Sleep and Memory

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Current behavioural evidence indicates that sleep plays a central role in memory consolidation. Neural events during post-learning sleep share key features with both early and late stages of memory consolidation. For example, recent studies have shown neuronal changes during post-learning sleep which reflect early synaptic changes associated with consolidation, including activation of shared intracellular pathways and modifications of synaptic strength. Sleep may also play a role in later stages of consolidation involving propagation of memory traces throughout the brain. However, to date the precise molecular and physiological aspects of sleep required for this process remain unknown. The behavioural effects of sleep may be mediated by the large-scale, global changes in neuronal activity, synchrony and intracellular communication that accompany this vigilance state, or by synapse-specific ‘replay’ of activity patterns associated with prior learning.

Introduction

In the last decade, there has been a revival of interest in the theory that sleep is essential for memory formation. This has been fuelled primarily by behavioural studies in humans which show beneficial effects of sleep on memory consolidation (reviewed in Stickgold, 2005). However, the neurobiological processes underlying these effects remain unclear (Frank and Benington, 2006). In this article, we address the possible role of sleep in neurophysiological processes involved in memory consolidation at the synaptic and brain systems levels. We first briefly summarize key steps involved in these two levels of consolidation, then examine current evidence that suggest that sleep influences these processes. We conclude with a discussion of remaining key questions regarding sleep’s role in consolidation, and suggest future strategies to better understand the underlying mechanisms.

Synaptic and Systems Mechanisms of Memory Consolidation

Memory formation can be broken down into several discrete steps. Relevant sensory information must first be attended to and registered as a memory trace – a process referred to as acquisition. Following acquisition, memories either undergo a process of consolidation (enhancement and/or stabilization for long-term storage) or are forgotten. Forgetting can be thought of as a process that acts in opposition to consolidation, and can occur either through interference (where prior or subsequent memory formation actively prevents consolidation of information) or decay (the passive disappearance of unconsolidated memories over time) (Wixted, 2004). Memory is often broadly categorized as either explicit or implicit. The main difference between the two memory types is that consolidation of explicit memory (e.g. episodic and semantic memory) is dependent on medial temporal lobe structures such as the hippocampus, whereas consolidation of implicit memory (e.g. priming and procedural/skill memory) is not. However, consolidation of both implicit and explicit memory seems to rely on two general mechanistic processes, referred to as synaptic and systems consolidation (Dudai, 2004). See also: Learning and Memory

‘Synaptic consolidation’ (Figure 1a and d) refers to rapid, activity-dependent changes in synaptic strength within specific neural circuits following memory acquisition, which likely represents a cellular scaffold for subsequent memory consolidation. There are three definable features of this process. The first is that it occurs within the first hours after acquisition (Figure 1a). This can be seen, for example, in the decreasing sensitivity of motor skill learning to behavioral interference over the first few hours after...
Sleep and Memory Consolidation

**Time-dependency**

As discussed earlier, a key feature of synaptic consolidation is that it occurs within the first hours following acquisition. Thus if sleep plays a role in synaptic consolidation, one would expect that sleep immediately following acquisition would be critical for memory. There are several examples in the behavioral literature where sleep is indeed required during the first hours following acquisition in order for optimal consolidation to occur. One recent study found that memory for new vocabulary words was stabilized when subjects slept within 3 h of learning them, but impaired when sleep was delayed for several hours (Gais et al., 2006). Second example is contextual fear conditioning in rodents, which is impaired when animals are sleep deprived over the first 5 h following acquisition training, but not when they are deprived afterward (Graves et al., 2003). Third is visual imprinting in chicks, which requires sleep in the first few hours following exposure to imprinting stimuli, but is not facilitated by sleep after this critical window (Jackson et al., 2008).

**Dependence on NMDA receptors, kinases and synthetic pathways**

A second feature of synaptic consolidation is dependence on NMDA-R- and kinase-dependent intracellular signaling cascades, and synthesis of new mRNA and proteins. There are two lines of evidence that these cellular mechanisms may be specifically activated during post-acquisition sleep (as schematized in Figure 2c). First are reports of activation of these pathways which is correlated with the requirement for sleep, and occurs in the first hours of memory consolidation. For example, sleep-dependent consolidation of two-way active avoidance learning in rats is correlated with hippocampal IEG expression and protein phosphorylation in the first few hours following training.
Changes in synaptic strength

The third feature of synaptic consolidation is that it leads to rapid changes in synaptic strength in circuits activated by prior learning. Two lines of evidence indicate that this process is promoted by sleep. Ocular dominance plasticity (ODP), a canonical form of in vivo synaptic remodelling occurring in the visual cortex after brief monocular visual experience, is consolidated by a few hours of subsequent sleep (but not a similar period of wakefulness) (Frank et al., 2001) and is dependent on postsynaptic cortical activity during sleep (Jha et al., 2005; Frank et al., 2006). Because this type of plasticity involves both synaptic weakening (of deprived eye inputs) and synaptic strengthening (of non-deprived eye inputs) within the visual cortex (Mioche and Singer, 1989), it is possible that either, or both, of these processes occur during the sleep-dependent ODP consolidation. However, evidence for specific strengthening of synapses during sleep is suggested from studies of chick imprinting. In cerebral areas implicated in this form of learning, increases in both postsynaptic density size and glutamate receptor numbers occur at the time during which sleep is required for consolidation (Horn, 2004). Some of these changes in synaptic strength may be mediated by thalamocortical and neocortical electroencephalogram (EEG) oscillations that occur during non-REM (NREM) sleep (Figure 2a). For example, neuronal firing patterns similar to sleep spindle (12–15 Hz) oscillations during NREM sleep have been shown to potentiate postsynaptic responses in cortical target neurons in vivo and in vitro (Steriade and Timôfoev, 2003; Rosanova and Ulrich, 2005). Conversely, slow-wave EEG oscillations (0.5–4 Hz) may promote synaptic weakening (Tononi and Cirelli, 2003; Czarnecki et al., 2007). Whether or not NREM oscillations normally promote synaptic consolidation is unknown, but spindles and slow-wave oscillations are up-regulated in cortical circuits involved in learning new tasks during the first hours of subsequent sleep. This upregulation is correlated with subsequent behavioural measures of memory consolidation (Huber et al., 2004; Nishida and Walker, 2007). Moreover, artificially augmenting these oscillations during the first hours of NREM sleep improves hippocampus-dependent declarative memory consolidation during sleep (Marshall et al., 2006). See also: Neural Activity and the Development of Brain Circuits; Sleep and Memory.

Sleep and Systems Consolidation

Time-dependent expansion of memory traces

Systems consolidation involves gradual integration of memory traces through more spatially distributed brain areas over a period of days to months. A hallmark of this process is a corresponding expansion of activation patterns in hippocampal and neocortical structures during recall. Several findings indicate that sleep may facilitate these events (Figure 2b). Two recent brain-imaging studies assessed the effect of a night of post-acquisition sleep or sleep deprivation on explicit memory recall days to months later. Both report that sleep (but not sleep deprivation) aided subsequent recall (2 days or 6 months later, respectively) and led to greater overall activation and/or functional connectivity between hippocampal and neocortical brain areas during recall (Gais et al., 2007; Sterpenich et al., 2007). Similar effects of post-acquisition sleep on an implicit motor skill task have also been reported (Fischer et al., 2005).

Findings from animal studies further suggest that sleep promotes the transfer of memory traces between different brain areas. During sleep, hippocampal and neocortical neurons in rodents and primates ‘replay’ patterns of firing triggered during prior waking (e.g. during maze running). To what extent this reflects actual systems consolidation is not clear, but coordinated replay has been reported in the neocortex and hippocampus (Ji and Wilson, 2007) and between various sensory and motor cortical areas following a sequential reaching task (Hoffman and McNaughton, 2002). In addition, correlational analyses suggest that slow-wave and spindle oscillations can synchronize neural activity across various brain regions (e.g. between neocortex and hippocampus) during NREM sleep (Isomura et al., 2006; Hoffman et al., 2007).

Dependence on kinases and synthetic pathways

A second key feature of systems consolidation is that it requires continued activation of NMDA-Rs, kinase pathways and protein synthesis machinery over a period of days to months (Wang et al., 2006). The possibility that sleep...
A fruitful approach may be to consider whether sleep facilitates memory consolidation through permissive or instructive mechanisms. Instructive mechanisms are generally defined as those that both directly mediate a process, and also provide information about how it should proceed. Thus we define instructive mechanisms of consolidation as those that are sufficient to mediate the potentiation or depression of specific synapses within neural circuits engaged by prior learning. In contrast, permissive mechanisms are defined as those that can facilitate consolidation, but do not inform how it progresses. For example, permissive mechanisms could be required for changes in synaptic strength, but would not determine which specific synapses are strengthened or weakened. Sleep may facilitate memory consolidation through either permissive or instructive mechanisms, or through a combination of permissive and instructive mechanisms, as described in the next sections.

**Potential permissive mechanisms**

Sleep is associated with large-scale changes in neurotransmission, transcription, translation and neural activity across the brain, which could promote synaptic plasticity without informing how specific synaptic connections should change. For example, expression of genes required for macromolecular biosynthesis and transport, and overall protein synthesis, are preferentially upregulated in the cortex during sleep (Ramm and Smith, 1990; Mackiewicz et al., 2007); these changes likely play a supportive role in synaptic plasticity and memory consolidation (Figure 2c–e).

However, an upregulation of synthesis and ‘housekeeping’ activities alone would be insufficient for informing specific synaptic changes. Sleep also leads to widespread changes in neurotransmitter release throughout the cortex (Figure 2a). These changes include increases in acetylcholine release (and decreases in serotonin and noradrenaline release) relative to wakefulness during REM sleep, and decreases in acetylcholine, noradrenaline and serotonin release during...
NREM sleep (Gottesmann, 1999). Specific changes in the neurotransmitter milieu during sleep may facilitate synaptic plasticity and memory consolidation (Benington and Frank, 2003), but because they appear to be uniform throughout structures like the cortex, they are unlikely to modify specific synapses activated by prior learning. For example, the decrease in overall cholinergic transmission during NREM sleep has long been hypothesized to mediate transfer of memory traces from hippocampus to the neocortex (Hasselmo, 1999). In support of this idea, artificially augmenting cholinergic neurotransmission (by administering a cholinesterase inhibitor) during post-acquisition NREM sleep interferes with some forms of declarative memory consolidation (Gais and Born, 2004). Finally, a recent hypothesis suggests that NREM slow-wave activity downregulates synaptic strength across the entire neocortex (Tononi and Cirelli, 2003). This homeostatic downsampling is hypothesized to offset Hebbian synaptic strengthening that occurs during waking, and presumably, memory formation. Because it is proposed that all cortical synapses are scaled back during sleep – without corresponding instructions for specific changes at specific synapses – this hypothesis is consistent with a permissive mechanism.

**Potential instructive mechanisms**

As discussed earlier, some features of sleeping brain activity depend on prior experience during wakefulness, and have the potential to specifically activate (and modify) circuits and synapses engaged by prior learning. One potentially instructive mechanism for sleep-dependent consolidation is ‘replay’ of neuronal activity present during wakefulness. Replay during sleep is clearly associated with prior waking experience (Hoffman and McNaughton, 2002; Ji and Wilson, 2007), involves reactivation of specific synaptic connections involved in performance of the learned task, and has unique features that may promote synaptic modifications. For example, replay events during NREM sleep occur at a faster rate than that observed during actual task performance (Ji and Wilson, 2007). This time compression would increase the frequency of activation for a given set of synapses, and thus may increase their likelihood for potentiation (Benington and Frank, 2003). A second use-dependent feature of NREM sleep, which may represent an instructive mechanism of consolidation, are localized changes in sleep spindles and slow-wave activity in the cortex. Recent findings indicate that the prevalence of these oscillations in specific neural circuits is associated with their activation during prior learning (Huber et al., 2004; Nishida and Walker, 2007), and that their ‘up’ states activate specific synaptic connections between neurons (Luczak et al., 2007).

**Conclusions**

Despite a wealth of behavioural, molecular and electrophysiological findings, a definitive explanation of how sleep influences memory continues to elude scientists. Several important clues, however, have emerged over the past few years. Rather than a simple, passive reduction of internal brain activity and external sensory input, sleep is a time of massive central nervous system activation. Some of these sleep-associated events can influence synaptic plasticity within the hippocampus and neocortex, and in some studies these are correlated with synaptic or systems-level memory consolidation. Because sleep is not a uniform brain state, the precise mechanisms underlying memory consolidation have proven difficult to isolate. However, a first step in addressing this problem will be to determine if putative causal mechanisms are permissive or instructive, as that information will guide more focused future investigations. One major goal for future investigations will be to develop animal models where molecular and neurophysiological events can be studied in parallel with behavioural outcomes. A second important strategy will be to develop simple, repeatable behavioural assays that will clearly identify which aspects of consolidation are influenced by specific aspects of sleep.

**References**


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**Further Reading**

Key concepts

- Memory consolidation involves plastic changes at the synaptic and brain systems levels; these changes occur over timescales of minutes (synaptic consolidation) to days or months (systems consolidation).
- Cellular changes occurring during early post-learning sleep suggest that synaptic consolidation may occur preferentially during sleep.
- Brain-imaging and gene-expression studies have provided limited evidence that sleep may facilitate the gradual redistribution of memory traces throughout the brain.
- Sleep may facilitate consolidation through large-scale changes in neural activity, neurotransmission or gene expression associated with rapid eye movement (REM) and non-REM (NREM) vigilance states.
- It remains unclear whether sleep-dependent consolidation is mediated by permissive (global) or instructive (synapse-specific) mechanisms.

Glossary: None

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Effectors of synaptic consolidation (GluR1/2, CaMKII, Arc, cytoskeleton proteins)

System

Network

Synaptic stimulation

Modulatory inputs (dopamine, ACh, serotonin)

Hippocampus

Neocortex

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Figure 1  Synaptic and systems levels of memory consolidation. In the first hours following acquisition, a memory trace is represented in specific neural circuits (in this example, within the hippocampus, highlighted in grey, (a)). The memory trace is then gradually integrated into a broader neuronal network, including areas not involved in acquisition (in this example, in the neocortex, (b)), and distributed over time throughout the neocortex (c). Synaptic consolidation (schematized in (d)) involves activation of NMDA-R- and kinase-dependent signalling cascades which promote de novo mRNA and protein synthesis. NMDA-R activation increases calcium (Ca$^{2+}$) influx, whereas neurotransmitter-mediated activation of G protein-coupled receptors stimulate cyclic adenosine monophosphate (cAMP) production. These intracellular signals in turn promote the phosphorylation-dependent activation of kinases (e.g. PKA, CaMKII and extracellular signal-regulated kinase (ERK)) (Wang et al., 2006). These kinases activate cAMP response element-binding (CREB) protein-dependent immediate early gene (iEG) expression (e.g. zif268, arc/arg3.1, c-fos) (Abel and Lattal, 2001). Products of these transcripts are then translated, together with additional effectors of synaptic potentiation or depression (e.g. glutamate receptor subunits, BDNF and CaMKII). Systems consolidation (schematized in (e)) requires subsequent activation of CaMKII and synthetic pathways over a period of days to months (Wang et al., 2006), as memory traces expand through more broadly distributed brain areas.
Figure 2. Potential roles of sleep in synaptic and systems consolidation. (a) Representative changes in release of acetylcholine (ACh) and noradrenaline (NA) in the cortex (relative to waking) during REM and NREM sleep. Representative EEG traces for the two sleep states show cortical activity similar to that of waking during REM sleep, and high-amplitude EEG oscillations – including sleep spindles and slow-wave activity (SWA) – during NREM sleep. (b) Sequence of events showing the transfer over time of the memory trace from hippocampus to neocortical distributed network (see Figure 1a–c for detailed description). (c)–(e) Potential cellular mechanisms underlying sleep facilitation of consolidation. Functions demonstrated to occur specifically during sleep are shown in colour; mechanisms correlated with sleep (i.e. known to be active at the time when sleep is required for consolidation) are indicated with a question mark. Mechanisms that have not been studied with respect to sleep are shown in gray. (c) Mechanisms implicated in sleep facilitation of synaptic consolidation are schematized in a neuron within the circuits activated by prior learning (in this example, a neuron in the hippocampus). NMDA-R activation during sleep may be necessary for some early forms of consolidation (Gais et al., 2008), whereas PKA, CaMKII and CREB activation and protein synthesis are correlated with the time-dependent requirement for sleep in other forms of learning (Bourtchouladze et al., 1998; Horn, 2004; Saha and Datta, 2005). Increased expression of the IEG zif268 occurs during REM sleep following some forms of learning (Ribeiro et al., 1999), whereas arc/arg3.1 and c-fos expression are correlated in time with the requirement for sleep following other learning paradigms (Horn, 2004; Bock et al., 2005). (d) The same signalling pathways may be activated in additional neural circuits during subsequent systems consolidation (schematized as a neuron in the neocortex which is synaptically connected with the original hippocampal neuron). Changes in neurotransmission or activity during sleep (e.g. synchronized bursting activity produced by SWA and spindles) could promote intercellular communication between these brain areas (represented by red arrows). During subsequent stages of systems consolidation (e), these same sleep-dependent mechanisms may promote further expansion of memory traces throughout the neocortex (indicated by red arrows).
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