Sleep and Memory

SJ Aton, *University of Pennsylvania, Philadelphia, Pennsylvania, USA*
J Seibt, *University of Pennsylvania, Philadelphia, Pennsylvania, USA*
MG Frank, *University of Pennsylvania, Philadelphia, Pennsylvania, USA*

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.

Advanced article

Article Contents

Online posting date: 15th September 2009

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 suggests 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.

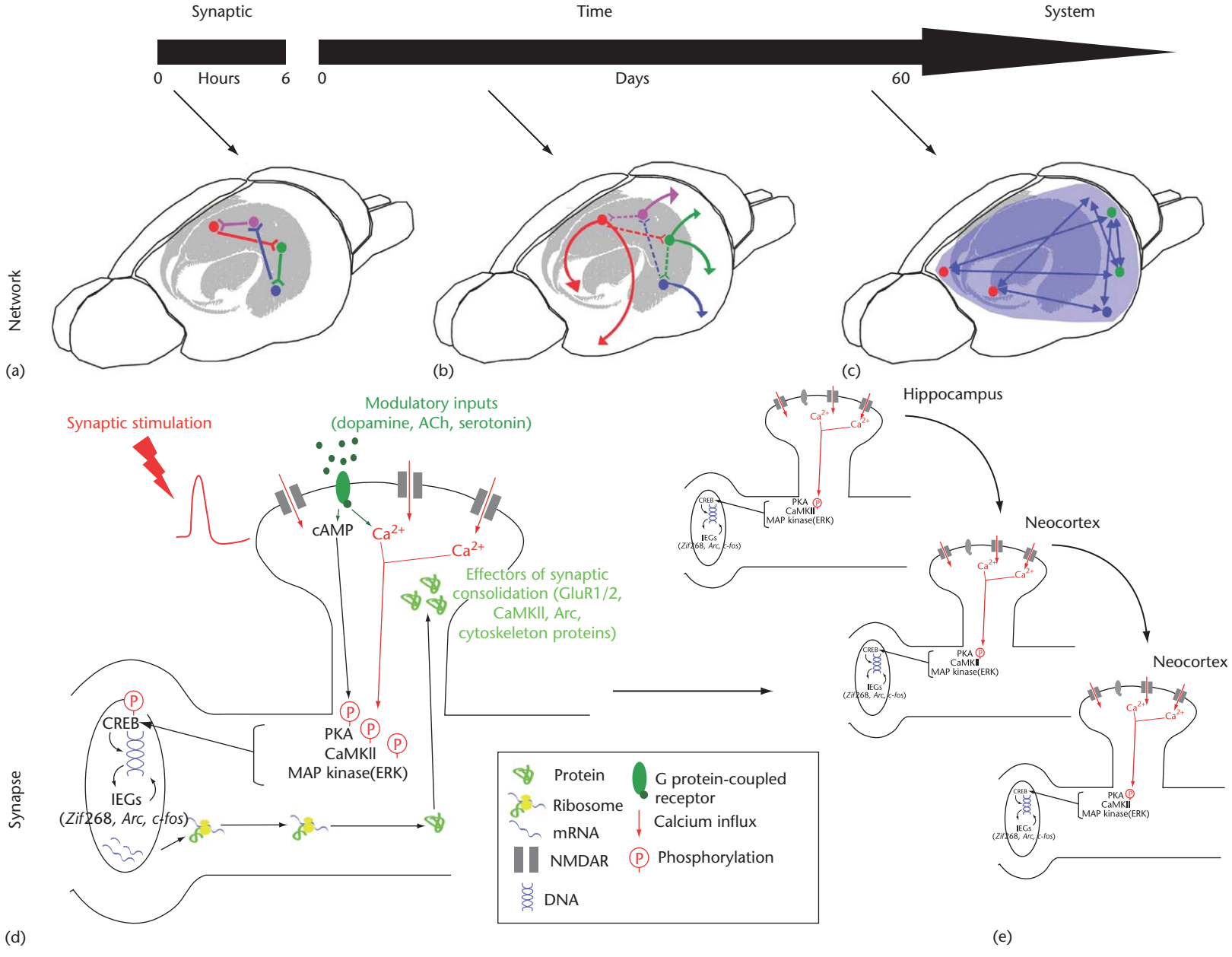
Synaptic and Systems Mechanisms of Memory Consolidation

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 defining 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 behavioural interference over the first few hours after acquisition (Brashers-Krug *et al.*, 1996; reviewed in Dudai, 2004). A second feature of synaptic consolidation is that it requires activation of *N*-methyl-D-aspartate receptor (NMDAR)- and kinase-dependent intracellular signalling cascades, and synthesis of new messenger ribonucleic acid (mRNA) and proteins (**Figure 1d**). For example, during the first hours after fear conditioning training in rodents,

ELS subject area: Neuroscience

How to cite:
Aton, SJ; Seibt, J; and, Frank, MG (September 2009) Sleep and Memory. In: Encyclopedia of Life Sciences (ELS). John Wiley & Sons, Ltd: Chichester.
DOI: 10.1002/9780470015902.a0021395



consolidation is sensitive to pharmacological disruption of NMDAR-dependent kinase pathways and *de novo* mRNA and protein synthesis in brain areas activated by learning (Abel and Lattal, 2001). These cellular mechanisms are also required for long-term potentiation (LTP) and long-term depression (LTD) – well-studied processes of synaptic strengthening and weakening, respectively, which occur *in vitro* and *in vivo*. Importantly, the third defining feature of synaptic consolidation is that it involves rapid changes in synaptic strength within specific neural circuits. Examples of this include findings that specific types of learning are followed by the same postsynaptic changes (increased postsynaptic density area, phosphorylation of key target proteins and enhancement of synaptic responses) that occur during LTP (Horn, 2004; Whitlock *et al*., 2006). **See also**: Long-term Depression and Depotentiation; Long-term Potentiation; NMDA Receptors; Protein Phosphorylation and Long-term Synaptic Plasticity; Protein Synthesis and Long-term Synaptic Plasticity

'Systems consolidation' (**Figure 1b**, **c** and **e**) refers to more protracted, activity-dependent expansion of memory traces from their original source to more widespread cortical areas. Two key defining features of systems consolidation are the gradual integration of memories through more distributed brain areas over a period of days to months (**Figure 1b** and **c**), and dependence on NMDAR-dependent kinase pathways and protein synthetic machinery during this process (**Figure 1e**). Evidence for the expansion and redistribution of memory traces comes from longitudinal brain-imaging studies, which demonstrate that long-term consolidation is associated with more distributed brain activation during recall (Frankland *et al*., 2004; Takashima *et al*., 2006). Additional, behavioural evidence for this gradual redistribution is seen in patients with damage to medial temporal lobe structures. These individuals frequently experience explicit memory loss for recent events, whereas more remote memories remain accessible (Dudai, 2004). Evidence that NMDARs, kinases and protein syntheses are required for this process have come from animal studies of learning where pharmacological and genetic blockade of these pathways days or even months after learning impairs subsequent recall (Wang *et al*., 2006). **See also**: Amnesia

Sleep and Memory Consolidation

Despite decades of debate (Ellenbogen *et al*., 2006), consensus in the field is gradually building that sleep promotes memory consolidation (Stickgold, 2005). The critical question, which we address here, is *how* consolidation could be achieved during sleep. A simple explanation is that sleep protects memory traces from interference associated with wakefulness, by reducing sensory input to the brain (Wixted, 2004). However, recent studies specifically addressing this issue report improvements in memory associated with sleep which cannot be explained entirely by a reduction in interference (Mednick *et al*., 2002; Gais *et al*., 2006; Korman *et al*., 2007). For example, Mednick *et al*. found improvements in subjects' performance on a visual perception task when a 1-h nap was allowed between training sessions. However, no improvement was seen in control subjects who were kept awake, but blindfolded, over the same time period – thus simply limiting visual interference (without sleep) was insufficient for consolidation (Mednick *et al*., 2002). Therefore, it is likely that sleep modulates memory via more direct effects on synaptic and systems consolidation.

Sleep and Synaptic 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 behavioural 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). A 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). A 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 NMDAR- and kinase-dependent intracellular

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 NMDAR- and kinase-dependent signalling cascades which promote *de novo* mRNA and protein synthesis. NMDAR 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, 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.

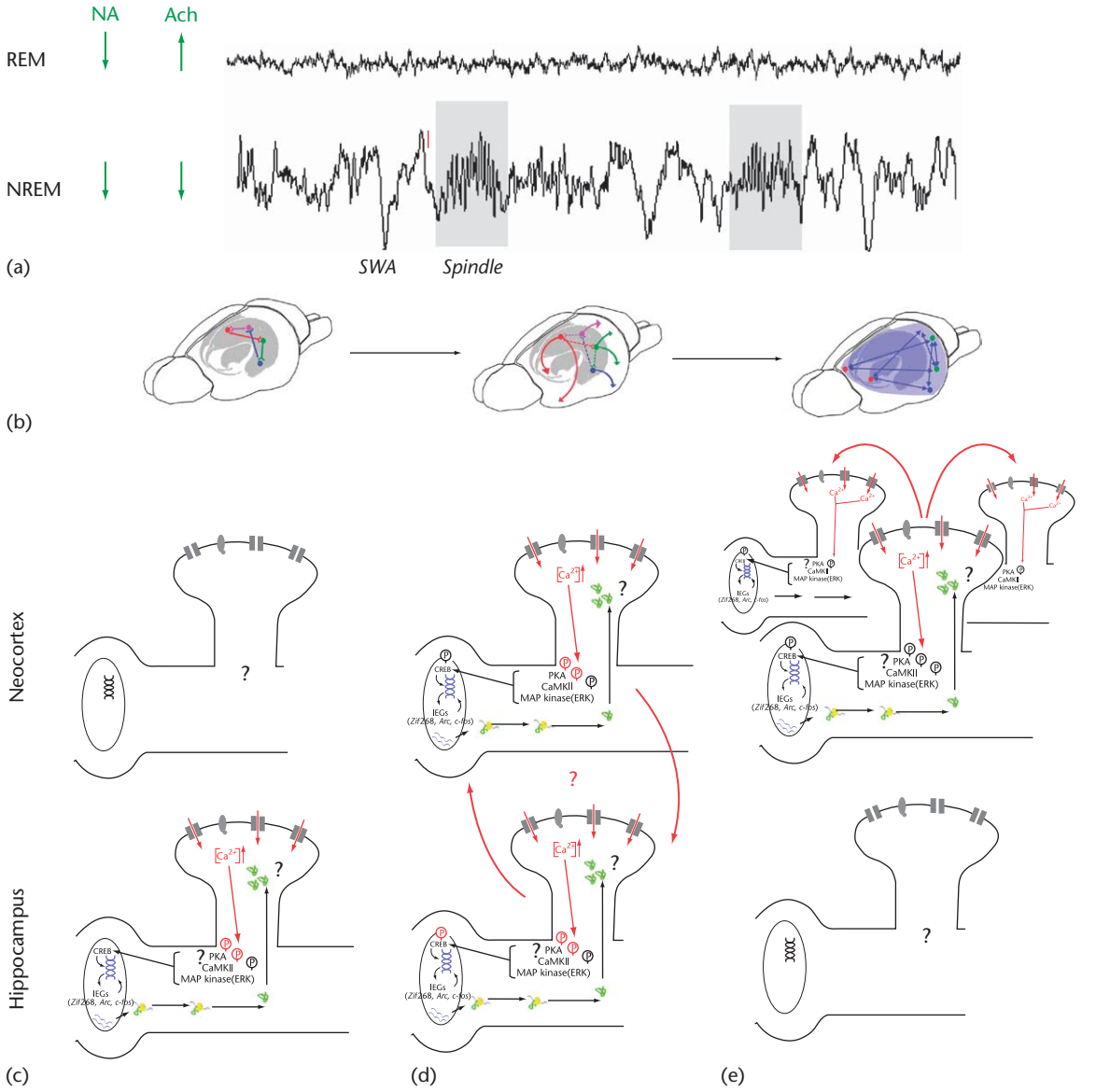


Figure 2 Potential roles of sleep in synaptic and systems consolidation. (a) Representative changes in release of acetylcholine (ACh) and noradrenaline (NA) in the cortex (relative to waking) during REM and NREM sleep. Representative EEG traces for the two sleep states show cortical activity similar 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). NMDAR 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).

signalling 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 (Saha and Datta, 2005; Ulloor and Datta, 2005). Increased hippocampal expression of the LTP-related gene *zif268* has been reported during rapid eye movement (REM) sleep in the first 1–2 h following exposure of rodents to novel, enriched environments (Ribeiro *et al*., 1999). And finally, sleep-dependent consolidation of chick imprinting occurs at a time when there are dramatic increases in IEG expression (including Fos and *arc/arg3.1*, both of which are involved in synaptic plasticity), and calcium-calmodulin-dependent protein kinase II (CaMKII) activation in neural circuits activated by training (Horn, 2004; Bock *et al*., 2005).

The second set of findings demonstrates that interfering with these mechanisms blocks improvements in consolidation which are associated with sleep. For example, one recent study found that subjects' sleep-dependent improvements on a visual task could be blocked by administering an NMDAR antagonist over the first 6 h of sleep (Gais *et al*., 2008). In the example of contextual fear conditioning cited earlier, consolidation is disrupted by administration of protein synthesis and protein kinase A (PKA) inhibitors during the first 1–4 h following acquisition (the same timeframe when sleep is required) (Bourtchouladze *et al*., 1998; Schafe *et al*., 1999).

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 a 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 occurs 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 Timofeev, 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 upregulated 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

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 NMDARs, kinase

pathways and protein synthesis machinery over a period of days to months (Wang *et al*., 2006). The possibility that sleep may promote such events (**Figure 2d** and **e**) has been minimally explored, but is suggested by several findings. For example, whole-brain measurements show that sleep is associated with an upregulation of many genes important for synaptic plasticity and memory consolidation (Mackiewicz *et al*., 2007). Many of these genes are likely to be translated during sleep, as sleep promotes cerebral protein synthesis (Ramm and Smith, 1990). More direct evidence for an expansion of a memory trace during sleep via these signalling cascades comes from a study of IEG expression during sleep. *In vivo* LTP induction in the hippocampus during waking leads to expanding waves of *zif268* expression, that gradually propagate throughout the neocortex during subsequent REM sleep episodes (Ribeiro and Nicolelis, 2004). This broadening expression pattern could reflect the activity-dependent consolidation of synaptic changes associated with LTP induction across the neural network during sleep.

Summary, Caveats and Future Strategies

In summary, current findings in humans and animals support the theory that sleep promotes memory consolidation. The vast majority of behavioural studies show that sleep promotes explicit and implicit memory consolidation. Investigations using brain imaging in human subjects, and electrophysiological and molecular measures in animals, have revealed an intriguing pattern of neural and intracellular events consistent with this theory. More specifically, sleep immediately following acquisition appears to promote the activation of intracellular cascades necessary for synaptic consolidation and can lead to additional changes in synaptic strength. Human and animal studies further suggest that during sleep, memory traces expand from circuits initially engaged by acquisition (e.g. the hippocampus) to become more distributed across cortical areas over time (**Figure 2b**, **d** and **e**).

Although these findings are impressive when taken together, several caveats regarding their interpretation merit discussion. First, as described earlier, some behavioural and neurophysiological findings are consistent with the theory that sleep promotes memory consolidation. However, it does not always follow that sleep is *required* for these processes to occur. Without additional experiments, in many cases one cannot rule out that similar consolidation processes might also occur during waking. Second, sleep is associated with intriguing and suggestive changes in neuronal activity, gene transcription and translation; however, in most studies these events are not directly shown to be necessary for memory consolidation. Third, there are few animal models where sleep and waking behaviour, *and* synaptic and network events, can be studied simultaneously *in vivo*. Currently, findings at various levels (molecular, neuronal, systems and behavioural) have been collected from different model organisms, leading to a morass of disconnected results. A fourth and final caveat is that sleep – like waking – affects physiology at many levels, and should not be considered a homogeneous brain state. In addition to diverse, large-scale changes in brain activity and consciousness, REM and NREM sleep are associated with distinct profiles of hormone and neurotransmitter release (**Figure 2a**) and massive changes in transcription and translation across the brain. This diversity makes the isolation of putative causal factors exceedingly difficult. An important future strategy to overcome this issue will be to focus on defining which aspects of sleep are not only *necessary*, but also *sufficient*, for consolidation.

Does Sleep Facilitate Consolidation through Permissive or Instructive Mechanisms?

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 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 downscaling 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 occurs 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

Abel T and Lattal KM (2001) Molecular mechanisms of memory acquisition, consolidation and retrieval. *Current Opinion in Neurobiology* **11**: 180–187.

Benington JH and Frank MG (2003) Cellular and molecular connections between sleep and synaptic plasticity. *Progress in Neurobiology* **69**: 77–101.

Bock J, Thode C, Hannemann O, Braun K and Darlison MG (2005) Early socio-emotional experience induces expression of the immediate-early gene Arc/arg3.1 (activity-regulated cytoskeleton-associated protein/activity-regulated gene) in learning-relevant brain regions of the newborn chick. *Neuroscience* **133**: 625–633.

Bourtchouladze R, Abel T, Berman N *et al*. (1998) Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA. *Learning & Memory* **5**: 365–374.

Brashers-Krug T, Shadmehr R and Bizzi E (1996) Consolidation in human motor memory. *Nature* **382**: 252–255.

Czarnecki A, Birtoli B and Ulrich D (2007) Cellular mechanisms of burst firing-mediated long-term depression in rat neocortical pyramidal cells. *Journal of Physiology* **578**: 471–479.

Dudai Y (2004) The neurobiology of consolidations, or, how stable is the engram? *Annual Review of Psychology* **55**: 51–86.

Ellenbogen JM, Payne JD and Stickgold R (2006) The role of sleep in declarative memory consolidation: passive, permissive, active or none? *Current Opinion in Neurobiology* **16**: 716–722.

Fischer S, Nitschke MF, Melchert UH, Erdmann C and Born J (2005) Motor memory consolidation in sleep shapes more

effective neuronal representations. *Journal of Neuroscience* **25**: 11248–11255.

Frank MG and Benington JH (2006) The role of sleep in memory consolidation and brain plasticity: dream or reality? *Neuroscientist* **12**: 477–488.

Frank MG, Issa NP and Stryker MP (2001) Sleep enhances plasticity in the developing visual cortex. *Neuron* **30**: 275–287.

Frank MG, Jha SK and Coleman T (2006) Blockade of postsynaptic activity in sleep inhibits developmental plasticity in visual cortex. *Neuroreport* **17**: 1459–1463.

Frankland PW, Bontempi B, Talton LE, Kaczmarek L and Silva AJ (2004) The involvement of the anterior cingulate cortex in remote contextual fear memory. *Science* **304**: 881–883.

Gais S, Albouy G, Boly M *et al*. (2007) Sleep transforms the cerebral trace of declarative memories. *Proceedings of the National Academy of Sciences of the USA* **104**: 18778–18783.

Gais S and Born J (2004) Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proceedings of the National Academy of Sciences of the USA* **101**: 2140–2144.

Gais S, Lucas B and Born J (2006) Sleep after learning aids memory recall. *Learning & Memory* **13**: 259–262.

Gais S, Rasch B, Wagner U and Born J (2008) Visual-procedural memory consolidation during sleep blocked by glutamatergic receptor antagonists. *Journal of Neuroscience* **28**: 5513–5518.

Gottesmann C (1999) The neurophysiology of sleep and waking: intracerebral connections, functioning and ascending influences of the medulla oblongata. *Progress in Neurobiology* **59**: 1–54.

Graves LA, Heller EA, Pack AI and Abel T (2003) Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. *Learning & Memory* **10**: 168–176.

Hasselmo ME (1999) Neuromodulation: acetylcholine and memory consolidation. *Trends in Cognitive Sciences* **3**: 351–359.

Hoffman KL, Battaglia FP, Harris K *et al*. (2007) The upshot of up states in the neocortex: from slow oscillations to memory formation. *Journal of Neuroscience* **27**: 11838–11841.

Hoffman KL and McNaughton BL (2002) Coordinated reactivation of distributed memory traces in primate cortex. *Science* **297**: 2070–2073.

Horn G (2004) Pathways of the past: the imprint of memory. *Nature Reviews. Neuroscience* **5**: 108–120.

Huber R, Ghilardi MF, Massimini M and Tononi G (2004) Local sleep and learning. *Nature* **430**: 78–81.

Isomura Y, Sirota A, Ozen S *et al*. (2006) Integration and segregation of activity in entorhinal-hippocampal subregions by neocortical slow oscillations. *Neuron* **52**: 871–882.

Jackson C, McCabe BJ, Nicol AU *et al*. (2008) Dynamics of a memory trace: effects of sleep on consolidation. *Current Biology* **18**: 393–400.

Jha SK, Jones BE, Coleman T *et al*. (2005) Sleep-dependent plasticity requires cortical activity. *Journal of Neuroscience* **25**: 9266–9274.

Ji D and Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature Neuroscience* **10**: 100–107.

Korman M, Doyon J, Doljansky J *et al*. (2007) Daytime sleep condenses the time course of motor memory consolidation. *Nature Neuroscience* **10**: 1206–1213.

Luczak A, Bartho P, Marguet SL, Buzsaki G and Harris KD (2007) Sequential structure of neocortical spontaneous activity in vivo. *Proceedings of the National Academy of Sciences of the USA* **104**: 347–352.

Mackiewicz, M, Shockley, KR, Romer, MA *et al*. (2007) Macromolecule biosynthesis – a key function of sleep. *Physiological Genomics* **31**: 441–457.

Marshall L, Helgadottir H, Molle M and Born J (2006) Boosting slow oscillations during sleep potentiates memory. *Nature*.**444**: 610–613.

Mednick SC, Nakayama K, Cantero JL *et al*. (2002) The restorative effect of naps on perceptual deterioration. *Nature Neuroscience* **5**: 677–681.

Mioche L and Singer W (1989) Chronic recordings from single sites of kitten striate cortex during experience-dependent modifications of receptive-field properties. *Journal of Neurophysiology* **62**: 185–197.

Nishida M and Walker MP (2007) Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS ONE* **2**: e341.

Ramm P and Smith CT (1990) Rates of cerebral protein synthesis are linked to slow-wave sleep in the rat. *Physiology & Behavior* **48**: 749–753.

Ribeiro S, Goyal V, Mello CV and Pavlides C (1999) Brain gene expression during REM sleep depends on prior waking experience. *Learning & Memory* **6**: 500–508.

Ribeiro S and Nicolelis MAL (2004) Reverberation, storage, and postsynaptic propagation of memories during sleep. *Learning & Memory* **11**: 686–696.

Rosanova M and Ulrich D (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *Journal of Neuroscience* **25**: 9398–9405.

Saha S and Datta S (2005) Two-way active avoidance training-specific increases in phosphorylated cAMP response element-binding protein in the dorsal hippocampus, amygdala, and hypothalamus. *European Journal of Neuroscience* **21**: 3403–3414.

Schafe GE, Nadel NV, Sullivan GM, Harris A and LeDoux JE (1999) Memory consolidation for contextual and auditory fear conditioning is dependent on protein synthesis, PKA, and MAP kinase. *Learning & Memory* **6**: 97–110.

Steriade M and Timofeev I (2003) Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron* **37**: 563–576.

Sterpenich V, Albouy G, Boly M *et al*. (2007) Sleep-related hippocampo-cortical interplay during emotional memory recollection. *PLoS Biology* **5**: e282.

Stickgold R (2005) Sleep-dependent memory consolidation. *Nature* **437**: 1272–1278.

Takashima A, Peterson KM, Rutters F *et al*. (2006) Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. *Proceedings of the National Academy of Sciences of the USA* **103**: 756–761.

Tononi G and Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. *Brain Research Bulletin* **62**: 143–150.

Ulloor J and Datta S (2005) Spatio-temporal activation of cyclic AMP response element-binding protein, activity-

regulated cytoskeletal-associated protein and brain-derived nerve growth factor: a mechanism for pontine-wave generator activation-dependent two-way active-avoidance memory processing in the rat. *Journal of Neurochemistry* **95**: 418–428.

Wang H, Hu Y and Tsien JZ (2006) Molecular and systems mechanisms of memory consolidation and storage. *Progress in Neurobiology* **79**: 123–135.

Whitlock JR, Heynen AJ, Shuler MG and Bear MF (2006) Learning induces long-term potentiation in the hippocampus. *Science* **313**: 1093–1097.

Wixted JT (2004) The psychology and neuroscience of forgetting. *Annual Review of Psychology* **55**: 235–269.

Further Reading

Maquet P, Smith C and Stickgold R (eds) (2003) *Sleep and Brain Plasticity*. Oxford: Oxford University Press.