8

The Memory, Cognitive and Psychological Functions of Sleep: Update from Electroencephalographic and Neuroimaging Studies

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1. Introduction

Sleep is a universal biological feature in almost all, if not in all species, and represents a global state of immobility with greatly reduced responsiveness to environmental stimuli, which can be distinguished from coma or anaesthesia by its rapid reversibility (Cirelli & Tononi, 2008). It is by no means a dormant state. When it is prevented, the body tries to recover the lost amount. The existence of sleep rebound after deprivation reveals that sleep is not simply a period of reduced activity or alertness regulated by circadian or ultradian rhythms (Dinges et al., 2005). Notably, in most vertebrates and all mammal species, including man, sleep displays a specific architecture roughly described as a cyclic occurrence of rapid eye movement (REM) sleep and non-REM sleep. Further, dramatic changes in brain electrophysiology, neurochemistry and functional anatomy biologically distinguish the different sleep stages from one another (Hobson & Pace-Schott, 2002; Pace-Schott & Hobson, 2002). Also, human and animal neurophysiologic studies have shown that the magnitude of changes in brain metabolism and neuronal activity in many discrete brain structures during certain sleep stages exceeds that during most of the waking periods (Gottesmenn, 1999; Maquet et al., 1996; Nofzinger et al., 1997; Steriade & Timofeev, 2003).
Although the precise functions of sleep are still beyond comprehensive understanding (Cirelli & Tononi, 2008), many studies point to the critical role of sleep for physiological functioning and adaptation. Its vital importance is well documented by the fact that its deprivation in rodents and flies can cause death more quickly relative to food deprivation (Rechtschaffen, 1998). Thus, sleep is shown to serve many energetic and metabolic, immune, thermoregulatory, cardiovascular, and respiratory functions, all responsible for normal brain and body homeostasis (Siegel, 2009; Tononi & Cirelli, 2006). Notably, along with these functions, sleep is shown to play a key role for important cognitive and psychological processes, among which learning and memory have been most intensively studied (Diekelmann & Born, 2010; Rasch & Born, 2007; Stickgold, 2005; Walker, 2008; Walker & Stickgold, 2006; 2010). Accordingly, an extensive body of research has revealed a cruicial

role for sleep in human cognitive abilities (Mander et al., 2008; Schabus et al., 2006; 2008; Yoo et al., 2007b), heuristic creativity and insightfulness (Cai et al., 2009; Stickgold et al., 1999; 2001; Wagner et al., 2004; Yordanova et al., 2008; 2009; 2010), constructive thinking and decision making (Durrant et al., 2011; Venkatraman et al., 2011), and emotional regulation (Walker, 2009; Walker & van der Helm, 2009). The latter engages consolidation of emotional memory (Nishida et al., 2009; Wagner et al., 2001; 2006; Walker, 2009) and emotional processing (Gujar et al., 2011a; 2011b; Yoo et al., 2007a). Collectively, these various associations suggest that sleep provides unique conditions for off-line memory consolidation, reconsolidation and information reprocessing to take place. However, it is still not precisely known whether these mechanisms are distinctly different from the restoring and energetic functions of sleep, whether the two types of functions are coupled, or whether the latter simply facilitate the cognitive functions of sleep.

Many electroencephalographic (EEG) and neuroimaging studies including functional magnetic resonance imaging (fMRI) have found that the structural and functional organization of the neural substrate undergoes changes during sleep in relation to human cognition. The entity of neural mechanisms underpinning cognitive and psychological functions of the brain is generally recognized as brain plasticity, i.e., as the capability of the neural substrate to reorganize over time as a result of previous experiences. In this chapter, studies demonstrating that sleep affects cognition by neural plasticity mechanisms in humans will be updated and overviewed to provide a converging framework for better understanding the role of sleep for memory, cognitive abilities and psychological functioning. Since mechanisms of brain plasticity are closely related to sleep physiology, architecture and neurobiological regulation, the reader will be first introduced to neurobiology of sleep.

2. Neurobiology of sleep

2.1 Sleep architecture and physiology

The heterogeneous nature of sleep can be seen in human and in most animal polysomnographic (PSG) records, which traditionally use electrophysiological techniques including electroencephalography (EEG), electromyography (EMG) and electro-oculography (EOG) to characterize sleep at system levels. In humans, overnight sleep is characterized by a cyclic occurrence of non-REM sleep and REM sleep. Non-REM sleep includes lighter sleep stages 1 and 2 and stages 3 and 4 of the deeper slow wave sleep (SWS) (Rechtschaffen & Kales, 1968). Whereas SWS dominates the first half of the night, REM sleep and stage 2 of non-REM sleep dominate the second half. This ultradian dynamics reflects the circadian regulation of sleep that is distinguishable from its homeostatic regulation seen after sleep deprivation or prolonged wakefulness (Borbély 1982; Borbély & Ackermann, 1999). Normally, sleep onset begins with a brief period of stage 1 of non-REM sleep, which is subsequently followed by sleep deepening marked by appearance of stage 2 of non-REM sleep and a further progressive transition to stages 3 and 4 of SWS. The latter is followed by a relatively short transient of stage 2 of non-REM sleep, after which a period of REM sleep appears. This progression of sleep stages, and in particular, the non-REM sleep - REM sleep alternation forms one sleep cycle with approximately 90 min duration. About 5 or more such sleep cycles are usually observed in the normal human overnight sleep (Broughton, 1987; Rechschaffen & Kales, 1968; Sinton & McCarley, 2000).

2.2 Electrophysiological signatures of sleep stages

The distinct sleep stages of either human overnight sleep or human daily naps can be determined by their specific "macroscopic" electrophysiological signatures, which are described by Rechschaffen & Kales (1968) and are commonly used for human sleep stages scoring. Unlike the desynchronized mode of EEG activity during wakefulness, the electrophysiological signatures of different sleep stages are more complex, which reflects a more heterogeneous nature of sleep than that of wake (Hobson & Pace-Schott, 2002). Basically, wakefulness is divided into active wake, characterized by desynchronized low-voltage fast EEG activity including beta (~ 15-30 Hz) and gamma (> 30 Hz) rhythms as well as by theta (~ 5 Hz) EEG activity with frontal-midline location, and quiet wake, characterized by posterior alpha (~ 10 Hz) and central sigma (~ 12-14 Hz) EEG rhythms that replace the desynchronized EEG mode of the active wake (Niedermeyer, 1993). The electrophysiological signatures of both active and quiet are show in Figure 1.

Sleep initiation is described as a replacement of waking EEG by theta or slower rhythms paralleled by an appearance of very slow circular eye movements, and both electrophysiological features form stage 1 of non-REM sleep (Broughton, 1987; Sinton & McCarley, 2000). Stage 2 of non-REM sleep is defined by presence of the classical EEG sleep spindles oscillating at ~ 12-15 Hz with central-parietal location, slower sleep spindles oscillating at ~ 9-13 Hz with frontal location and sporadic biphasic slow waves known as K-complexes (Anderer et al., 2001; De Gennaro & Ferrara, 2003). Sleep spindles are present also in the deeper SWS stages, but in less pronounced and discrete forms, among which spindle activity in the frequency range of ~ 8-12 Hz with frontal location is recognized to dominate SWS (Cantero et al., 2002; Salih et al., 2009). K-complexes are regarded as precursors of EEG components of the SWS (Amzica & Steriade, 1997; De Gennaro & Ferrara, 2003). These "macroscopic" human electrophysiological signatures of distinct sleep-wake stages are shown in Figure 1.

SWS is hallmarked by synchronous high-voltage (> 75 μV) EEG delta (~ 1-4 Hz) waves and slow (< 1 Hz) oscillations (SO) (Achrermann & Borbely, 1997; Crunelli & Hughes, 2010; Steriade et al., 1993), both recognized as slow wave activity (SWA) (Fig. 1). SO are also shown to occur in stage 2 of non-REM sleep (Crunelli & Hughes, 2010; Nir et al., 2011), and the SO during both stage 2 of non-REM sleep and SWS are shown to group and synchronize sleep spindles and delta waves (Mölle et al., 2002; Mölle et al., 2004; Steriade, 2001). Whereas sleep spindles originate form interactions between thalamo-cortical circuits involving γ-aminobutyric (GABA)-ergic thalamic neurons and glutamate-ergic cortical neurons (De Gennaro & Ferrara, 2003; Steriade, 2006), SO are shown to have a neocortical origin (Achrermann & Borbely, 1997; Nir et al., 2011; Steriade et al., 1993), although they are also proposed to emerge form the thalamus (Crunelli & Hughes, 2010). Another important EEG signature of SWS seen not only in animals but also in human intracranial EEG recordings, is reflected by hippocampal sharp-wave/ripple (SWR) bursts. Hippocampal sharp waves generated in the hippocampal CA3 region are fast depolarizing events, on which high-frequency oscillations (~ 80-200 Hz) originating from an interaction between inhibitory interneurons and pyramidal cells in CA1 (so-called ripples) are superimposed (Buzsáki, 2006; Csicsvari et al., 1999). Notably, SO have been shown to group also SWR in rodents (Battaglia et al., 2004; Sirota et al., 2003), and a temporal phase-coupling between SO, sleep spindles and SWR has been demonstrated in human depth EEG records during SWS (Clemens et al., 2007; 2011; Nir et al., 2011). The complex relationship between these sleep signatures is regarded as reflecting brain plasticity mechanisms at a system level, which is

important for the memory consolidation and reconsolidation during SWS (Diekelmann & Born, 2010).

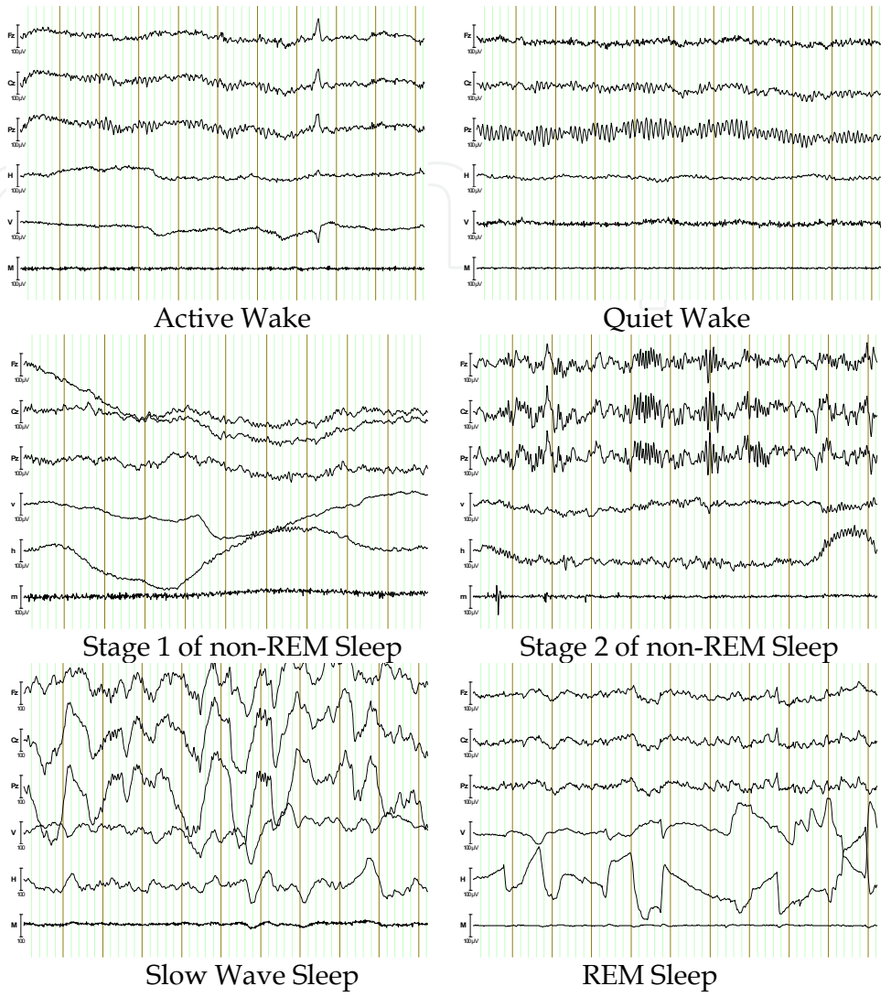

Fig. 1. Electrophysiological signatures of distinct sleep-wake stages: EEG recorded from Fz, Cz and Pz, vertical (v) and horizontal (h) eye movements, and electromyogram (m). Calibration marks are set-up at 100 μV, time (horizontal) marks are 1 s.

Unlike non-REM sleep electrophysiology, REM sleep EEG signatures (Fig. 1) include low-voltage desynchronized wake-like EEG activity comprising theta and fast (beta and gamma) rhythms accompanied by a swift occurrence of rapid eye movements (REM) upon lack of muscle tone (Aserinsky & Kleitman, 1953; Cantero et al., 2003; Clemens et al., 2009). Hippocampal theta rhythm is a prominent REM sleep EEG signature in rodents (Gottesmann, 1999; Kirov & Moyanova, 2002) and felines (Hobson & Pace Schott, 2002), while in human hippocampus and neocortex it is less coherent (Cantero et al., 2003). Further, REM sleep is hallmarked by ponto-geniculo-occipital (PGO) waves. PGO waves are driven by intense bursts of synchronized activity that propagate from the pontine brainstem mainly to the lateral geniculate nucleus and visual cortex (Callaway et al., 1987; Hobson & Pace-Schott, 2002; Pace-Schott & Hobson, 2002). They occur in temporal association with

REM in rats and felines (Callaway et al., 1987; Stickgold et al, 2001), as well as in humans (Lim et al, 2007; Miyauchi et al., 2009), and are suggested to reflect both dream mental states of REM sleep and cognitive processing during this sleep stage (Stickgold et al., 2001). REM sleep signatures are shown to reflect mechanisms of brain plasticity at synaptic and genetic levels (Ribeiro et al., 1999; 2002), which may promote not only REM sleep specific processes, but also a further transformation of consolidated memories (Walker & Stickgold, 2010).

2.3 Mechanisms of sleep regulation

The regulation of sleep is active in its own rights, and is closely related to sleep's physiology and functions (Hobson, 2005; Pace-Schott & Hobson, 2002). The respective neurobiological mechanisms are represented by complex reciprocal interactions between different neuronal populations and their chemical modulators and transmitters in distinct functional states across sleep-wake cycle leading to distinct functional states (Gottesmann, 1999; Hobson et al., 1975; Hobson & Peace-Schott, 2002; Peace-Schott & Hobson, 2002). Two major brain regions are mostly considered in sleep regulation, especially when functions of sleep are concerned (Pace-Schott & Hobson, 2002). The first engages neuronal populations located in the diencephalon, in particular, the hypothalamus, mostly involved in the circadian regulation of sleep. The second brain region engages brainstem or meso-pontine and basal forebrain nuclei spread in the reticular ascending system (RAS) and projecting noradrenaline (NA), serotonin (5-Hydroxytryptamine, 5-HT) and acetylcholine (Ach) neuromodulatory signals to upper brain structures including the basal ganglia and amygdala, thalamus, hippocampus, and cortex. These mechanisms are essential for the ultradian alternating expression of non-REM sleep-REM sleep periods (Gottesmann, 1999; Hobson et al., 1975; Pace-Schott & Hobson, 2002). Briefly, during wake, brainstem/meso-pontine NA, 5-HT, Ach, and hypothalamic histamine (HIS) neurons projecting to upper brain structures and cortex, are all active, thus sustaining functional brain states optimal to the environmental requirements (Gottesmann, 1999; Hobson & Pace-Schott, 2002; Pace-Schott & Hobson, 2002). As sleep deepens from stages 1 and 2 to SWS, all these neuromodulators progressively decrease their activities, with their lowest levels observed during SWS. This leads to strongly diminished or lacking RAS neuromodulation of upper brain structures and cortex, which in turn, is responsible for the appearance of non-REM sleep EEG signals represented by sleep spindles, K-complexes and SWA, all originating from thalamo-cortical and cortico-cortical interplay (McCormick & Bal, 1997; Pace-Schott & Hobson, 2002; Steriade & Timofeev, 2003). In REM sleep, all NA, 5-HT and HIS neurons cease their firing. In contrast, Ach excessive over-activity emerges projecting to the cortex and all sub-cortical structures, which produces the electrophysiological signatures of REM sleep (Gottesmann, 1999; Pace-Schott & Hobson, 2002).

2.4 Neuroimaging of sleep and wake

Several neuroimaging studies using either fMRI or positron-emission tomography (PET) have investigated the pattern of brain activation across wake, non-REM and REM sleep. These studies have demonstrated that anterior cingulate cortex, right and left amygdaloid complexes, pons, parahippocampal cortex, and extrastriate visual cortex are more active during REM sleep compared with wake and non-REM sleep, whereas the activation of other brain areas including right and left dorsolateral prefrontal cortices, right and left parietal cortices and precuneus, posterior cingulate cortex, and primary visual cortex, is suppressed in REM sleep compared with wake. All these brain regions have been shown to be the most

suppressed during non-REM sleep (Broun et al., 1997; 1998; Maquet et al., 1996; Miyauchi et al., 2009; Nofzinger et al., 1997). Yet, other brain structures are shown to specifically increase their activation in relation to distinct non-REM sleep stages and their EEG signatures. For example, blood oxygen level-dependent (BOLD) signal from the thalamus is strongest during spindle activity in stage 2 of non-REM sleep (Schabus et al., 2007), whereas during SO in SWS, brain functional activation is strong in the medial temporal cortex, the parahippocampal cortex, and neocortical areas (Dang-Vu et al., 2005; 2008; Maquet et al., 1997).

2.5 Mental characteristics of the sleep-wake stages

Notably, from a cognitive point of view, the mental characteristics of sleep-wake stages well correspond to their brain activation patterns found in neuroimaging studies (Fosse et al., 2001; 2004; Hobson & Pace-Schott, 2002; Hobson et al., 2000; Stickgold et al., 2001). Thus, wake is characterized by strongest and most logic thoughts in the presence of sensory input, executive control and goal-directed behavior. Sleep onset is hallmarked by the so called hypnagogic hallucinations, and as sleep deepens from stage 2 of non-REM sleep to SWS, thinking becomes more and more scares, and almost absent during SWS. Yet, there are logic thoughts mostly associated with previous wake experiences (Fosse et al., 2004; Hobson, 2005; Hobson et al., 2000; Stickgold et al., 2001). During REM sleep, mental activity is likely hallucinatory, and is behaviorally expressed in vivid, bizarre and elusive dreams (Fosse et al., 2004; Hobson et al., 2000; Stickgold et al., 2001). Also, REM sleep mentality is characterized by a most salient emotional tone upon lack of sensory input (Hobson et al., 2000) and executive control, as evidenced by the neuroimaging data (suppression of the dorsolateral prefrontal cortex, e.g., Maquet et al., 1996).

3. Sleep and memory

Likewise the heterogeneous structure of sleep, memory categories believed to exist in human brain are distinctly different. Roughly, they can be divided into declarative and non-declarative or procedural memory, and the same categorization holds true for the processes of learning (Dienes & Perner 1999). Declarative memory is considered to comprise consciously accessible memories of fact-based information (i.e., knowing "what"). Several subcategories of the declarative system exist, including episodic memory (autobiographical memory for events of one's past) and semantic memory (memory for general knowledge, not tied to specific events, but rather tied to its verbal components) (Tulving 1985). Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, especially the hippocampus, and thus, declarative memory is also known as hippocampus-dependent memory (Eichenbaum, 2000). In contrast, procedural or implicit memory is regarded as non-conscious, comprising memory of knowing "how", such as learning of actions, habits, and skills, as well as implicit learning (Dienes & Perner 1999). Procedural memory formation appears to be less dependent on medial temporal lobe structures, and to include sensori-motor cortices, basal ganglia and cerebellum (Forkstam & Petersson 2005).

3.1 Overview of human EEG data

Since the discovery of SO (< 1 Hz) in cats (Steriade et al., 1993) and (~ 0.7-0.8 Hz) in humans (Achrermann & Borbely, 1997), this hallmark of human non-REM sleep, and SWS in

particular, has been proposed as an essential mechanism underlying the consolidation of hippocampus-dependent memories (Buzsáki, 1989; Marshall & Born, 2007; Mölle et al., 2004; Steriade, 2001). In human SWS, "up" and "down" EEG states of SO are shown be dissimilarly associated with a number of electrophysiological events. Specifically, the "up" state of the SO is marked by increased occurrence of delta slow waves and sleep spindles, whereas during the 'down" state of SO, delta slow wave and sleep spindle activities markedly decrease (Mölle et al., 2002; 2004). Thus, human SO are demonstrated to group both slow waves and spindles. Further, a rapid increase of the underlying neuronal activity (depolarizing state) and a rapid decrease in it (hyperpolarizing state) have recently been shown to characterize human SO "up" and "down" wave forms, respectively (Nir et al., 2011). Finally, human studies have demonstrated time and phase coupling between SO, slow waves, sleep spindles, and hippocampal SWR bursts (Clemens et al., 2007; 2011; Nir et al., 2011). Collectively, these findings strongly indicate that non-REM sleep/SWS SO represent an EEG mechanism involved in plastic changes sub-serving the hippocampus-dependent memory consolidation.

Indeed, SO have been shown to be strongly associated with both procedural (Huber et al., 2004) and declarative (Mölle et al., 2004) memory consolidation taking place in human non-REM sleep/SWS. Later, to verify the specific role for SO in hippocampus-dependent memory consolidation, a series of studies, in which brain rhythms have been modulated using trans-cranial direct current stimulation (tDCS), has been conducted in humans. This method is now recognized as a reliable tool for modulating both the internally generated brain rhythms and the activity of underlying neuronal populations, depolarized under anodal tDCS and hyperpolarized under cathodal tDCS, respectively (Fröhlich & McCormick, 2010; Reis et al., 2008).

Initially, weak (not perceived by subjects) anodal tDCS oscillating at 0.75 Hz (slow oscillation stimulation, SOS) has been delivered during the transition from stage 2 of non-REM sleep to SWS after declarative and procedural learning before sleep. Compared with a sham condition, stimulation has selectively produced a gain in only declarative memory after sleep. Importantly, it has also produced a substantial increase in SO (~ 0.75 Hz) and frontal slow alpha spindle (8-12 Hz) activity, possibly by entraining these sleep EEG rhythms (Marshall et al., 2006). These findings have provided strong evidence for the role of SO and/or frontal slow spindle activity for the hippocampus-dependent memory consolidation. However, they have not addressed the question of whether SOS itself or whether endogenous SO boosted by the SOS have resulted in improvement of the consolidation of declarative memory found. This question was addressed in two later studies. In these studies, weak anodal tDCS oscillating at frequencies not common for the respective functional brain states was applied. In particular, SOS oscillating at 0.75 Hz was applied during quiet or resting wake retention period after learning declarative and procedural tasks. SOS did not affect either declarative or procedural memory consolidation, nor did it affect working memory and mood at retest. However, in contrast to its EEG effects during non-REM sleep (Marshall et al., 2006), it produced only a local (at the frontal sites of stimulation) increase in EEG power in SO (0.4-1.2 Hz) frequency band, accompanied by a widespread and strong increase in theta (4-8 Hz) EEG power. Further, when delivered in active wake state during encoding of a verbal learning memory task, the 0.75 Hz SOS produced virtually the same EEG effects as during quite wake (local increase in SO and widespread increase in theta power), but it significantly improved encoding of declarative verbal information (Kirov et al., 2009). Recently, tDCS oscillating at 5 Hz (wake and/or REM

sleep EEG rhythm, theta stimulation) was applied in the first non-REM sleep cycle of overnight sleep, during the transition from stage 2 of non-REM sleep to SWS, after subjects have learned tasks of both declarative and procedural memory before sleep. Notably, theta stimulation disrupted the normal progression of SWS, SO (0.5-1 Hz) and SWA (1-4 Hz) EEG power in the course of the stimulation. Also, it significantly decreased slow spindle activity (8-12 Hz) only frontally. These EEG changes were associated with a strong impairment of only declarative memory consolidation at recall after sleep (Marshall et al., 2011). Collectively, these findings strongly indicate that SO, SWA and frontal slow spindle activity reflect specific EEG mechanisms of hippocampus-dependent memory consolidation, which do not act beyond non-REM sleep/SWS. Moreover, they provide one of the strongest evidence for the assumption that during active wake, encoding of memory is reflected by theta EEG oscillations, which possibly reflect a transfer of information from the cortex to the hippocampus (Sederberg et al., 2003). Essentially, they strongly support the notion that memories encoded during wake undergo off-line consolidation during non-REM sleep/SWS by mechanisms involving an interplay between the hippocampus and the cortex, as reflected by the SO and frontal slow alpha activity (Buzsáki, 2006; Mölle et al., 2002; 2004; Marshall et al., 2006). Another recent investigation clearly showed strong and positive correlations between SO and sleep spindle EEG activities during the earliest portion of overnight non-REM sleep/SWS and rates of off-line improvement of both declarative and non-declarative memories (Wilhelm et al., 2011). These sleep EEG rhythms correlated positively with gain of improvement of only memories that were expected to be of further relevance, and not with memories that were not, with the latter memories being not found affected by sleep. Notably, this study demonstrates that SO and sleep spindles during non-REM sleep/SWS, are important EEG patterns not only for memory consolidation but also for memory reprocessing or reconsolidation (Wilhelm et al., 2011).

Some of the observations in the studies of Marshall et al. (2006; 2011) and Wilhelm et al. (2011) deserve further mentioning. These studies clearly show associations of non-REM sleep/SWS EEG signatures with either memory consolidation or reconsolidation in the first non-REM sleep cycle (Marshall et al., 2006; 2011) and even before the occurrence of the first SWS period (Wilhelm et al., 2011). A more recent study demonstrates that during the first half of overnight sleep, SO and SWA represent a global electric brain event that can be reliably recorded from hippocampus, medial temporal lobe and neocortex, whereas during the second half, both SO and SWA are expressed rather like a local phenomenon without strong phase and time coupling (Nir et al., 2011). Thus, regarding the studies using oscillating tDCS during sleep (Marshall et al., 2006; 2011) together with these of Wilhelm et al. (2011) and Nir et al. (2011), it can be concluded that SO, frontal slow alpha activity and sleep spindles, all represent important sleep EEG signatures reflecting processes of hippocampus-dependent memory consolidation and reconsolidation, which processes take place in the earliest part of non-REM sleep.

Similarly, classical sleep spindles, the major EEG signature of stage 2 of non-REM sleep, have been proposed to reflect mechanisms of brain plasticity that take place during non-REM sleep (Sejnowski & Destexhe, 2000; Steriade, 2001). Many human studies have demonstrated that either number, density, or EEG power spectral activity of spindles during stage 2 of non-REM sleep have been significantly involved in both declarative (Clemens et al., 2005; Gais et al., 2002) and procedural (Clemens et al., 2006; Fogel & Smith, 2006; Fogel et al., 2007b; Nishida & Walker, 2007; Shabus et al., 2004; Tucker & Fishbein, 2009) memory consolidation. Moreover, Nishida & Walker attempted to distinguish between use-

dependent and experience depended sleep processes. They subtracted sleep spindle EEG activity measured at a "non-learning hemisphere (left)" from that measured at a "learning hemisphere (right)" and were able to demonstrate strong positive correlations with offline memory improvement that were not evident for either hemisphere alone (Nishida & Walker, 2007). Thus, classical sleep spindles appear to represent an EEG pattern reliably associated with memory processes.

3.2 Overview of human neuroimaging data

Notably, the first human neuroimaging study almost entirely confirm previous rodent findings, which have shown that sleep-dependent memory consolidation relies on reactivation of the so-called hippocampus place cells during SWS in response to spatial or maze navigating tasks (Wilson & McNaughton, 1994). Thus, Peigneux et al. (2004) using a combination of PET and sleep EEG (PSG) methods, showed for the first time such a reactivation of hippocampal and neocortical regions in humans. At encoding during wakefulness, subjects were trained (or not) to learn and find their way inside a complex three-dimensional virtual town. Compared with the non-trained group, subjects who learned the task at encoding during wake displayed an increase in their regional cerebral blood flow (rCBF) in a bilateral pattern of neural activation, including the right and left hippocampus, the right and left parahippocampal gyri, superior parietal lobules, right and left precuneus, lingual and posterior cingulate gyri, middle and superior occipital cingulate gyri, and the anterior lobes of cerebellum. In the trained group, rCBF was consequently measured during stage 2 of non-REM sleep, SWS and REM sleep. The neural pattern of activity found at training sessions during wakefulness was reactivated only during SWS. This pattern of reactivation during SWS strongly correlated with the level of improvement on the task at recall after sleep (Peigneux et al., 2004). Three years later, Rasch et al. (2007) also used a combination of fMRI and PSG methods to investigate specifically the role for SWS in declarative memory consolidation. The authors first established a robust association between declarative learning (card place location) stimuli and a smell, olfactory stimulus (the smell of a rose). Subjects learned object locations in a two-dimensional (2D) object location memory task in the evening before sleep. During the first two periods of subsequent SWS, the odor cue was presented again (in an alternating 30 s on/30 s off mode). In a control condition, odorless vehicle was delivered. At retrieval testing after sleep, memory of card locations was distinctly enhanced when the odor was presented during SWS as compared to presentation of vehicle alone. Re-exposure to odor during SWS improved retention of memory in a hippocampus-dependent manner: bilateral reactivation of the hippocampus and medial prefrontal lobe, as measured by BOLD signal (Rasch et al., 2007). Further, an fMRI study demonstrated that compared with total sleep deprivation, post-learning sleep enhances hippocampal responses during recall of word pairs (declarative memory) 48 h after learning, thus indicating intra-hippocampal memory processing during sleep (Gais et al., 2007).. At the same time, it was shown that sleep induced a memory-related functional connectivity between the hippocampus and the medial prefrontal cortex. Six months after learning, recalling the same declarative memories reactivated the medial prefrontal cortex even more strongly than they did during encoding before sleep, thus showing that sleep leads to long lasting changes in representation of memories at a system (hippocampal-cortical) level. Although this study does not show

reactivation of the hippocampus and medial prefrontal cortex during sleep, basing on previous findings, the authors assume an important role of hippocampal-cortical connectivity for sleep-dependent declarative memory consolidation (Gais et al., 2007). The last convincing evidence concerning the role for SWS in memory formation comes from a recent fMRI study where the effect of declarative memory reconsolidation on declarative memory consolidation during SWS and wake was investigated (Diekelmenn et al., 2011). By using an experimental protocol similar to that previously applied by Rasch et al. (2007), the authors aimed at reactivating memories in humans by presenting associated odor cues either during SWS or during wake. During wake, reactivation of memories was followed by an interference task to probe memory stability, and as expected (Brown & Robertson, 2007; Robertson, 2009), this reactivation resulted in destabilized memories. In contrast, reactivation during SWS immediately stabilized memories, thereby directly increasing their resistance to interference. Importantly, BOLD signal revealed quite different patterns of reactivation during SWS and wake. The reactivation during SWS was mainly seen in the hippocampus and posterior cortical regions, whereas reactivation during wake was primarily found in the prefrontal cortical areas, thus showing that reactivation of memory serves distinct functions depending on brain state: wake versus SWS (Diekelmann et al., 2011). It is to be noted that similar differences between effects of oscillating trans-cranial direct current stimulation on both EEG activity and memory processes was also shown during wake when compared to SWS, although these differences distinguished specifically verbal memory encoding from declarative memory consolidation (Kirov et al., 2009; Marshall et al., 2006; 2011).

To our knowledge, only one neuroimaging study was able to provide convincing evidence for reactivation of brain regions during REM sleep in association with sleep-dependent consolidation of procedural memory (Maquet et al., 2000). In this study, three groups of subjects learned a serial reaction time task (SRTT) during wakefulness. To verify which brain regions are activated by SRTT, one group was scanned by using of PET either during training or during the subsequent rest wake period, and was not further examined. Subjects from a second group were trained on the task during two sessions in the afternoon, and then scanned during the night after training, both during wake and during various sleep stages. This group was retested at recall after sleep to verify that sleep-dependent learning had occurred. A third group was scanned at the same time points as the second group was, however, under absence of learning (no learning condition). Sleep architecture in the latter two groups was assessed by a routine PSG, and rCBF was measured across both three groups and all time points. Interestingly, although the third group improved implicit learning component of SRTT at recall after sleep, no any changes in sleep architecture between the learning and the non-learning conditions were found. However, as measured by the rCBF, a specific pattern of brain activation found in the first group during and after learning was reactivated only in the second group, and only during REM sleep. This pattern engaged a set of brain regions located in occipital and premotor cortices (Maquet et al., 2000). A later PET study by the same group (Laureys et al., 2001) confirmed that specific brain reactivation occurs during REM sleep in relation to procedural memory consolidation (Maquet et al., 2000). The authors showed that the left premotor cortex is functionally more correlated with the left posterior parietal cortex and bilateral pre-supplementary motor area during REM sleep in subjects previously trained to a reaction time task relative to untrained

subjects. The increase in functional connectivity during post-training REM sleep additionally suggests that the reactivated brain areas participate in an optimization of a network that subtends subject's visuo-motor response (Laureys et al., 2001).
Altogether, the above neuroimaging findings show that the mechanisms of memory processing during early night non-REM sleep/SWS are distinctly different from those that take place in REM sleep. The former include complex interactions between hippocampus and cortex, thus reflecting brain plasticity mechanisms at system and neural levels. The latter include local patterns of brain reactivation, which are proposed to reflect brain plasticity mechanisms at synaptic and genetic levels.

4. Sleep and cognitive functions

The strongest evidence for the important role that sleep plays in a variety of cognitive functions comes from many observations of effects of sleep loss and sleep deprivation on cognition (Killgore, 2010; Walker, 2008). The exclusively important role of sleep for cognitive functions has been best demonstrated in a study showing that even one night of total sleep deprivation results in inability to learn facts, i.e. deficient encoding of episodic memories (Yoo et al., 2007b). The neuroimaging correlates of this impaired learning ability will be presented below in the respective section.

4.1 Overview of human EEG data

Sleep spindles, the major hallmark of stage 2 of non-REM sleep, have been for long proposed to be associated with human individual cognitive abilities or intelligence. For example, Bódizs et al. (2005) found that both grouping of fast sleep spindles by cortical slow oscillation over the left frontopolar derivation (Fp1) and fast sleep spindle density over the right frontal area (Fp2, F4) during stage 2 of non-REM sleep, correlated positively with general mental ability. Further, a robust positive correlations were found between slow (< 13 Hz) and fast (> 13 Hz) spindle activity in stage 2 of non-REM sleep and both individual cognitive abilities and implicit/explicit memory-related abilities (Schabus et al., 2006). Later, Fogel et al. (2007a) showed first that number of spindles in stage 2 of non-REM sleep remains relatively stable within individuals from night to night. Second, the authors demonstrated that the number of spindles and EEG power of sigma (slow spindle) activity were positively correlated with performance intelligence quotient (PIQ), but not with verbal IQ. Also, perceptual/analytical skills measured by the PIQ accounted for most of the interindividual differences in spindles. Interestingly, in the same study, a relationship between rapid eye movements in REM sleep and VIQ in individuals with higher IQ scores was also demonstrated (Fogel et al., 2007a). However, Tucker & Fishbein (2009) demonstrated that while subject's intelligence correlated positively with pre-sleep acquisition and post-sleep retest performance on both procedural and declarative tasks, it did not correlate with over-stage 2 of non-REM sleep spindle events. These findings suggest that intelligence may not be a powerful modulator of sleep's effect on memory performance (Tucker & Fishbein, 2009).
One major question arising from the above described findings is whether sleep contributes to human intelligence in a state dependent manner (i.e., by providing neurobiological conditions for memory consolidation and reconsolidation), whether sleep is associated with intelligence in a trait dependent manner (i.e., strictly individual sleep characteristics are

related to individual intelligence), or whether sleep and human intelligence are related in both ways (Geiger et al., 2011; Fogel & Smith, 2011). It has been previously proposed that sleep serves human intelligence by complex interactions between its unique physiological and mental states, and individual sleep patterns and cognitive traits (Kirov, 2007). One study has addressed this question providing some evidence that stage 2 of non-REM sleep spindle increase after learning is related to elaborate encoding before sleep, whereas individual's general learning ability is well reflected by inter-individual (trait-like) differences in absolute sleep spindle activity (Schabus et al., 2008). However,, the precise mechanisms involved in the complex association between sleep and intelligence remain so far poorly understood (Kirov, 2007). As will be seen in the paragraph below, the role for sleep in human heuristic creativity and insightful behavior can further illuminate this issue.

Importantly, it has been consistently shown that sleep provides unique conditions for development of human heuristic creativity (Cai et al., 2009; Stickgold et al., 1999; Walker et al., 2002), among which the insightful behavior, as a higher form of human intelligence, is of major importance (Wagner et al., 2004; Yordanova et al., 2008; 2009; 2010; in press). Human insight refers to discovering of regularities that are out of awareness. Notably, it has been demonstrated that as twice as many subjects who had slept after initial learning of a number reduction task (NRT) gained insight into a hidden regularity relative to subjects who had been sleep deprived (Wagner et al., 2004). However, Wagner and co-authors (2004) have not objectively assessed sleep architecture by PSG. Thus, it has remained unclear how and through which mechanisms sleep promotes insight. This question was addressed in a series of later studies using the so-called split night design (Plihal & Born, 1997; 1999). The first study investigating sleep's role for insight by the split night design demonstrated that implicit knowledge acquired at encoding of NRT before sleep was transformed into insight throughout the early night sleep rich in SWS, thus pointing a role for SWS in insight (Yordanova et al., 2008). Further, the same study demonstrated that implicit learning of NRT acquired at encoding (during awakening before the second half of night) was not further transformed but was preserved by the late night sleep rich in REM sleep, thus indicating that REM sleep stabilizes implicit learning (Yordanova et al., 2008). In two later studies, Yordanova and co-authors demonstrated that SWS contributes to gaining insight in a state dependent instead of a trait-dependent manner. First, they revealed a topographic re-distribution of slow cortical potentials (SPs) indicating that a spatial reorganization occurred only after early sleep rich in SWS, but not after late sleep, and only for predictable responses on NRT. This SPs reorganization correlated with the amount of SWS (Yordanova et al., 2009). Second, they showed that only after SWS a pattern of brain activation shown as a precondition for insight (increased alpha and beta EEG desynchronization at the right hemisphere and a lack of such at the left) occurred (Yordanova et al., 2010). Finally, these authors were able to extract a specific for SWS EEG rhythm, slow (8-12 Hz) alpha activity at the right hemisphere, which was associated with transformation of implicit knowledge into insight on the NRT, and which was distinctly different form use-dependent (SWA and 12-15 Hz spindle activity) found at the left hemisphere in response to task performance (Yordanova et al., in press). Collectively, these findings strongly indicate that sleep promotes insight, as a higher form of human intelligence, in a state dependent rather than in a trait dependent way.

Finally, a recent study questioned which sleep mechanisms may play a role for abstraction of an implicit probabilistic structure in sequential stimuli using a statistical learning

paradigm, and searched for a predictive relationship between the type of sleep obtained and subsequent performance improvements (abstraction). Participants who consolidated over either a night of sleep or a nap improved significantly more than those who consolidated over an equivalent period of daytime wakefulness. Importantly, PSG revealed a significant correlation between the level of improvement or abstraction and the amount of SWS obtained (Durrant et al., 2011).

4.2 Overview of human neuroimaging data

The existing so far neuroimaging data concerning sleep and cognition do not reveal patterns of brain reactivation during sleep. Instead, they reveal altered brain activities associated with impaired cognitive processes in response to sleep deprivation. One of the most important findings is presented in the study of Yoo et al. (2007b). In this study, two groups of subjects were randomly assigned to either a sleep deprivation (SD) or a sleep control (SC) group. All subjects underwent an episodic memory encoding session during fMRI scanning, in which they viewed a series of picture slides and were retested two days later (after two recovery nights of sleep) for a recognition test session (without fMRI). Compared with SC group, SD subjects displayed much worse recognition at retest after two days, though they had two nights recovery sleep. This finding clearly shows that sleep deprivation impairs learning. The fMRI scans at learning/encoding demonstrated a significant impairment of activation in the hippocampal complex in the SD relative to SC group, a region known to be of critical importance for learning of new information (Yoo et al., 2007b). Another study showed that compared with normal sleep, SD produced impairment of spatial attention that correlated with a reduced activation in the posterior cingulate cortex, as measured by fMRI (Mander et al., 2008). Similarly, it is shown that SD produces lapses of attention manifested as delayed behavioral responses to salient stimuli. To identify changes in task-related brain activation associated with lapses after SD, fMRI scans during a visual selective attention task were conducted. It was demonstrated that SD-related lapses in attention corresponded to (1) reduced ability of frontal and parietal control regions to raise activation in response to lapses, (2) dramatically reduced visual sensory cortex activation and (3) reduced thalamic activation during lapses (Chee et al., 2008). Another fMRI study by the same group tested the hypothesis of whether SD impairs short-term memory due to reduced storage capacity or whether it affects processes contributing to appropriate information encoding. Scans were conducted during performing a short-term memory visual task and during presenting varying visual array sizes without engaging memory. Whereas the magnitude of intraparietal sulcus activation and memory capacity after normal sleep were highly correlated, SD elicited a diminished pattern of activation on both tasks, indicating that deficits in both visual processing and visual attention account for loss of short-term memory capacity (Chee & Chuah, 2007). Further, an fMRI study showed that SD abolishes selective attention in association with a decreased BOLD signal found within fronto-parietal cognitive control areas (the left intraparietal sulcus and the left inferior frontal lobe) and parahippocampal place area (PPA) during a selective attention task performance. Additionally, SD resulted in a significant decrement in functional connectivity between the PPA and the two cognitive control fronto-parietal areas (Lim et al., 2010). Interestingly, a single night of SD was shown to produce a strategy shift during risky decision making such that healthy human volunteers moved from defending against losses to seeking increased gains. An fMRI assessment revealed that this change in economic preferences was correlated

with the magnitude of an SD-driven increase in ventromedial prefrontal activation as well as by an SD-driven decrease in anterior insula activation during decision making (Venkatraman et al., 2011).

Regarding the above described neuroimaging findings together, it can be concluded that sleep is of critical importance for almost all, if not for all types of cognitive processes, including decision making. However, which mechanisms are responsible for substantial deficits of the many cognitive functions seen after sleep deprivation is still elusive.

5. Sleep and psychological functions

Herein, we will review existing data about sleep's role in functions different from the above described memory and cognitive ones. These include consolidation of affect, emotional regulation and dreaming mental states. As will be shown, the mechanisms, trough which sleep serves these psychological processes are distinctly different from those involved in its memory and cognitive functions. It is to be emphasized, however, that mostly REM sleep has been so far consistently and reliably associated with these human psychological processes. REM sleep characteristics are implicated for both normal psychological processes and psychopathology. Thus, REM sleep and its mental content incorporated in the co-occurring dreaming production have been proposed to aid resolution of personal emotional, affective and social conflicts (Cartwright et al., 2006; McNamara et al., 2001; 2005; 2010). Notably, REM sleep mechanisms and mental signatures have also been proposed to be involved in the pathogenesis of a number of psychopathological conditions, including posttraumatic stress disorder, anxiety, depression, schizophrenia, etc. (Benca et al., 1992; Gottesmann, 2010; Kirov & Brand, in press; Wagner et al., 2006; Walker, 2009; Walker & van der Helm, 2009). These observations are conceptualized in the so-called continuity hypothesis, according to which cognitive and emotional experiences generated, developed and used during wakefulness do continue to evolve during dreaming in REM sleep (Dumhoff & Hall, 1996; Pesant & Zadra, 2006). A recent study tested this hypothesis in both congenitally paraplegic and deaf-mute persons and matched controls. Surprisingly, perceptual representations, even of modalities not experienced during wakefulness, were quite common in dream reports not only in the control persons but also in the handicapped subjects (Voss et al., 2011). These interesting results give support to a protoconsciousness theory of REM sleep dreaming state that was recently forwarded by Hobson (2009). The REM sleep-dream protoconsciousness hypothesis proposes that development and maintenance of waking consciousness and other high-order brain functions (secondary consciousness) depends on brain activation during REM sleep (primary consciousness, i.e., simple awareness that includes perception and emotion in sleep), thus implicating for phylogenic aspects of dreaming. Accordingly, the neurobiology of REM sleep and co-occurring dreaming mentality reflect more basic (i.e., threaten, feeding, sexual, etc.) features not only in humans but also in lower species (Hobson, 2009). Interestingly, this view seems to have much in common with a previously proposed hypothesis about the psychological functions of REM sleep as an interactive genetic programming brain state (Jouvet, 1998). These two views (Hobson, 2009; Jouvet, 1998) predict that human experience during wakefulness is given more basic biological characteristics during REM sleep, which may have important adaptation roles. Also, they well fit with a more recent opinion about the memory functions of REM sleep, according to which memories consolidated during SWS undergo further transformation during REM sleep in terms of placing them in a more general and individually specific context (Walker & Stickgold, 2010).

5.1 Overview of human EEG data

Notably, human REM sleep has been so far shown to consolidate declarative (episodic or semantic) memory only when items have emotional salient components, and only when these emotional components have negative valence (Wagner et al., 2001; 2006; Nishida et al., 2009). Recently, REM sleep was shown to be very important for recalibration of the sensitivity of human brain to specific emotions (Gujar et al., 2011a).

Data concerning human sleep EEG findings about the role of REM sleep in psychological functioning are still scarce. One study investigated the effect REM sleep portion of a daily nap on episodic memory consolidation. No memorizing effects on emotionally neutral fact-based information were found. However, when episodic items were associated with negative emotional components, REM sleep strongly consolidated them. Moreover, the improvement strongly and positively correlated with all, REM sleep latency, amount of REM sleep, and importantly, with the theta (4-8 Hz) REM sleep EEG signature (Nishida et al., 2009). A more recent study tested whether boosting REM sleep EEG signatures could produce overnight improvement of memory consolidation. In this study, REM sleep EEG was potentiated by delivering theta (5 Hz) anodal trans-cranial direct current stimulation during REM sleep periods in the second half of night. The stimulation did enhanced gamma (25-45 Hz) EEG activity during REM sleep, but it did not improve either declarative or procedural memory consolidation at morning recalls. Instead, this increase in gamma EEG during REM sleep resulted in a worsened mood, as assessed by positive and negative affect scale, in the morning after sleep, accompanied by worsening on working memory, as assessed by a word fluency test (Marshall et al., 2011). Collectively, these studies demonstrate that specific REM sleep EEG rhythms are involved in affective behavior.

Interestingly, a recent study demonstrated the EEG signatures of dream recall from both REM sleep (theta, 5-7 Hz EEG activity) and stage 2 of non-REM sleep (alpha, 8-12 Hz EEG activity) (Marzano et al., 2011). These findings document different modes of mentality in REM sleep versus non-REM sleep. Furthermore, they suggest that the neurophysiological mechanisms underlying encoding and recall of episodic memories may remain the same across different states of consciousness.

5.2 Overview of human neuroimaging data

The existing so far human neuroimaging studies about the role for sleep in emotional regulation demonstrate deteriorated patterns of brain activation after total sleep deprivation (SD). By using fMRI, it has been shown that a disconnection between medial prefrontal cortex and amygdala following SD has been associated with improper response to negative emotional stimuli (Yoo et al., 2007a). Further, Sterpenich et al. (2007) showed that a successful recollection of emotional stimuli elicited larger BOLD responses in the hippocampus and various cortical areas, including the medial prefrontal cortex, in a sleep control (SC) group than in a sleep deprived (SD) group. In contrast, the recollection of negative items elicited larger responses in the amygdala and in occipital areas in the SD relative to the SC group (Sterpenich et al., 2007). A later fMRI study examined the effect of a single night SD on consolidation of aversive emotional stimuli and corresponding patterns of brain activation at retest that took place six months after encoding. At retest 6 months later, the recollection of subjects allowed to sleep, compared with SD subjects, was associated with significantly larger fMRI responses in the ventral medial prefrontal cortex (vMPFC) and precuneus, areas involved in memory retrieval, and in the extended amygdala and occipital cortex, areas involved in emotion modulation at encoding. These results

suggest that sleep during the first postencoding night profoundly influences long-term systems-level consolidation of emotional memory and modifies the functional segregation and integration associated with recollection of affective memories in the long term (Sterpenich et al., 2009). Finally, using fMRI, it was recently demonstrated that SD amplifies reactivity throughout human mesolimbic reward brain networks in response to pleasure-evoking stimuli. In addition, this amplified reactivity was associated with enhanced connectivity in the early primary visual processing pathways and extended limbic regions, yet with a reduction in coupling with medial frontal and orbitofrontal regions. These neural changes were accompanied by a biased increase in the number of emotional stimuli judged as pleasant in the sleep-deprived group, the extent of which exclusively correlated with activity in mesolimbic regions (Gujar et al., 2011b). These results may offer a neural foundation on which to consider interactions between sleep loss and emotional reactivity in a variety of mood disorders (Gujar et al., 2011b).

Collectively, the above findings demonstrate sleep-related mechanisms of emotional regulation and consolidation of affective memories that partially differ from those shown to be involved in emotionally neutral memory consolidation and in the cognitive functions of sleep. The emotional "fingerprint" seems to involve mostly connections between prefrontal cortices and amygdala. However, it still remains to be revealed which sleep portions or sleep stages might have contributed to the impaired brain activation patterns after SD responsible for the behavioral results.

6. Conclusions

It is undeniable that highly specific sleep EEG rhythms and patterns of brain activation *actively* serve the memory, cognitive and psychological functions of sleep. The corresponding mechanisms involve brain plasticity at system, neural, synaptic, and genetic levels, and are closely related to the neurobiology of sleep. However, these mechanisms are *distinctly different* for certain memory, cognitive and psychological categories that sleep promotes, being *dissimilarly associated* with distinct sleep portions and sleep stages. Thus, both declarative and procedural memory consolidation and reconsolidation occur in earliest part of non-REM sleep/SWS by mechanisms of brain plasticity at system and neural levels, engaged in hippocampus-cortical relationships. Those, occurring during REM sleep appear more complex. Their pattern of brain activation engages a large set of areas, and possibly involves brain plasticity mechanisms at synaptic and genetic levels. The emotional 'fingerprint" of memory consolidation seems to be presented by connections between amygdala and cortical areas.

Further, the mechanisms involved in other cognitive functions of sleep appear different from those involved specifically in its memorizing effects. Also, it seems that sleep contributes to cognitive processes in a state dependent rather than in a trait dependent manner, but a complex interaction between both also can be suggested. Thus, since some of the EEG data imply a trait dependent role for sleep in cognitive abilities, most of the neuroimaging data indicate a state dependent role. However, these conclusions need further experimental evidence.

Importantly, different types of sleep mentality incorporated in different forms of dreaming production suggest a role for dreams in memory and cognitive processes. Data from such studies may open new perspectives of research and may provide new views about cognitive functions of sleep.

Finally, it can be concluded that the mechanisms underpinning memory, cognitive and psychological functions of sleep substantially contribute to human intelligence. Further investigation of the relationship between sleep and intelligence is clearly warranted.

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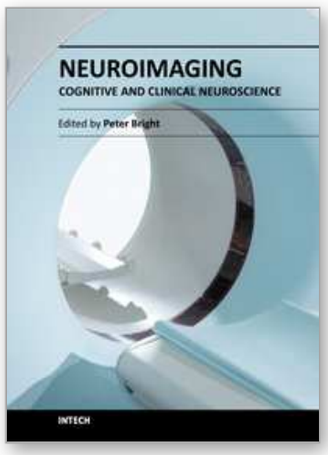

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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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