Sleep and Memory Processing: A Solid Relationship

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Abstract

The correlation between sleep and memory consolidation has recently drawn lot of attention and among these debates the link between the emotional memory and sleep, is of special note. Sleep is shown to importantly contribute to processes of memory. Sleep-dependent memory processing provides in the stabilisation, enhancement, and consolidation of a wide range of memory types including declarative (explicit) and non declarative (implicit). These specific types of memory would be consolidated during sleep, associated with specific sleep stage. In reviewed studies, a broad range of perceptual and motor procedural tasks were shown to be improved in performance after sleep. Overnight improvement on a procedural task correlates with SWS and Sleep spindles are reported to be associated with improvement of motor sequence task. Sleep enhances declarative memory for emotional words and pictures. Emotions can also enhance memory consolidation. In many of reports, psychiatric disorders such as depression exhibit the predominance of REM sleep, suggesting hyperactivity of amygdala. It also has been declared that Sleep (nap) will enhance emotional memory consolidation and this emotional memory benefit will be positively correlated with REM sleep. It has been well documented in some investigations that Theta activity during REM sleep will be strongly associated with emotional memory enhancement and furthermore sleep can selectively enhance offline consolidation of motor and emotional memory. It’s of note that SWS improves sleep-dependent motor adaptation, while spindles facilitates sleep-dependent, motor sequence task. And importantly, Emotional memory enhancement is strongly associated with REM sleep activity, involving the right-dominant prefrontal theta activity.

Review

Background in neuroscience of sleep, with regard to learning and memory

A large number of evidence has accumulated that sleep contributes to both learning and memory, with increasing emphasis placed on the role of sleep in memory and plasticity (Frank and Benington 2006; Wilhelm and others 2008; Miyamoto and Hensch 2003). Among the multiple functions of sleep, its role in the establishment of memories is likely to have important aspect, in contrast of brain’s normal processing of stimuli during wakefulness. The question of how sleep might contribute to human learning and memory has a long history, with a comment of ancient Roman rhetorician Quintilian in the first century of AD (Stickgold 2005). In the nineteenth century, the British psychologist David Hartley proposed that dreaming might strengthen associative memory within the brain. Testing Ebbinghaus’s memory decay, Jenkins and Dallenbach demonstrated that night sleep was more beneficial for memory retention than an equivalent amount of time awake (Walker 2008). Followed by striking discovery of rapid eye movement (REM) sleep by Aserinsky and Kleitman in 1953, research began to verify that sleep, or even specific sleep of stage actively play a role in the memory processing (Walker 2005; Walker and Stickgold 2006).

The brain has a cycle through periods of different neural and metabolic activity, divided biological states into wakefulness and sleep. Sleep is composed of REM and NERM sleep, which alternate across the night in human, with NREM sleep further divided into stage 1 to 4. Stages 3 and 4 are the deepest stage of sleep, and are referred to collectively as slow wave sleep (SWS) on the basis of the patterns of low-frequency cortical oscillations in the electroencephalogram (EEG) (Stickgold 2005; Born 2010). Sleep stages differ not only in the depth of sleep but also in the frequency, EEG oscillations, eye movements, muscle tone, involved dramatic change of neurochemistry and regional brain activation. Thus sleep can be considered as a heterogeneous state, which either does or does not affect memory processing. Each sleep stage holds a set of physiological and neurochemical mechanism that may contribute to memory processing and plasticity (Walker and Stickgold 2004).

Memory categories

There is more than a single type of memory. Memories are commonly divided into declarative memories and non-declarative memories. Declarative memory can be considered as the consciously accessible memories of fact based information. Non-declarative memories are normally used without conscious recollection. Declarative memories are further divided into episodic memories and semantic
memories (Henke 2010). Episodic memories consist of specific events of one's past, semantic memories are general information and knowledge. Non-declarative memories are also divided into several subcategories, such as procedural skills. In addition to speculum of memory systems, working memory is regarded as a specific process, implemented both the temporally storage and manipulation of information. (Fig. 1)

Current neural models of declarative memory information focus on the critical importance of strictures in the medial temporal lobe, exclusively the hippocampus. In contrast, non-declarative memory includes procedural memory, through action and behavior, depending on diverse neural components (Markowitsch and Staniloiu 2011; Born 2010).

Memory storage

There is no consensus on what “memory consolidation” means in terms of memory processing. After encoding, the memory representation can undergo several subsequent stages of development, the commonly considered of which is consolidation. The term memory consolidation originally referred to a process of memory stabilization, becomes increasingly resistant to interference. In other words, memory becomes more stable (Winocur and others 2010).

Recent findings have shown that consolidation can be thought as serving not only to stabilize memories, but also to enhance them. Although the stabilization process is likely to occur predominantly across time, the enhancement appears to occur during sleep. These additional memory consolidation process show the involvement of sleep dependence, occurring at the local synaptic level and system-level organization (Frankland and Bontempi 2005).

Thus, consolidation appears to be expanded to include more than one phase of post-encoding memory processing, with each brain states such as wake and sleep. Through the consolidation process, a memory can be retained for days to years, which time it can be recalled (Henke 2010; Winocur and others 2010; Sara and Hars 2006; Kandel 2006).

It is important to note that there is no consensus on how many distinct post-encoding processes exist, of which integration of recent acquired information with past experiences and knowledge, reactivation and reconsolidation of memory through recall. It is also interesting to note that sleep has been implicated in many of these steps (Walker and Stickgold 2004; Born 2010).

Sleep-dependent memory consolidation

A plethora of study has confirmed the beneficial effect of sleep on learning, affecting the structure of sleep. The act of learning can affect sleep and produce changes in the subsequent sleep (Fig. 2). A period of post-learning sleep enhances retention of declarative information and improves performance of procedural skills. Using a variety of behavioral paradigms, evidence of sleep dependent memory consolidation has been found in numerous species, including human being (Walker and Stickgold 2004).

Sleep after learning

A large number of early work investigating sleep and memory in human mainly focused on declarative tasks, the results demonstrated that REM sleep plays a specific role in memory consolidation and that post-training REM increases reflect a homeostatic response to adjust the increased input (Gais and others 2006). Although REM sleep is considered as the critical period for memory processing, recent studies has shown the importance of NREM sleep, altering brain plasticity accordingly based on synaptic homeostasis hypothesis (Frank and Benington 2006; Peigneux and others 2004; Brand and Kirov 2011).

In a computerized finger-tapping task, sleep after leaning resulted in consolidated and enhanced motor skill memories. Motor skill performance (number and accuracy of key-press sequences completed) was tested following offline time delays. Walker et al. reported that large and significant enhancements in motor performance were observed after sleep; representing the positive correlation with the amount stage 2 NREM sleep (Hotermans and others 2006; Walker 2008; Doyon and others 2009).

Based on evidence that motor skill memories are consolidated across a night of sleep, daytime nap enhanced motor memory consolidation, exhibiting correlation with regional spindle activity (Mednick 2011; Walker 2008).

In terms of declarative memory, several studies by Born and his colleagues demonstrated that the amount of slow wave sleep (SWS) was correlated with declarative memory consolidation. They found improvement on a related word-pair associate task after early night of sleep, which consists of rich SWS stages. The experiment of Direct Current Stimulation (DCS) demonstrated 0.75HZ slow oscillation induce by DCS increased not only the amount of SWS but also the retention of factual memories, suggesting a causal benefit of SWS neurophysiology. Related word pairs are favorable to strengthen or tag hippocampal-dependent memories, in which sleep
play a subtle role (Walker 2005; Mednick 2010).

Relating motor memory and SWS, motor adaptation task also the similar to those reported for the motor sequence task. The striking result is the increase of delta wave oscillation during SWS, localized in right parietal lobe, correlates with subsequent sleep-dependent improvement of performance. Together, sleep can facilitate sleep-dependent procedural memory consolidation, incorporating neural correlates such as SWS, spindle activity and ripple wave (Backhaus and Junghanns 2006; Eschenko and others 2008; Andrade 2011).

The neural basis for the role of sleep after learning has been increasingly investigated. A system level alteration in neural representation of a learned memory may occur during sleep, without such an alteration during wakefulness. Using functional magnetic resonance imaging (fMRI), several studies showed differential activation of brain regions and a re-organization of memories (Rauchs and others 2011).

Overnight, plastic reorganization of memory within brain may result in a more refined storage representation of information, such that the access and availability of memory recall in more efficient the following day. Therefore, sleep after learning of certain tasks looks to be required for the subsequent neural re-organization needed to consolidate memory (Walker and Stickgold 2004; Born and others 2006; Rauchs and others 2011).

Sleep before learning

While the merits of sleep after learning have been clearly demonstrated, it has become apparent that sleep before learning is also important for brain functioning. Animal studies have shown that sleep deprivation leads to change at a cellular and molecular level that inhibit hippocampal functioning and impair subsequent performance on hippocampus-dependent spatial learning task (Stickgold and others 2001). Yoo et al. reported the hippocampal deficits in humans produced by total sleep deprivation are strongly related with memory encoding by using fMRI (Yoo and others 2007).

The impact of sleep deprivation on the neural dynamics associated with encoding of new declarative memories has been revealed using event-related fMRI. In addition to performance, encoding impairments at a behavioral level, a highly significant and selective deficit in encoding activation was revealed in bilateral regions of hippocampus in the sleep deprived condition. It is apparent that sleep deprivation markedly impairs hippocampal memory function in humans (Walker 2009; Yoo and others 2007).

Neuroimaging studies performing sleep deprivation indicate the critical need for sleep before learning: without adequate sleep, hippocampal function obviously impaired, resulting in a decreased ability to encode new experiences the extent of which appears to be further governed by alterations in prefrontal encoding. Thus, sleep is not only critical after learning for the subsequent consolidation of memory, but also sleep before learning looks equally important in preparing brain structures for efficient memory formation (Yoo and others 2007; Chee and others 2011).

Sleep stage on consolidation

Early studies in rats and humans investigating whether different sleep stages have different roles mainly focused on REM sleep. REM sleep deprivation, by waking subjects up repeatedly at the first signs of REM sleep, itself influences memory function. The results of REM deprived studies have been remained controversial (Rauchs and others 2005; DANG-VU 2006; Diekelmann and Born 2010).

Several studies have shown that NREM stage 2 sleep of post-training sleep strengthen procedural motor memory (walker and others 2002; Fischer and others 2002; Nishida and Walker 2007). It is commonly recognized that sleep spindles, a thalamocortical rhythm manifested on the EEG as a brief 11-15 Hz oscillation, a defining characteristic of stage 2 NREM sleep, triggering intracellular mechanisms required for synaptic plasticity. Recent finding elucidated that those who generated more sleep spindles during a night of sleep went on to exhibit higher tolerance for noise during a subsequent, noisy night of sleep (Nishida and Walker 2007).

Although spontaneous spindles may have capacity of protecting sleep from disrupting stimuli, the further study should distinguish natural spindles from drug-induced spindle activities, considering medicated psychiatric disorders.

In humans, SWS has a critical role in both declarative and non-declarative memory consolidation. Tononi and his colleagues proposed synaptic homeostasis hypothesis, explaining the mechanisms assumes that consolidation is a by-product of the global synaptic downscaling during sleep. Slow oscillations are associated with downscaling: they show maximum amplitudes at
the beginning of sleep when overall synaptic strength is high, due to information uptake during encoding prior to sleep, and decrease in amplitude across SWS cycles as a result of the synaptic depotentiation (walker 2005).

Thus, it is not a particular sleep stage per se that mediates memory consolidation, but rather the neurophysiological mechanisms associated with those sleep stages. Specific neural correlates are complemented each other, representing electrophysiological unique oscillation (Rauchs and others 2005; Diekelmann and Born 2010). (Fig.2)

**Neuromodulators**

The specific neurochemical milieu of neurotransmitters and hormones differs strongly between slow wave sleep (SWS) and rapid eye movement (REM) sleep. Some of these neuromodulators contribute to memory consolidation. Interestingly, the most prominent contributions to memory processing seem to originate from the cholinergic and monoaminergic brainstem systems that are also involved in the basic regulation of sleep.

**Slow Wave Sleep (SWS)**

Cholinergic activity is at a minimum during SWS; this is thought to enable the spontaneous re-activation of hippocampal memory traces and information transfer to the neocortex by reducing the tonic inhibition of hippocampal CA3 and CA1 feedback neurons. Accordingly, increasing cholinergic tone during SWS-rich sleep blocked the sleep-dependent consolidation of hippocampus-dependent word-pair memories. Conversely, blocking the high cholinergic tone in awake subjects improved consolidation but impaired the encoding of new information, suggesting that acetylcholine serves as a switch between modes of brain activity, from encoding during wakefulness to consolidation during SWS. This dual function of acetylcholine seems to be complemented by glucocorticoids (cortisol in humans), the release of which is also at a minimum during SWS. Glucocorticoids block the hippocampal information flow to the neocortex, and if the level of glucocorticoids is artificially increased during SWS, the consolidation of declarative memories is blocked. Noradrenergic activity is at an intermediate level during SWS, and seems to be related to slow oscillations. In rats, phasic burst firing in the locus coeruleus (the brain's main source of noradrenaline) can be entrained by slow oscillations in the frontal cortex, with a phase-delay of almost 300 ms. It is possible that such bursts enforce plasticity-related immediate early gene (IEG) activity in the neocortex and thereby support at the synaptic level the stabilization of newly formed memory representations (Diekelmann 2010).

**REM sleep**

Cholinergic activity during REM sleep is similar or higher than during waking. This high cholinergic activity might promote synaptic consolidation by supporting plasticity-related IEG activity 162 and the maintenance of long-term potentiation (LTP).

Accordingly, blocking muscarinic receptors in rats by scopolamine during REM sleep impaired memory in a radial arm maze task. In humans, blocking cholinergic transmission during REM-rich sleep prevented gains in finger motor skill. Conversely, enhancing cholinergic tone during post-training REM-rich sleep improved consolidation of a visuo-motor skill. Noradrenergic and serotonergic activity reaches a minimum during REM sleep, but it is unclear whether this contributes to consolidation. It has been proposed that the release from inhibitory noradrenergic activity during REM sleep enables the re-activation of procedural and emotional aspects of memory (in cortico-striatal and amygdalar networks, respectively), thus supporting memory consolidation. However, enhancing noradrenergic activity during post-learning REM sleep in humans failed to impair procedural memory consolidation (Diekelmann 2010).

**Sleep-specific electrophysiological oscillations**

Sleep stages are characterized by specific electrical field potential rhythms that temporally coordinate information transfer between brain regions. Neocortical slow oscillations, thalamo-cortical spindles and hippocampal ripples have been associated with memory consolidation during SWS. The neocortical slow oscillations (of < 1 Hz) are thought to provide a supra-ordinate temporal frame for the dialogue between the neocortex and subcortical structures that is necessary for redistributing memories for long-term storage. The amplitude of the slow oscillations are increase when SWS is preceded by specific learning experiences and decreased when the encoding of information was prevented. These changes occur locally in the cortical regions that were involved in encoding process. Inducing slow oscillations during non-REM sleep by transcranial magnetic stimulation (TMS) using slow oscillating potential fields improved the consolidation of
hippocampus-dependent memories, indicating that slow oscillations have a causal role in the consolidation of hippocampus-dependent memories.

Thalamo-cortical spindles appear to prime cortical networks for the long-term storage of memory representations. Repeated spindle associated spike like discharges can trigger long term potentiation (LTP) and synchronous spindle activity occurs preferentially at synapses that were potentiated during encoding. Human studies have shown increases in spindle density and activity during non-REM sleep and SWS after learning of both declarative tasks and procedural motor skills.

In some studies these increases correlated with the post-sleep memory improvement and were localized to the cortical areas that were activated during encoding.

Hippocampal sharp wave-ripples accompany the sleep-associated re-activation of hippocampal neuron ensembles that were active during the preceding awake experience. The occurrence of sharp wave ripples is facilitated in previously potentiated synaptic circuits and sharp wave ripples might promote synaptic potentiation. During an individual ripple event only a small subpopulation of pyramidal cells fire, indicating modulation of select neuronal circuits. In humans (epileptic patients) the consolidation of picture memories that were acquired before a nap correlated with the number of ripples recorded from the entorhinal cortex, which is important output region of the hippocampus. Animal study showed that selective disruption of ripples by electrical stimulation during the post-learning rest periods in rats impaired formation of long-lasting spatial memories, suggesting that ripples have a causal role in sleep-dependent memory consolidation.

Ponto-geniculo-occipital (PGO) wave and the EEG theta rhythm appear to support REM sleep associated memory consolidation.

The significance of PGO-waves for memory consolidation is indicated by findings in rats of an increase PGO wave density following training on an avoidance task. This improvement was associated with increased activity of brain derived neurotropic factor (BDNF) in the dorsal hippocampus. The theta (4-8Hz) oscillations that characterize REM sleep are also considered to contribute to memory consolidation, based on the numerous studies shown hippocampus dependent learning. Theta activity occurring in conjunction with the activity in other EEG frequencies points to another important feature that is relevant to memory processing during REM sleep. During REM sleep, all EEG activity including theta activity show remarkable reduction in terms of both power and coherence between limbic-hippocampal circuit than SWS or wakefulness. The gamma band (>40 Hz) also behaves in similar way. These findings suggest that memory system would be disengaged during REM sleep.

Taking together, accumulated electrical results suggest that sleep plays an important role in balancing stabilization of the rehearsed material against the continued plasticity required for the further improvement (Fig. 3).

**Sleep and Brain Plasticity**

Memory depends on brain plasticity, lasting structural or functional neural changes in response to stimuli. Evidence of sleep-dependent plasticity would reinforce the idea that sleep is important as a mediator of memory consolidation.

Several studies have investigated whether daytime learning may alter brain activation during subsequent sleep at night (Born 2006).

A Positron Emission Tomography (PET) study has demonstrated that patterns of brain activity expressed during training on a motor sequence task replayed during subsequent REM sleep. Daytime task was initially associated with hippocampal activity.

Hippocampal activation is considered mainly during SWS, occurring hippocampal-neocortex dialogue resulted in transition of long-term memory.

The striking result showed the amount of reactivation of hippocampus during SWS remarkably proportional to the amount of subsequent task improvement. Sleep-dependent replay may potentially modify synaptic connections established in specific brain network, acquired during daytime wakefulness. Brain imaging studies conclusively suggest that sleep supports enhanced performance by altering the entire strategy used by the brain and allows more automatic execution of the tasks.

Cortical plasticity i.e. the formation and elimination of synapses is essential for learning, development and recovery process. Several hypotheses about the function of sleep postulate that sleep is causally linked to these processes. For instance, the synaptic homeostasis hypothesis (Tononi and Cirelli 2006) proposes that cortical plasticity is reflected in electroencephalographic activity in the slow-wave frequency range (slow wave activity, SWA)– the hallmark of deep sleep. According to the hypothesis, sleep slow waves are not only reflecting cortical plasticity but are also responsible for synaptic downscaling, a renormalization process that
recalibrates neural circuits.

On the neuronal level, such synaptic downscaling should lead to energy and space savings and increase the signal to noise ratio. The resulting increased efficiency in signal transduction might be responsible for sleep dependent performance improvements.

An increasing number of studies support the hypothesis. Thus, as SWA decreases in the course of a night, the responsiveness of cortical neurons in rats (Vyazovskiy et al., 2008), the size and number of synapses in Drosophila melanogaster (Bushey et al., 2011), and the frequency and amplitude of miniature EPSPs in cortical slices, the most direct measure of cortical responsiveness (Liu et al., 2010), decrease.

Human studies link such synaptic changes to changes in performance. For example, sleep dependent performance improvement on a visuo-motor learning task was positively correlated with the local increase of SWA (Huber et al., 2004). On the other hand, a suppression of sleep slow-waves abolished sleep dependent performance improvement on a texture discrimination task (Aeschbach et al., 2008).

For now, the synaptic homeostasis hypothesis represents a compelling hypothesis about the function of sleep integrating molecular, electrophysiological and behavioral findings allowing for testable experiments.

The Dreaming

The study of dreaming has provided the unexpected result in sleep-dependent memory consolidation. Dream reports can be meaningful for explaining brain during sleep. Stickgold et al. reported that dream construction occurs without activation of hippocampus-mediated episodic memories, applying the computer Tetris game to amnesic patients. Such an absence of episodic memory replays is supported by human PET studies showing the dorsolateral prefrontal cortex, normally involved in memory recall, is deactivated especially during REM sleep. Animal studies suggest that the flow of information from the hippocampus to the cortex is blocked during REM sleep.

Clinical Considerations

All major psychiatric disorders such as schizophrenia, bipolar disorder and major depression, have associated sleep disturbances mainly manifesting insomnia. But the interaction between psychiatric symptom and sleep disturbance might be bi-directional. Indeed, chronic, medicated schizophrenia patients show normal practice-dependent improvement in the finger tapping task, but show no overnight improvement. Major depressive patients show the similar result regarding motor memory consolidation, with interaction of REM suppressive agents such as Selective Serotonin Reuptake Inhibitors (SSRIs).

In the context of REM-dependent negative emotional memory enhancement, negative aversive memories may hold implications for the mechanistic understanding and treatment of mood disorders, including major depressive disorders. Depression is commonly associated with alterations in REM sleep, including a faster progression into REM (reduced REM latency) and an increase in the amount of REM. Considering the REM association with negative emotional memory such REM abnormalities in depression may represent an excessive consolidation process of prior negative affective experiences, due to the increased REM amount and faster speed of entry into REM, could selectively and disproportionately reinforce negative memories at night, thereby potentiating the mood disorder. Likewise, post-traumatic stress disorder (PTSD) is also associated with a dysregulation of REM sleep, with reports of increased sympathetic autonomic tone. There may similarly be an adverse consequence to such trauma-induced REM-sleep changes in PTSD, which if they persist, could counter-productively amplify, rather than ameliorate, the acquired affective experience.

Such basic research findings may help the growing translational appreciation of the interaction between affective mood disorders and sleep physiology.

Thus, in one major psychiatric illness, at least, one process of sleep dependent memory consolidation seems to be totally dysfunctional.

Conclusion(s)

The field of sleep and memory has grown remarkably, with a lot of studies ranging from molecular biology in animals to neurophysiology in humans. These reports have provided converging evidence that claims sleep's role in memory processing, including both initial learning and post-training sleep associated neural plasticity.

Although the evidence has proved that sleep itself is beneficial for memory processing, several major questions remain: the types of memory, consolidation and neural correlates. Regarding procedural skill learning and declarative memory consolidation, there are strong evidences. But the rules determining which are consolidated during sleep remain unclear. The interaction between NREM and REM sleep should be
further investigated, including the elucidation of neural correlates such as SWS, sleep spindles and ripple waves. The search for answers to these questions is the task of the next decade of research into sleep dependent memory processing.

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Illustrations

Illustration 1

Memory categories

![Memory categories diagram]

Illustration 2

Developing stages of memory and its interplay with sleep

![Developing stages of memory diagram]
Illustration 3

Sleep stages and EEG
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