep. The authors propose that the presence of short temporal windows during which the brain is open to external stimuli during NREM sleep is consistent with the fact that even during deep sleep meaningful events can be detected.

2.4 Dynamic Interactions in REM Sleep

Although REM sleep has been less thoroughly investigated using this technique, fMRI resting-state connectivity analyses showed that activity in the so-called default-mode network (Raichle et al. 2001) is functionally uncoupled during NREM sleep (i.e. there is diminished connectivity) then recoupled during REM sleep where it is similar to wakefulness (Chow et al. 2013). Additionally however, REM sleep was specifically characterized by a widespread, temporally dynamic interaction between unimodal sensorimotor areas and higher-order association cortices (including in the default-mode network). Indeed, the two systems become anticorrelated and fluctuated rhythmically, reciprocally alternating epochs with a frequency ranging from 0.1 to 0.01 Hz. The functionality of these slowly alternating activation patterns remains unknown.

2.5 Phasic REM Events and the Source of Spindles

Finally, magnetoencephalography (MEG) is distinct from fMRI in that it is noise-free and operates on a neuronal timescale, i.e. within the scale of milliseconds while having good localizing power. Hence, its features offer interesting opportunities to track the time course and spatial evolution of the magnetic correlates of cerebral activity associated with both endogenous and exogenous events during sleep. For instance, MEG was used to investigate cortical responses to diverse sensory and/or noxious stimuli during sleep (Kakigi et al. 2003; Wang et al. 2004). Furthermore, MEG allowed the differentiation of cerebral networks activated before, during and after ocular saccades initiation during REMs in REM sleep (Corsi-Cabrera et al. 2008; Ioannides et al. 2004), or to compute the source location of maximal spindle activity, which was found in precentral and/or post-central areas (Gumenyuk et al. 2009). Finally, it is worth noting that combined EEG and MEG studies have revealed heterogeneous MEG sources for human sleep spindles suggesting that multiple generators are active, whereas sleep spindles as measured by the EEG seem to be generated by a different, diffusely synchronous system (Dehghani et al. 2010a, b). These results are in line with animal studies that identified two thalamo-cortical systems, i.e. the core and matrix systems, which produce focal or diffuse activation (Jones 1998). Further imaging

(Dehghani et al. 2011) and computational (Bonjean et al. 2012) investigations suggest that synchronous spindles captured by the EEG emerge from asynchronous spindles recorded using MEG, in line with the hypothesis that the spatial coherence for spindles in the EEG is actually a consequence of diffuse matrix projections of the thalamus to layer 1 compared with the focal projections of the core pathway to layer 4 recorded in the MEG (Destexhe and Sejnowski 2003). Hence, MEG represents a complementary and useful non-invasive tool to improve our understanding of the complex neurophysiological mechanisms that subtend sleep phenomena.

3 Neural Models of Memory Consolidation During Sleep

Memory consolidation refers to a temporal process lasting from a few minutes to several years by which initially fragile memory traces undergo a series of transformations eventually leading to their strengthening into long-term memory stores (McGaugh 1966). Memory consolidation and the progressive modification of the acquired information are instances of brain plasticity, i.e. the capacity of the brain to adapt its function and structure over time to accommodate novel experience. Thus reorganization of cortical networks, disinhibition of neuronal assemblies, modification and remodelling of synaptic connections can be seen as instances of memory formation and consolidation processes. In this respect, experimental evidence suggests that the neurophysiological conditions of sleep are favourable for the consolidation of novel memories and their durable inscription in long-term memory stores (Peigneux et al. 2011).

3.1 Neuronal Replay and the Hippocampal-Neocortical Dialogue

It has been proposed that memory consolidation relies on complementary learning systems subtended by different neuroanatomical structures (Marr 1971; McClelland 1994). In the first step, information is quickly learned but only temporarily held into a transitory memory store. Robust encryption then takes place at a slower rate in lasting memory stores. Repetitive interactions between transitory and lasting memory stores allow connections subtending new memory items to be gradually reorganized and reinforced. Hence, two-stage models assume a progressive transfer of the learned information from transitory to lasting memory stores, where it will be progressively integrated into pre-existing networks. Expanding on this framework, the hippocampal-cortical dialogue model (Buzsaki 1996) proposes that memory consolidation takes place through repeated interactions between transitory and lasting long-term memory stores across multiple iterations of the sleep-wake cycle.

During wakefulness, learning-related information collected at the neocortical level is transferred and transiently stored in the hippocampus. During NREM sleep, characterized by decreased cholinergic activity, information preferentially flows in the opposite direction, from hippocampal to neocortical stores (Hasselmo 1999).

Consequently, repeated activation of the acquired information in the hippocampus during post-learning NREM sleep will eventually lead to a progressive transfer toward neocortical long-term memory stores. Conversely, higher cholinergic levels during REM sleep would promote information feedback toward hippocampal repositories. Memories will thus be stored and consolidated for the long-term across repeated SWS-REM sleep cycles. It is surmised here that neuronal patterns in hippocampal and neocortical stores are synchronized by the alternation of "up" and "down" states of slow oscillations during SWS (Fig. 3), an interpretation in line with neuroimaging findings reporting differential brain responsiveness between these two states (e.g. see above Dang-Vu et al. 2008, 2011). More precisely, the high-frequency bursts of neuronal activity in the hippocampus (i.e. the sharp wave ripples) and the thalamo-cortical spindles are triggered during the depolarizing ("up") phase of the slow oscillations. These sharp waves ripples synchronize with spindles that then propagate within the neocortex, inducing long-term potentiation (LTP) processes that would eventually modify synaptic strengths in interconnected neuronal networks (Rosanova and Ulrich 2005), hence promoting a progressive transfer of hippocampus-dependent memories to neocortical stores. It remains debated whether the consolidated information is erased from hippocampal stores upon transfer, or whether hippocampal pointers still contribute retrieving the information stored in long-term memory as proposed by the multiple trace theory (Nadel et al. 2000). It is worth noting here that the hippocampal-neocortical model associates the consolidation process mostly with SWS and hippocampus-dependent declarative and spatial memories. A broader, less-specific variant called the "neuronal replay hypothesis" proposes that cortical or subcortical activation patterns associated with novel learning are reactivated during subsequent sleep stages (either NREM or REM stages), eventually leading to the replay of the learned information and its gradual integration and/or transfer into long-term memory stores, an assumption supported by neuroimaging data showing reactivation of learning-related activity both during REM (Maquet et al. 2000; Peigneux et al. 2003) and NREM sleep (Peigneux et al. 2004; Rasch et al. 2007).

3.2 Synaptic Homeostasis and Memory Consolidation

An alternative, but not exclusive model for memory consolidation during sleep is the synaptic homeostasis theory (SHY) (Tononi and Cirelli 2006). The theory proposes that memory consolidation benefits from the local use-dependent synaptic downscaling phenomenon that takes place during sleep, as a secondary consequence of the growth of synaptic connections associated with novel learning at wake. This model posits that memory acquisition during wakefulness is

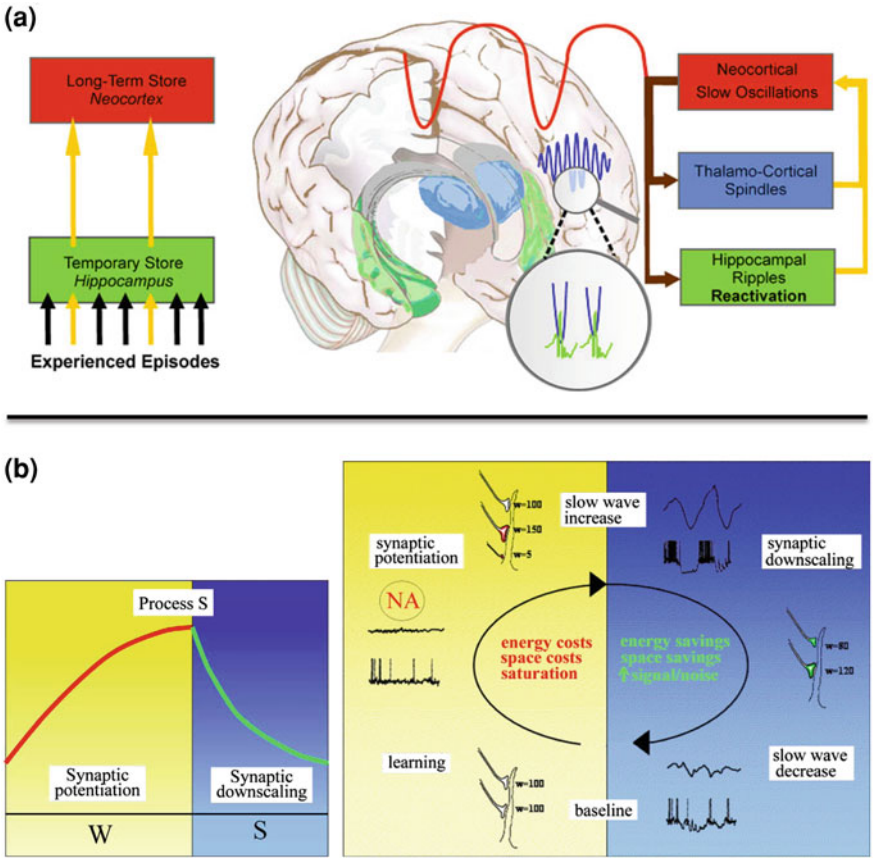

Fig. 3 Neural models of memory consolidation during sleep. **a** Hippocampal-neocortical dialogue. Information gained during novel experience is transiently stored in the hippocampus, and then progressively transferred into neocortical long-term memory stores. Transfer of information from hippocampal to neocortical areas during NREM sleep is promoted by SWS oscillations. Hippocampal ripples associated with the reactivation of the learned information are triggered during the depolarizing ("up") phase of the slow oscillations, and synchronized with thalamo-cortical spindles. Reprinted with permission from Born and Wilhelm 2011. **b** Synaptic homeostasis theory (SHY). Memory acquisition during wakefulness is associated with locally increased synaptic potentiation and elevated energy and space costs, eventually leading to the saturation of the learning-related neuronal network and decreased plasticity. Local neuronal saturation then leads to proportionally increased slow oscillatory activity during post-training NREM sleep, providing the necessary conditions to downscale synaptic strength to baseline level. This depotentiation process improves the signal-to-noise ratio in learning-related neuronal ensembles, consolidating the learned experience. Reprinted with permission from Tononi and Cirelli 2006

associated with locally increased synaptic potentiation and elevated energy and space costs, eventually leading to the saturation of the learning-related neuronal network and decreased plasticity. Local neuronal saturation will then lead to

proportionally increased slow oscillatory activity during post-training NREM sleep (Fig. 3). According to this model, homeostatically regulated slow oscillations during SWS offer optimal conditions to downscale synaptic strength to their baseline level, thus restoring the conditions for synaptic plasticity, while preserving the necessary differentiation between learning-related potentiated and other non-potentiated synapses. Hence slow oscillations would refine the synaptic weight and indirectly improve the signal-to-noise ratio in learning-related neuronal ensembles. In this context, weak memory traces will be removed and stronger traces remain, without the need for a transfer between remote brain structures. Consequently, this theory might be more appropriate to account for the consolidation of memories that are not dependent of the hippocampus, e.g. perceptual or motor memories processed at the neocortical level. In man, support for this theory was found in EEG studies showing locally increased slow oscillations during post-training NREM sleep in brain areas involved in a motor adaptation process (Huber et al. 2004; Landsness et al. 2009).

3.3 Dissociated and Integrated Memory Consolidation Processes Reconciled?

Despite different mechanisms and predictions, the hippocampo-neocortical and the synaptic homeostasis theories should not be seen as conflicting, as they more likely represent complementary phenomena in memory consolidation processes. For instance, increased hippocampal activity was observed using fMRI during the acquisition of an oculomotor sequence in fast-learning participants, who subsequently exhibited overnight improvement in performance, contrarily to slow-learning participants who did not initially engage hippocampal activity during learning and failed to improve performance overnight (Albouy et al. 2008). One can surmise that hippocampal tagging in fast learners actually reflects an initial homeostatic-like synaptic potentiation in hippocampal areas that might then trigger further processes possibly leading to the hippocampo-neocortical information transfer. Additionally, it must be mentioned that the role of REM sleep in the consolidation of recent memories is not considered much in these conceptualisations (although admittedly envisioned in the Buzsaki 1996 model), thus not entirely accounting for experimental evidence. For instance, combined EEG and fMRI data have yielded evidence for links between an overnight improvement of visual discrimination skills and the number of slow waves initiated in lateral occipital areas during post-training NREM sleep. This is paralleled by an association between the duration of REM sleep and increased oxygen consumption [i.e. higher Blood Oxygen Level Dependent (BOLD) response] at overnight retesting (Mascetti et al. 2013).

In this respect, the dual process (Plihal and Born 1997) and the sequential process (Giuditta 1984) hypotheses might more specifically acknowledge for the fact that both NREM and REM sleep stages are likely to contribute in the cascade of neuronal events eventually leading to memory consolidation. According to the

dual process hypothesis, NREM sleep would be especially suited for the consolidation of declarative, hippocampus-dependent memories, whereas REM sleep would subtend the consolidation of procedural (hippocampus-independent) memories (Plihal and Born 1997, 1999). However, this marked distinction between declarative and procedural memory processes as a function of sleep stages is far to be supported by the existing literature, that relates the consolidation of information belonging to a wide range of memory domains (from verbal to motor material) with NREM sleep-related processes (see Sect. 4). Alternatively, the sequential hypothesis proposes that effective memory consolidation actually requires different steps of information processing during NREM then REM sleep episodes (Ficca et al. 2000; Giuditta 1984), for instance protection of recent memories against interference during NREM then their consolidation during REM sleep (Scrima 1982).

4 Brain Plasticity and Memory Consolidation During Sleep

The contribution of sleep to memory consolidation is now widely acknowledged in the literature. Animal studies have supported the hypothesis that post-training sleep activity recorded in learning-related brain areas might represent the neural signature of memory-related cognitive processes. For instance, cell recording studies in the rat hippocampus and cortex following exposure to a spatial environment (Kudrimoti et al. 1999; Lee and Wilson 2002; Louie and Wilson 2001; Nadasdy et al. 1999; Pavlides and Winson 1989; Wilson and Mcnaughton 1994) and in the song area of young zebra finches (e.g. Dave et al. 1998; Dave and Margoliash 2000; Margoliash 2001) revealed neuronal replay phenomenon during sleep, suggesting the reactivation of neural activity associated with previous experience.

4.1 REM Sleep and the Neuronal Replay of Procedural Memories

In humans, evidence supporting the neural replay hypothesis was initially found using $H_2{}^{15}O$-PET. Brain areas activated during practice on a probabilistic serial reaction time (SRT) task, a form of implicit motor sequence learning (Cleeremans and McClelland 1991; Peigneux et al. 2000) were found more active during subsequent REM sleep in subjects previously trained on the task than in untrained subjects (Maquet et al. 2000; Fig. 4). In addition, rCBF in the left premotor cortex was correlated with activity in the pre-supplementary motor area and in the posterior parietal cortex involved in sequence learning, much more during post-training REM sleep than during REM sleep without a prior sequence learning experience (Laureys

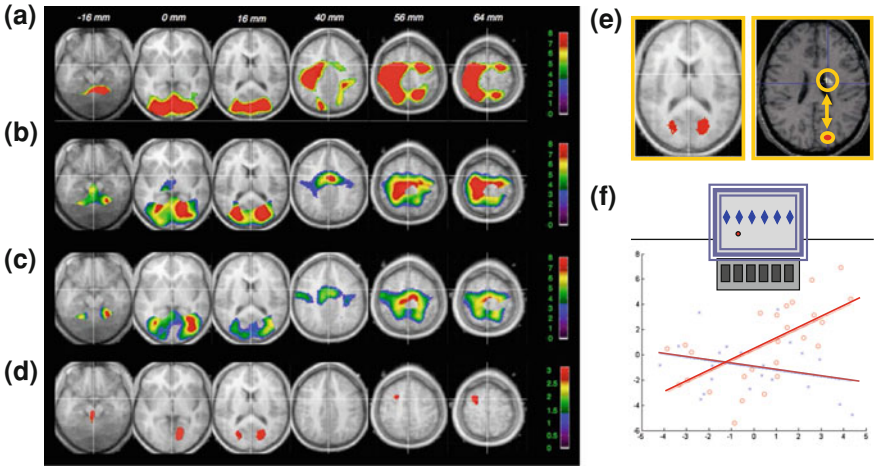

Fig. 4 Neuronal reactivation during REM sleep. **a** Brain areas where activity during active wakefulness is associated with learning on a motor procedural SRT task; **b** Brain areas active during REM sleep after learning on the SRT task; **c** Brain areas active during baseline REM sleep (no prior learning experience); **d** Brain areas where activity is significantly higher during REM sleep after SRT practice than during baseline REM sleep, and already active during learning; **e** Higher activity in cuneus during REM sleep after SRT practice than after practice of randomly presented stimuli; and **f** temporal correlations during post-training REM sleep between cuneus and striatum activity after practice on the probabilistic (*red*) but not on the random (*blue*) SRT. Adapted with permission from Maquet et al. 2000 and Peigneux et al. 2003

et al. 2001). This suggests that motor memory traces are replayed in the cortical network during REM sleep. Furthermore, reactivation in learning-related areas during REM sleep was specific to the reprocessing of the implicit rules driving the succession of the displayed locations in the sequence, more than to the mere optimization of basic visuomotor skills. Indeed, reactivation in learning-related areas during REM sleep was only found in subjects trained to the rules-based SRT task, but not in other participants trained on the same task but using a random material (Peigneux et al. 2003). These results indicate that the reactivation of local brain activity during REM sleep was related to the implicit acquisition of the probabilistic rules that defined stimulus sequences. Furthermore, learning-related cuneus activity during REM sleep also correlated with rCBF variations in the striatum, a key area in probabilistic sequence learning (Peigneux et al. 2000), significantly more in participants trained to the probabilistic than in those trained to the random SRT task (Fig. 4). Finally, the level of sequence learning achieved prior to sleep also correlated with increases in rCBF during REM sleep, suggesting that post-training cerebral reactivation is modulated by the strength of the memory traces developed during learning (Peigneux et al. 2003). None of these post-SRT learning effects was observed during NREM sleep. As a whole, these results support the hypothesis that REM sleep is involved in the reprocessing and optimization of the high-order, complex information contained in the material to be learned.

4.2 NREM Sleep and Reactivation of Hippocampus-Dependent Memories

Using this same probabilistic SRT task, no effects were observed during NREM sleep periods. This result is seemingly contradictory with animal findings that yielded evidence for neuronal reactivations during NREM sleep (but see e.g. Poe et al. 2000 and Louie and Wilson 2001 for experience-dependent changes in neuronal firing during REM sleep). One possibility for this apparent discrepancy is that learning complex sequential regularities in the probabilistic SRT task is dependent upon the activity of striato-cortical networks (Peigneux et al. 2000), whereas reactivations studies in rodents mostly used hippocampus-dependent spatial orientation tasks (e.g. Wilson and Mcnaughton 1994). In line with this interpretation, activity in hippocampal and medial temporal areas subtending navigation learning in a virtual town (i.e. a spatial, hippocampus-dependent learning task) was enhanced during subsequent NREM sleep, and mostly SWS (Peigneux et al. 2004), but not after training on the SRT task. In this PET study, hippocampal activity during post-training SWS was proportional to the overnight improvement in performance in the navigation task. These results suggest that learning-dependent modulation in hippocampal activity during human sleep actually reflects the offline processing of recent episodic and spatial memory traces, eventually leading to the plastic changes underlying subsequent improvements in performance. As a whole, PET studies indicate that distinct memory traces pertaining to different cerebral structures and memory systems, acquired under different learning conditions, are reactivated during subsequent and distinct sleep stages. Although these results seemingly concur with the dual process hypothesis positing that NREM sleep subtend consolidation of declarative, hippocampus-dependent memories whereas REM sleep subtend consolidation of procedural memories (e.g. Plihal and Born 1997, 1999), such conclusion should be taken thoughtfully. Indeed, the demonstration of segregated patterns of neuronal activity during different stages of sleep associated with the consolidation of different memory systems does not invalidate other interpretations. For instance, other neurophysiological mechanisms contributing to the memory consolidation processes might not have been detectable using the PET technique, limiting possible interpretations. Hence, these results do not allow rejecting alternative accounts, for instance, the sequential hypothesis (Giuditta 1984) assuming that effective memory consolidation requires information processing steps first during NREM then REM sleep episodes.

4.3 Neuronal Reactivations in the Light of Combined EEG/FMRI

Functional MRI also evidenced learning-related cerebral activation during sleep. After intensive training on a perceptual texture discrimination task, increased activity was observed during post-training SWS (versus the night before learning)

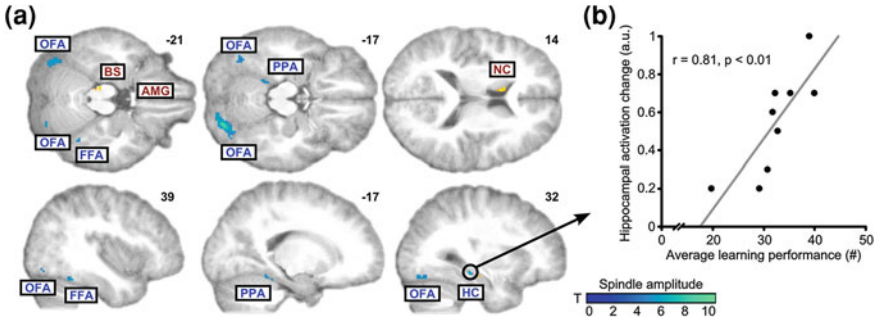

Fig. 5 Spindles, memory for face-scene associations and neuronal reactivation in the light of combined EEG-fMRI. **a** Brain areas showing learning-specific increases in coupling to spindle amplitude (cold colours) relative to control condition (*BS* brainstem; *FFA* fusiform face area; *HC* hippocampus; *NC* caudate nucleus; *OFA* occipital face area; *PPA* parahippocampal place area). **b** Correlation between learning performance and increased spindle-related hippocampal activity during subsequent sleep. Adapted with permission from Bergmann et al. 2012

in stimulated areas of the primary visual cortex (V1). Overnight improvements in behavioural performance additionally correlated with the amplitude of the BOLD signal in trained regions during SWS (Yotsumoto et al. 2009), in line with EEG findings of locally increased initiation of slow waves after training on visual orientation discrimination task (Mascetti et al. 2013). Similarly, sleep spindle-related reactivation after learning face-scene paired associates was observed in category-specific cortical areas during NREM sleep (Bergmann et al. 2012). In this EEG/fMRI study, learning face-scene associations triggered a stronger combined activation of neocortical and hippocampal regions during subsequent sleep, as compared to visuomotor practice. Also, reactivations were in temporal synchrony with spindle events and tuned by ongoing variations in spindle amplitude, but restricted to the face- and scene-selective visual cortical areas activated during pre-sleep learning. Finally, participant's performance at the end of learning was correlated with spindle-coupled hippocampal activation (Fig. 5). These results can be also interpreted in the framework of a prior EEG study showing that fast spindles are driven by the depolarizing *up* state of neocortical slow oscillations and enhance the likelihood of succeeding slow oscillations together with slow spindles. As prior learning enhanced this pattern, it suggests that slow oscillation-spindle cycles and fast spindles contribute in sleep-dependent memory and consolidation processes (Molle et al. 2011). Altogether, spontaneous reactivation studies suggest the reprocessing of previously learned information during post-learning sleep, a reactivation possibly organized by sleep spindles and slow oscillations in the case of hippocampal-neocortical memories.

4.4 Cueing Memories During Sleep

In a complementary approach, researchers have assumed that presenting learning-related cues during post-training sleep would trigger the reactivation of previously associated memory traces. Accordingly, non-awakening presentation during SWS of an odour associated with the learning of cards positions in the game "Memory" enhanced subsequent retrieval performance above levels achieved after a normal, undisturbed night of sleep (Rasch et al. 2007). Presentation of another odour was ineffective, demonstrating the specificity of the cueing effect. As well, presentation of the associated odour during REM sleep or wakefulness did not enhance performance. Functional MRI recordings additionally showed that cueing the associated odour during post-learning SWS triggered hippocampal BOLD responses, associated with performance improvement in the declarative memory task. Cueing-related consolidation of a finger-tapping motor procedural memory task was tested in the same study. At variance with the declarative paired association task however, re-presentation of the cue odour during SWS or REM sleep was ineffective to improve memory. This result is discrepant with other data suggesting that presentation of cues coincidently with REMs actually boost procedural learning. For instance, prior studies (Guerrien et al. 1989; Smith and Weeden 1990) found that cueing during post-training REM sleep using auditory stimulations delivered during learning improves behavioural performance when tested on the next day. Since odour pathways directly link to the hippocampus, it is possible that odour stimulation is not appropriate to trigger non hippocampus-dependent procedural memories, and that other sensory modalities should be exploited. Accordingly, another behavioural/EEG study trained participants to play two melodies on a keyboard. Auditory presentation of one of the two melodies during a post-learning subsequent nap resulted in higher performance improvement for the sleep-replayed than for the other melody (Antony et al. 2012), suggesting that auditory cueing during sleep is beneficial for sensorimotor memories to the same extent than odour cueing for non-declarative memories. However, auditory stimulations were delivered during NREM sleep again in this latter study, leaving under discussion the possibility to trigger memory consolidation processes during REM sleep. Notwithstanding, other studies confirmed that sounds are as effective as odours to trigger memory consolidation processes. In an EEG study (Rudoy et al. 2009), participants learned the location of different objects, each object being associated with a congruent sound (e.g. a bark associated with the image of a dog). During the subsequent nap, half of the object-associated sounds were delivered. Recall was higher for the cued than the non-cued images, again suggesting specificity in the triggered reactivations and in the ensuing consolidation processes. Similarly, participants were scanned during SWS using fMRI while presented the object-associated auditory cues (van Dongen et al. 2012). Although memory performance was similar in the experimental and control conditions, evoked BOLD responses in the right parahippocampal area were higher during SWS for the cued than for the control sounds. Furthermore, the connectivity

between the parahippocampal and the posterior visual areas increased upon presentation of the cue sounds. According to the authors, this suggests that cue-related evoked responses during sleep are not merely limited to the processing of auditory stimulations, but actually generalize to the visual areas recruited during the task. This effect is congruent with the report of spindle-related reactivation of paired associates both in hippocampal and task-specific face or locations-related areas (Bergmann et al. 2012).

5 Imaging the Effect of (a Lack of) Sleep on Memory Consolidation

Alternative and less constraining strategies have been devised to test the hypothesis that recently acquired memories are consolidated during sleep, without the need to record brain activity during sleep episodes. We have seen that reactivation studies globally rely on the assumption that post-training sleep processes promote plastic brain changes and consolidation of memories. Conversely, it can be assumed here that sleep deprivation should hamper sleep-related consolidation processes, eventually leading to an alteration of overnight memory performance and/or of the cerebral organization underlying access to consolidated memories.

5.1 Sleep Deprivation and the Consolidation of Procedural Memories

Pioneering the sleep deprivation strategy with neuroimaging methods, Maquet et al. (2003) trained participants on a motor pursuit task, a paradigm of procedural memory. Subjects were either sleep-deprived or allowed to sleep the night following training, then scanned using fMRI 3 days later while practicing again the pursuit task, both on new and previously learned trajectories. Sleep deprivation during the post-training night resulted in only a small improvement in performance for both trajectory types, whereas performance for the learned trajectories was selectively and dramatically enhanced in participants who slept after training. Additionally, the analysis of fMRI data showed that sleep deprivation hampered learning-related changes in cerebral connectivity in the superior temporal sulcus and cerebellum, and between frontal and supplementary eye fields, a connectivity that was found reinforced in the post-training sleep condition. Parallel changes in behavioural performance and cerebral activity patterns after periods of post-learning wakefulness versus sleep were also found using different fMRI settings both for the consolidation of motor and visual skill learning (Fischer et al. 2005; Walker et al. 2005a, b). In a more recent fMRI study (Albouy et al. 2012), performance in a visuomotor adaptation task was found to be stabilized after sleep but deteriorated after sleep

deprivation, hence disclosing a behavioural advantage of post-training sleep. Besides, participants deprived of sleep on the post-learning night continued to recruit cerebello-cortical networks involved at the earliest stages of visuomotor learning, whereas participants allowed to sleep after learning exhibited similar patterns of cerebral activity during learning and retest. Additionally, increased activity in hippocampal and frontal areas during learning was associated with a better resistance against the detrimental effects of sleep deprivation. As suggested by other fMRI studies, hippocampal activity during learning in interaction with activation within striatal structures might contribute to consolidating motor adaptation (Albouy et al. 2012) and motor sequential (Albouy et al. 2008, 2013a, b) skills. Hippocampal activity possibly contributes to consolidation by tagging at an early learning stage the memories to be consolidated during subsequent sleep episodes (Albouy et al. 2008), or by initiating at an earlier stage the process of consolidation, benefitting from continued post-training neural activity processes during wakefulness (Peigneux et al. 2006). However, the reorganization of brain patterns underlying performance for procedural memories after sleep is not necessarily accompanied by overt changes in behaviour. Indeed, sleep after implicit learning on a probabilistic SRT task is associated with a diminished differentiation between event-related fMRI responses for the items following versus those violating the sequential rules embedded in the material to be learned (Fig. 6), although overnight changes in performance were similar in the sleep and sleep-deprived post-learning conditions (Urbain et al. 2013). Modified BOLD responses were also found in a set of cortical and subcortical areas previously shown to be part of the network subtending implicit sequence learning (Peigneux et al. 2000) and its offline processing during REM sleep (Maquet et al. 2000; Peigneux et al. 2003). Also in the Urbain et al. (2013) study, likewise prior studies using the probabilistic SRT task (Maquet et al. 2000; Peigneux et al. 2003), there was actually no hippocampal activity associated with the acquisition process. This may suggests that the hippocampal tagging associated with motor sequence learning in other studies, thought to predict sleep-dependent improvement (Albouy et al. 2008, 2013a, b), relates to the deterministic and spatially predictable succession of the elements in learned sequences. Whereas, such spatially-based mapping is not possible for a less predictable succession of stimuli in the probabilistic SRT task, hence preventing hippocampal tagging.

5.2 Sleep Deprivation Changes the Neural Substrate of Declarative Memories

Studies conducted in the declarative memory domain also yielded evidence for an effect of post-training sleep deprivation on the consolidation of verbal and non-verbal, hippocampus-dependent material. As discussed above, van Dongen et al. (2012) demonstrated higher evoked BOLD responses for cued than control sounds

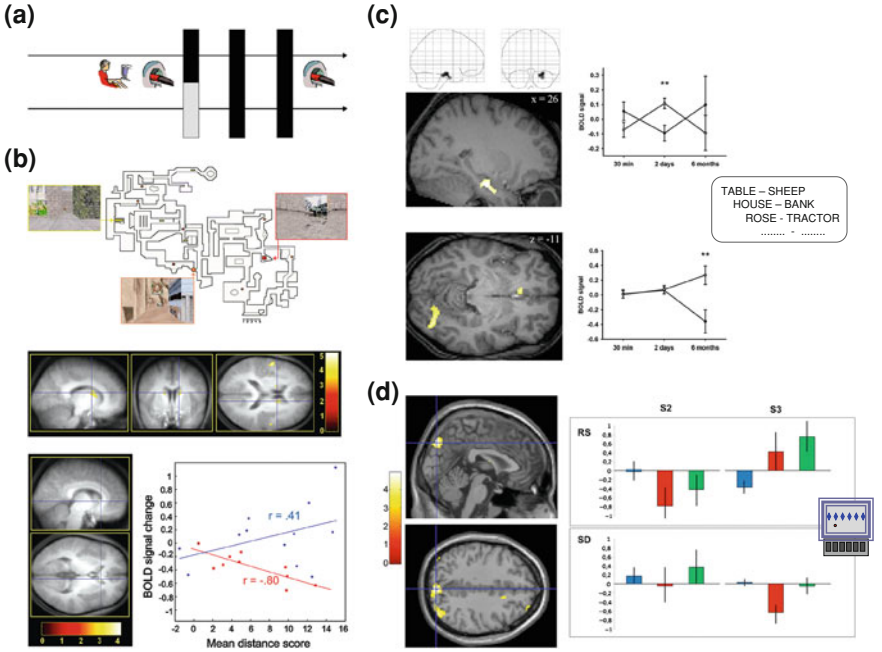

Fig. 6 Imaging the effects of sleep loss on the neural substrates of memories. **a** Typical sleep deprivation paradigm. Participants are trained on a novel task then tested for retrieval in the fMRI scanner, and then are either kept awake for the night (sleep deprivation, *grey bar*) or allowed to sleep normally (regular sleep, *black bar*). After two supplementary nights (*black bars*) aimed at ensuring that subsequent brain recordings will not be impeded by sleep deprivation-related effects, participants are retested at Day 4 during memory retrieval in the fMRI scanner. **b** Sleep-dependent shifts in the brain substrate of topographical learning. In participants allowed sleeping after topographical learning (i.e. finding routes in a virtual town), navigation performance becomes associated with activity in striatal regions (*red dots*), which is not the case in participants deprived of sleep on the first post-training night, in whom performance remains associated with hippocampal activity (Orban et al. 2006; Rauchs et al. 2008a, b). **c** Hippocampal-neocortical transfer or memories on the long-term. Successful retrieval of learned word pairs is associated with higher hippocampal activity in participants allowed to sleep on the post-training night (as compared to sleep deprived participants) when tested 2 days after learning, but no longer 6 months later. Conversely, activity in the medial prefrontal cortex is modulated by post-training sleep during successful word pairs retrieval 6 months after learning, but not after 2 days, giving support to the hypothesis that sleep promotes a progressive transfer of information from hippocampal to neocortical long-term memory stores (Gais et al. 2007). **d** Sleep-dependent neurophysiological processes in implicit sequence learning. In participants trained on a probabilistic SRT task then allowed to sleep after learning, there is diminished differentiation between event-related BOLD responses for items following versus those violating the sequential rules embedded in the material to be learned, although overnight changes in performance are similar in the sleep and sleep-deprived post-learning conditions (Urbain et al. 2013). Adapted with permission from Orban et al. 2006; Gais et al. 2007 and Urbain et al. 2013

in parahippocampal regions during SWS after learning object-location associations. Additionally, retrieval of reactivated object-location associations, but not retrieval of non-cued associations, correlated with pre- to post-sleep connectivity changes between parahippocampal and medial prefrontal areas. These results indicate that cueing during sleep may also modify connectivity patterns within the cerebral networks subtending memory retrieval at wake. Nonetheless, performance similarly improved for cued and uncued associations after sleep, hence failing to demonstrate a specific effect of sleep at the behavioural level. Therefore, it also shows that like in the procedural memory domain, reorganization of brain activity patterns underlying performance after sleep is not necessarily accompanied by overt changes in behaviour. Orban et al. (2006); Rauchs et al. (2008b) first evidenced this dissociation between recorded cerebral activity and behaviour, by showing that post-learning sleep promotes a shift in cerebral activity patterns underlying topographical memories. Participants were scanned during route-finding tasks immediately after learning their way in a virtual town and 3 days later. Half of them were allowed regular sleep, whereas the other half was totally sleep-deprived during the first post-learning night. Results disclosed a striking dissociation between unchanged behavioural performance and distinctive neural bases for route retrieval at delayed testing in sleep versus sleep-deprived participants. Whereas route finding elicited increased activity in a well-known navigation-related hippocampo-neocortical network (e.g. Maguire et al. 1998) at immediate and delayed retrieval both in sleep and sleep-deprived participants, activity in routine behaviour-related striatal areas was associated with delayed retrieval activity only in participants allowed to sleep after training (Fig. 6). Furthermore, higher activity in the striatum was associated with higher navigation accuracy in the sleep condition, whereas the relationship was reversed in sleep-deprived participants. These data suggest that brain activity is reorganized during post-training sleep in such a way that navigation, initially based on a hippocampus-dependent spatial strategy, becomes progressively contingent on a response-based strategy mediated by the striatum. A follow-up study investigated whether sleep globally promotes consolidation of all memory components embedded in virtual navigation (Rauchs et al. 2008a), or rather favours the development of specific representations (Rauchs et al. 2008b). Again, behavioural performance did not differ between participants allowed regular sleep during the post-learning night and those who were sleep deprived, neither when tested in a natural setting that engages both spatial and contextual memory processes nor when looking more specifically at each of these memory components. At the neuronal level however, fMRI analyses disclosed sleep-dependent changes in the cerebral activity subtending memory retrieval in each of these experimental conditions. This further shows that covert changes in cerebral responses might precede, or exist without, overt changes in behaviour.

5.3 *Long-Term Consequences of Sleep Deprivation on the Consolidation of Memories*

The sleep-dependent phenomenon is not unique to spatial learning. Indeed, a lack of overt changes in behaviour paralleled with covert modulations of brain activity following sleep has been reported also using verbal and emotional material. Additionally, sleep-dependent changes in brain activity have been evidenced on the long-term. Hippocampal activity during the retrieval of previously learned pairs of words was found to be higher 2 days later in participants who had slept as compared to those who were kept awake the night after learning, but not when tested 6 months later. The reverse pattern was found in the medial prefrontal cortex, where activity was similar 2 days after learning but word retrieval-related activity was enhanced 6 months later in the post-training sleep condition (Gais et al. 2007; Fig. 6). Similarly, a consistent decrease in hippocampal activity was observed during recognition of learned pictures over a 3-month period, whereas activity gradually increased in the ventral medial prefrontal cortex (Takashima et al. 2006). Additionally, functional MRI studies disclosed larger emotional stimulus retrieval-related responses 3 days after learning in the hippocampus and medial prefrontal cortex in the sleep condition as compared to the sleep deprived condition. This short-term increase in the BOLD response to emotional material was associated with a higher sleep-dependent connectivity and the additional involvement of emotion-related responses in the amygdala (Sterpenich et al. 2007), followed 6 months later by increased connectivity patterns between long-term neocortical stores and emotion-related areas (Sterpenich et al. 2009). These studies support the hippocampal-neocortical dialogue hypothesis (Buzsaki 1996) of a progressive transfer of the information from hippocampal toward neocortical stores over time and sleep, and suggest that this process might be modulated by additional parameters such as emotion or contextual information.

6 Conclusions

Non-invasive neuroimaging studies conducted in the past two decades have markedly increased our knowledge of the functional neuroanatomy of sleep and sleep stages, and have helped us to understand how sleep-related processes contribute to the consolidation of memories. Following PET studies that revealed regional patterns of cerebral activity characterizing the specificity of vigilance states in man, fMRI and MEG investigations have allowed a better understanding of the source and organization of synchronous oscillations in SWS. Additionally, these studies shed light on the organization and regulation of phasic events such as sleep spindles. The role of NREM sleep has been thoroughly studied, but REM sleep still deserves in-depth scrutiny to gain a similar level of understanding about its underlying neural mechanisms and function.

Neuroimaging studies also provided support for contemporary neural models for memory consolidation, indicating that these models are not opposite but might be seen as complementary mechanisms in the cascade of events leading to the enduring storage of recent memories. Whereas the so-called reactivation studies have shown that the neural activity during the acquisition of novel information can be recapitulated during post-training sleep, cueing paradigms additionally indicated that selected external stimuli modulate and might even enhance the process of consolidation during sleep. Finally, studies conducted using sleep deprivation paradigms have shown, as a counterpoint to reactivation studies, that post-training sleep deprivation impedes the reorganization and optimization of memory-related cerebral activity patterns at delayed retrieval. Also, they demonstrated that sleep-dependent changes in memory-related brain activity patterns could be dissociated from changes (or not) in behavioural performance, suggesting that long-term memory consolidation can be achieved using different cerebral strategies.

Further progress might be expected from a combination of existing neuroimaging and neurophysiological techniques. We now have the technical capabilities to perform multimodal recordings and even simultaneous stimulation (e.g. using transcranial direct current stimulation) of brain activity during natural sleep. The combination of these methods should allow us to gain a deeper understanding of the neurophysiological basis of the symphony of brain oscillations during sleep, and the role of these oscillations in memory consolidation. At the current stage however, we also need to use our technical capabilities and existing knowledge to investigate the sleep-related pathophysiological mechanisms leading to disruptions in brain plasticity and memory consolidation. For instance, evidence suggests that nocturnal interictal epileptic activity in idiopathic epilepsies disrupts SWS-related synaptic homeostatic processes underlying brain plasticity mechanisms (Bolsterli et al. 2011; Bolsterli Heinzle et al. 2014) and leads to overnight memory consolidation deficits, that can however disappear after the initiation of a pharmaceutical treatment normalizing (i.e. suppressing) nocturnal epileptic activity (Urbain et al. 2011). Imaging brain activity under pathological and normalized interictal conditions might help us understanding the impact of paroxysmal activities on the organization of the cerebral networks subtending memory consolidation. Along these lines, neuroimaging approaches might also help us unraveling the neurophysiological mechanisms underlying the relationships between sleep disorders and mental health problem. Hopefully, this will ultimately help to increase the range of possible therapeutic interventions.

Further progress may also arise from increased collaboration and back-and-forth communication between animal and human research. Animal research is crucial to provide novel research directions to develop hypothesis-driven studies in man. For instance, animal research recently demonstrated that sleep in mice is associated with a dramatic increase in the volume of the interstitial space, resulting in increased convective exchanges of cerebrospinal fluid with interstitial fluid, and in turn increasing the rate of beta-amyloid clearance during sleep. This process is disrupted by sleep deprivation (Xie et al. 2013). Beta-amyloid accumulation is a well-known hallmark of Alzheimer's disease (AD), a neurodegenerative pathology

characterized not only by long-term memory deficits but also by disturbances in circadian rhythms and sleep. Whether sleep disruptions are an aggravating factor in the formation of amyloid plaques in AD, eventually leading to impaired brain connectivity, should be investigated further, using a combination of neuroimaging and polysomnographic recordings. Hence animal research can provide novel directions to understand the disrupted neurophysiological mechanisms subtending learning and memory processes in relation with sleep.

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