Neuromodulatory control of memory consolidation in sleep

How fluctuations in neuromodulator levels during sleep might promote an active role of sleep in the consolidation process

Abstract

The scientific study of the role of sleep in the memory consolidation process is filled with controversy, but recent evidence implicates unique neurobiological processes within sleep that actively enhance memories. Memory consolidation requires cellular events at activated synapses, and the transfer of information from the hippocampus to various cortical targets, processes in which neuromodulators play crucial roles. Especially acetylcholine and noradrenaline have been shown to be important in memory consolidation. In this review aspects of memory consolidation will be discussed. The relevance of fluctuations in acetylcholine and noradrenaline levels during sleep in this process will be considered in order to discuss the question whether sleep only permits or actively promotes memory consolidation.

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Marina Boon (s2477424), 10-07-2016, supervised by P. Meerlo

Content

Introduction 2
Four hypotheses on the role of sleep in memory consolidation 2
Memory formation and consolidation 3
A permissive or promoting role of sleep in memory consolidation 6
Acetylcholine 6
Noradrenalin 9
Conclusion 12
References 12

Introduction

In the last decades a substantial increase in the knowledge about sleep mechanisms has aided in the unravelling of the mystery of why humans spend one-third of their lives asleep. Although sleep may serve multiple functions (Siegel 2009), it has become clear that the sleeping brain offers an ideal environment for solidifying newly learned information in the brain. The process of 'consolidation' refers to this transformation of new initially labile memories into more stable representations (Diekelmann & Born 2010). The consolidation of memories is thought to rely on the reactivation of 'memory traces' or neuronal circuits. Neuromodulators can reconfigure neuronal circuits, which often massively alters their output (Atherton et al. 2015). Besides a crucial role of neuromodulators in memory consolidation, they also contribute to the basic regulation of sleep (Pace-Schott & Hobson 2002). The precise mechanisms through which neuromodulators aid memory consolidation and the relevance of fluctuations in neuromodulator levels during sleep in this process remain largely unknown. Since sleep duration has slowly declined over the last 50 years, and suboptimal sleep duration and poor sleep quality are becoming widespread in modern society (Bixler 2009), the discussion about the role of sleep in memory consolidation is of high relevance.

Four hypotheses on the role of sleep in memory consolidation

Since the beginning of sleep research, four competing hypotheses about the role of sleep in memory consolidation have been suggested (Ellenbogen, Payne, et al. 2006). The first hypothesis states that sleep contributes nothing to memory. This hypothesis resulted mainly from observations that a diminished amount of rapid eye movement (REM) sleep in human subjects on antidepressant drugs or with brain stem lesions seems to have little detrimental effect on learning and memory (Vertes et al. 2004; Siegel 2001). Proponents of this hypothesis argue that recall performance is not better after sleep than after wake and that any improvements of memory that are observed overnight can be explained by the mere passage of time (Vertes et al. 2004). To test this hypothesis, waking control groups have been employed to compare their performance with an experimental sleep group. Nearly all of these studies show that participants in a sleep group perform better than participants in the waking control group, despite the groups having equal amounts of time between learning and recall (Ellenbogen, Hulbert, et al. 2006; Lau et al. 2010; Ellenbogen et al. 2007; Schoen & Badia 1984; Payne & Kensinger 2011). This finding strongly argues against the hypothesis that sleep offers nothing for memory.

The second hypothesis states that sleep does not consolidate memories, but only transiently sustains memories by protecting them from interference that might occur during the waking state as a consequence of processing new information (Ellenbogen, Payne, et al. 2006). This hypothesis about a passive protective role of sleep in memory consolidation has been around since 1924 when Jenkins and Dallenbach concluded that forgetting is mostly a matter of "interference, inhibition, or obliteration of the old by the new" (Jenkins & Dallenbach 1924). Sleeping would provide a temporary shelter from interfering mental activity during wakefulness (Ellenbogen, Payne, et al. 2006). According to this hypothesis, recall performance will be improved immediately after sleep, but only until exposure to interference in the subsequent day. And, since no consolidation occurs during sleep, the memories will be as vulnerable in the waking day as they would be if the person had not slept. This hypothesis is opposed by observations that declarative memory recall is enhanced when sleep follows within a few hours of learning, independent of acute fatigue or circadian rhythms (Gais et al. 2006). Furthermore, it has been shown that sleep increases the resistance to interference presented in the subsequent day (Ellenbogen, Hulbert, et al. 2006). A better resistance of memories against interference after sleep implicates that consolidation of memories does occur during sleep. Sleep should, therefore, be more than a period of passive protection against interference.

The last two hypotheses both assert that consolidation takes place during sleep. The third hypothesis states that sleep creates conditions conducive to memory consolidation, but plays no other unique role in the consolidation of memory and the fourth states that unique properties of sleep are directly involved in the memory consolidation process (Ellenbogen, Payne, et al. 2006). The distinction between these two hypotheses rests on knowledge of the precise physiologic markers of consolidation, interference and their relationship to sleep. Studies that aim to provide insight in the debate of an active or permissive role of sleep in memory consolidation often focus on electrophysiological phenomena (Ellenbogen, Payne, et al. 2006). In this review specifically the importance of neuromodulators in this debate will be discussed, since these physiologic markers are of big relevance due to their role in both sleep cycle regulation and memory consolidation.

Alternation between the two different brain states, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, is thought to be caused by cholinergic, serotonergic, and noradrenergic systems in the pons, locus coeruleus (LC) and dorsal raphe (DR) (McCarley & Massaquoi 1992). The change in the level of acetylcholine, serotonin and noradrenalin in the different sleeping brain states compared to a waking state is, therefore, of importance when studying the effects of the different brain states on cognitive performances. Especially acetylcholine and noradrenalin have been shown to also directly affect neurons in brain regions that are of importance in memory consolidation (Alger et al. 2015; Diekelmann & Born 2010). The relevance of the change in the level of these two neuromodulators during sleep in memory consolidation will be further discussed in this review. Addressing the question whether these changes in neuromodulator levels are unique properties of sleep contributing to memory consolidation, will provide insight in the discussion whether sleep does or does not have an active role in memory consolidation.
But, before assessing the importance of specific physiological properties of sleep for memory consolidation, it needs to be shortly discussed what is currently known about the process of memory formation and consolidation.

Memory formation and consolidation

Having the ability to learn and remember offers people the possibility to develop certain skills and develop as a person. Oliver Sacks (1933-2015), a British neurologist, goes even further when he writes about a Korsakov patient with a memory of no longer than certain seconds, and states that *"We have, each of us, a life story, an inner narrative–whose continuity, whose sense, is our lives…and this narrative is us, our identities… A man needs such a narrative, a continuous inner narrative, to maintain his identity, his self*." (p. 111 Sacks 1995) In that same line of thought, he believes that the brain embodies the self and Sacks, therefore, believed that the brain is "the most incredible thing in the universe" and important to study (Interview Sacks 1993). A lot of research has indeed been done on the brain and its function to hold information.
It can be assumed that the brain encodes internal as well as external events as spatiotemporal activity patterns that are processed in a neuronal circuit (Korte & Schmitz 2016). The weight of synaptic connections between neurons in such a functional entity is what defines the output of a neuronal circuit. Therefore it is though that information storage is defined as a change in the pattern of synaptic strength in a specific neuronal circuit involved in the learned behaviour. This change in pattern of synaptic strength is created by inducing activity-dependent synaptic plasticity at appropriate synapses, and thereby changing the output of that neuronal circuit. This is described in the synaptic plasticity and memory hypothesis formulated by Martin et al. (2000) and is experimentally well-supported (Korte & Schmitz 2016). After the first storage or 'encoding', the initially labile memories are transformed into more stable representations that become integrated into the network of pre-existing long-term memories; a process referred to as memory consolidation. The exact mechanisms underlying the persistence of some pieces of information and the forgetting

of others remain to be identified, but a lot of research has been done on the formation of memory at both the cellular and the network level.

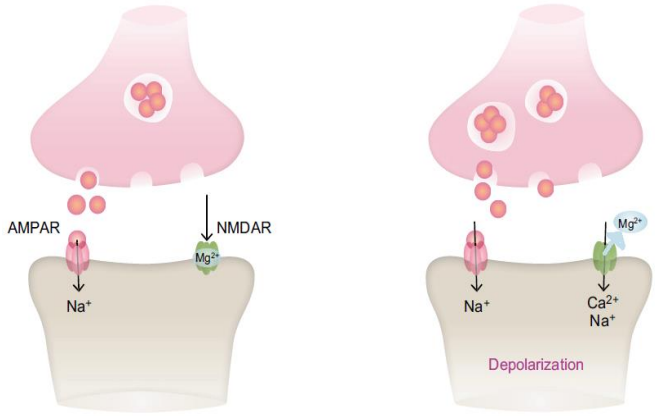

Figure 1 A basic condition of a glutamatergic synapse before (*left*) and during (*right*) depolarization. The AMPA receptor (AMPAR) binds glutamate and regulates Na^+ influx in the postsynaptic dendrite (*left*). During depolarization, releasing of the Mg^{2+} block from the NMDA receptor (NMDR) and additional glutamate binding allows influx of Na^+ and Ca^{2+} into the cell (*right*). Modified from Korte & Schmitz (2016).

On a cellular level, the timing of neural activity is crucial for information storage. A key concept in our knowledge of the learning and memory process is that when activation of the pre- and post-synapse coincide, a strengthening of these specific synapses occurs (Hebb 1949). In 1973, such an enhancement in synaptic strength has been observed for the first time, by Bliss & Lomo (1973). After they applied a short train of high-frequency pulses under in vivo conditions to a hippocampal neuronal pathway, they could observe a long-lasting strengthening in the electrophysiological response properties of the recorded neurons. This phenomenon was called long-term potentiation.

Long-term potentiation, or LTP, is defined as an increase in synaptic strength that lasts for at least one hour (Bliss & Lomo 1973). LTP is mostly studied at glutamatergic synapses onto pyramidal neurons (for a review, see e.g. Lynch 2004). Under basic synaptic conditions, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors regulate the Na^+ influx in the postsynaptic dendritic spine depending on the amount of released glutamate. Ion channels of N-methyl-D-aspartate (NMDA) receptors are blocked by Mg^{2+} ions. If the postsynaptic membrane is depolarized, the Mg^{2+}block of the NMDA receptor channel is removed and Ca^{2+} and Na^+ ions enter the spine (Herron et al. 1986; Figure 1).

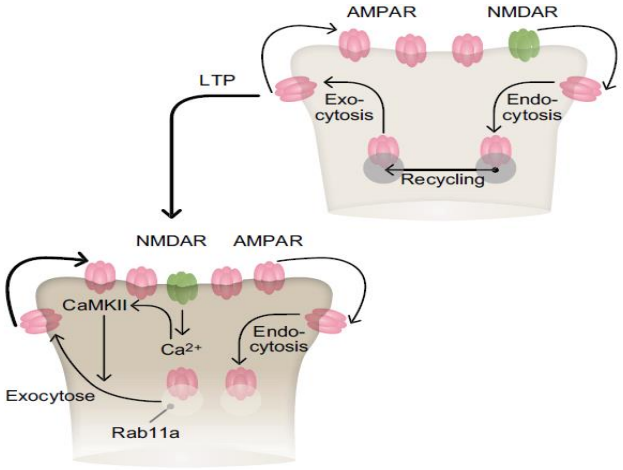

Figure 2 Basic cellular processes resulting in long-term potentiation (LTP) in a glutamatergic synapse. Under baseline synaptic conditions (*top*), AMPA receptors cycle between intracellular compartments and the outer membrane of the post-synapse. After LTP induction, AMPA receptors (AMPAR) are inserted into the membrane, and these receptors are then stabilized at the synapse through a Ca^{2+}-mediated process that includes protein kinases (e.g., CaMKII) and the fusion of recycling endosomes mediated by Rab11a, ultimately mediating the synaptic strength. Modified from Korte & Schmitz (2016).

The strength of excitatory synapses can be calculated by the ratio AMPA receptor-mediated synaptic currents to NMDA receptor-mediated synaptic currents of a population of stimulated synapses (Ungless et al. 2001). The number of AMPA receptors on the post-synapse is regulated by endocytosis and exocytosis. After LTP induction by frequent stimulation, enhanced AMPA receptor exocytosis occurs through activation of synaptic NMDA receptors, ultimately mediating the increase in synaptic strength (Lu et al. 2001; Figure 2). In this process the removal of Mg^{2+} ions from NMDA receptors allows the influx of Ca^{2+} into the postsynaptic cytosol, which activates Ca^{2+}-dependent enzymes (e.g. CAMKII). This facilitates the insertion of AMPA receptors into the postsynaptic membrane by the phosphorylation of specific AMPA receptor subunits.

The previous history of a nerve cell is important in the probability of a specific synapses of a neuron to undergo plasticity changes. This “plasticity in synaptic plasticity” is named metaplasticity (Abraham & Bear 1996) and it is manifest as a change in the ability to induce subsequent synaptic plasticity, such as long-term potentiation. So, due to certain prior neuronal activity, a neuron might be less prepared to change its synapses or it may be more prone to changes in response to a stimulus (Korte & Schmitz 2016). Neuromodulators are crucial factors in regulating the excitability of a neuron. Neuromodulators, therefore, play an important role in setting the scene for encoding memories (Kemp & Manahan-Vaughan 2008).

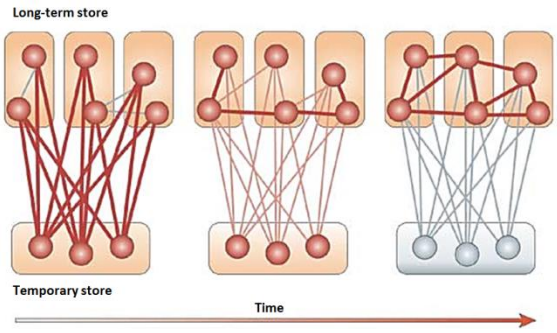

Figure 3 Model of the consolidation of information in the brain. The two-stage model of memory consolidation assumes two physically separated areas in the brain that act as a long-term store and temporary store. The temporary store allows learning at a fast rate and serves as an intermediate buffer that holds the information only temporarily. The long-term store learns at lower rate, but once memories are encoded here, they are held for a longer period of time. The movement from the temporary store to the long-term store is driven by repeated re-activation of the memory trace in the temporary store, inducing the re-activation of the trace in the long-term store. This process is referred to as consolidation. Modified from Frankland & Bontempi (2005)

Re-activation of neuronal circuits is not only important for cellular events at activated synapses (LTP), but it is also used in the transfer of memories from a temporary store to a long-term store. At the network level, memories are thought to be encoded in both a temporary store and a long-term store simultaneously. The temporary store is fast learning, but only holds information temporarily. Therefore, this store serves as an intermediate buffer for newly encoded information. During memory consolidation, the repeated re-activation of the newly encoded memory traces in the temporary store, drives the concurrent re-activation in the long-term store. This will gradually strengthen the memory traces in the long-term store. This way, a memory trace is ‘transferred’ from the temporary store to the long-term store. This process is referred to as the two-stage model of memory consolidation (Figure 4; Frankland & Bontempi 2005).

For declarative memories, the fast- and slow-learning stores are thought to be located in respectively the hippocampus and the neocortex (Diekelmann & Born 2010).

Memories can be reactivated during either 'online' states, such as task-relevant situations, or 'offline' states, such as during quiet wakefulness or sleep. The relative contributions of different sleep phases to the consolidation of memory remain uncertain (Vertes et al. 2004; Walker & Stickgold 2004). However, replay of memory trances has been shown to occur predominantly during SWS (Siapas & Wilson 1998) and stabilizating of retrieved memories is thought to occurs mainly during REM sleep, for example due to the expression of the transcription factor ZIF268 (Jones et al. 2001). Together, this supports a two-stage model in which sustained high frequency activity during SWS leads to structural changes in cortical networks that are stabilized during subsequent REM sleep (Ribeiro et al. 2004).

In summary, memory consolidation requires the repeated re-activation of neuronal networks, which leads to cellular events at the involved synapses, and the transfer of information from a temporary store to a long-term store. The different sleep stages fulfil different roles in the consolidation process, however, the exact mechanisms through which this occurs remains unknown. Physiological factors that might play an important role in this process are neuromodulators, since neuromodulators can influence the excitability of a neuron, thereby affecting the re-activation of neuronal circuits and controlling memory consolidation.

A permissive or promoting role of sleep in memory consolidation

The two hypothesis that do acknowledge sleep-dependent consolidation differ in the magnitude of importance for memory consolidation they assign to the physiological properties of sleep (**Fout! Verwijzingsbron niet gevonden.**). The permissive consolidation hypothesis states that sleep enables the ideal circumstances for consolidation to take place, whereas the active consolidation hypothesis states that memory consolidation occurs during sleep because unique properties of sleep directly engage consolidation (Ellenbogen, Payne, et al. 2006).

Acetylcholine

In the discussion on a permissive or active role of sleep in memory consolidation, the observation that the level of acetylcholine in the brain is lowered 100-175% during slow wave sleep (SWS) compared to during waking (Marrosu et al. 1995) is of importance, because of the influential inhibitory role of acetylcholine in the induction of LTP in the hippocampus.

Acetylcholine has been shown to suppress the activation of glutamatergic receptors in the CA1 region of the hippocampus (Hasselmo & McGaughy 2004; Hounsgaard 1978). The exact mechanism trough which acetylcholine suppresses glutamatergic receptors remains largely unknown. However, it is argued that activation of muscarinic acetylcholine receptors can stimulate the synthesis and release of endogenous cannabinoids (Alger et al. 2014). By acting on the principal cannabinoid receptor of the brain, CB1R, cannabinoids could suppress glutamate transmission (Alger et al. 2014; Elphick & Egertová 2001). Activation of cannabinoid receptors does not change in postsynaptic responsiveness to glutamate, but specifically decreases in the probability that glutamate is released in response to an action potential (Sullivan 1999). This decrease in the probability of release was the result of cannabinoid receptor-mediated inhibition of specific presynaptic calcium currents (Q- and N-type) that would otherwise support glutamate release in hippocampal neurons.
As was said earlier, induction of LTP in the hippocampus needs synaptic activation of glutamate receptors (Figure 3; Bashir et al. 1993) The reduced suppression of glutamatergic receptors, due to lowering the level of acetylcholine during quiet waking or SWS will increase the spontaneously occurring re-activation of hippocampal memory traces (temporary store). The reduced acetylcholine level during quiet waking or SWS, therefore, facilitates feedback from the hippocampus to the neocortex by releasing most glutamatergic synapses from suppression. The lowered acetylcholine levels during quiet waking or SWS can, thus, induce LTP processes that would eventually modify synaptic strengths in interconnected neuronal networks (Rosanova & Ulrich 2005). This phenomenon is therefore aiding the stabilization of fragile new memories into long-term memories.

The benefit of reduced acetylcholine levels for memory consolidation, especially during SWS, was demonstrated in a study by Gais & Born (2004) in which the drug physostigmine was administered to subjects. Administration of physostigmine reduces acetylcholine breakdown by inhibiting cholinesterase (Santucci et al. 1989). Gais and Born (2004) performed a declarative paired-associate wordlist task, which is known to depend on the hippocampus (Squire 1998). An elevated level of acetylcholine, due to physostigmine, was shown to reduce the benefit of sleep for declarative memory consolidation in the subjects that slept across the first half of the night (a portion of sleep with relatively large amounts of SWS; Figure 5). The same treatment had no effect on memory during wakefulness (Figure 5). They conclude that their findings are in line with predictions that a low cholinergic tone during SWS is essential for declarative memory consolidation, because the integration of materials into neocortical networks require a period of release from cholinergic suppression of feedback transmission in the hippocampus (Gais & Born 2004).
The heightened acetylcholine levels due to physostigmine could be considered as resembling the high acetylcholine levels during waking. The negative effects of heightened acetylcholine levels on memory consolidation could, therefore, be considered as a result of interfering factors, as would be the case during wakefulness. The results of Gais and Born (2004) show that the suppression of

acetylcholine during a SWS-rich period is a necessary condition for sleep-related declarative memory consolidation to occur.

Hippocampus-independent procedural memory for mirror tracing performance showed no detrimental effect of physostigmine during either sleep or wakefulness (Gais & Born 2004). This indicates that the loss of cholinergic tone disinhibits hippocampal feedback synapses specifically, aiding the consolidation of declarative memories rather than procedural memories, which are

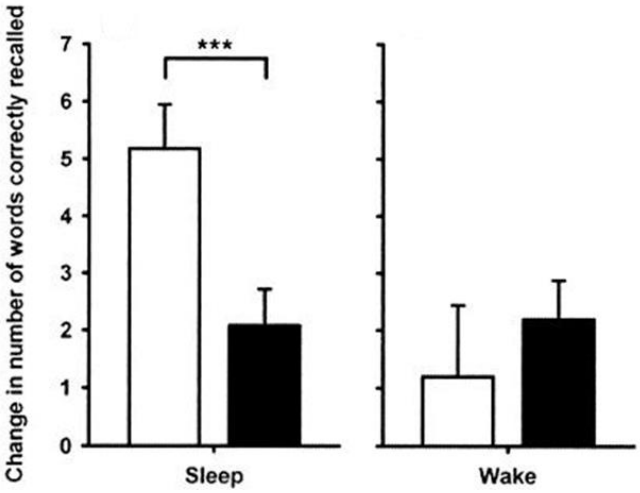

Figure 4 Memory performance in a declarative paired-associate wordlist task after administration of physostigmine and placebo in sleep and wake periods. Memory is indicated by the difference in performance between learning and recall sessions (physostigmine, filled bars; placebo, open bars). Placebo-treated subjects retained significantly more words under the sleep than the wake condition (open bar left vs open bar right; P < 0.001). Physostigmine completely eliminated the consolidating effect of sleep on hippocampus-dependent declarative memory (P < 0.001; *left*), whereas it had no effect during wakefulness (P > 0.40; *right*). (Gais & Born 2004)

hippocampus independent. According to Gais and Born (2004) these results fit well with models of a hippocampal–neocortical dialogue (Hasselmo 1999), which consider acetylcholine an important modulator of the direction of information flow between hippocampus and neocortex during sleep and wakefulness.

Rasch et al. (2006) studied the relation between low acetylcholine levels and memory consolidation by administration of (a combination of) muscarinic and nicotinic receptor antagonists (respectively scopolamine and mecamylamine). Scopolamine and mecamylamine administration during wakefulness induces a low cholinergic tone, which mimics the dip in acetylcholine levels naturally occurring during SWS. Compared to placebo, the combined blockade of muscarinic and nicotinic receptors during wakefulness significantly improved consolidation of declarative memories tested 10 hr later (Rasch et al. 2006; Figure 6 *left*).
They compared the effects of acetylcholine receptor blockade on the consolidation of declarative memories to the effects of the blockade on encoding. Therefore, they performed a number learning task 1 hr after substance administration. Subjects recognized distinctly fewer number after combined administration of scopolamine and mecamylamine than after placebo administration (Rasch et al. 2006; Figure 6 *middle*), indicating that combined blockade of acetylcholine receptors impairs encoding of new material. The observed improvement in consolidation during wakefulness after blockade of acetylcholine receptors could, thus, have resulted from a reduction in interference.
Neither scopolamine nor mecamylamine alone enhanced declarative memory consolidation (Rasch et al. 2006; Figure 6 *right*). As was found by Gais and Born (2004), consolidation of procedural memories was unaffected by a dip in acetylcholine levels (Rasch et al. 2006).
Rasch et al. (2006) propose that the natural shift in central nervous system cholinergic tone from high levels during wakefulness to minimal levels during SWS optimizes declarative memory

consolidation during a period with no need for new memory encoding. Sleep would, thus, represent a period where the various processes that optimize declarative memory consolidation, including a drop in acetylcholine levels, are established without interfering with cognitive processing demands characterizing the wake phase (Rasch et al. 2006).

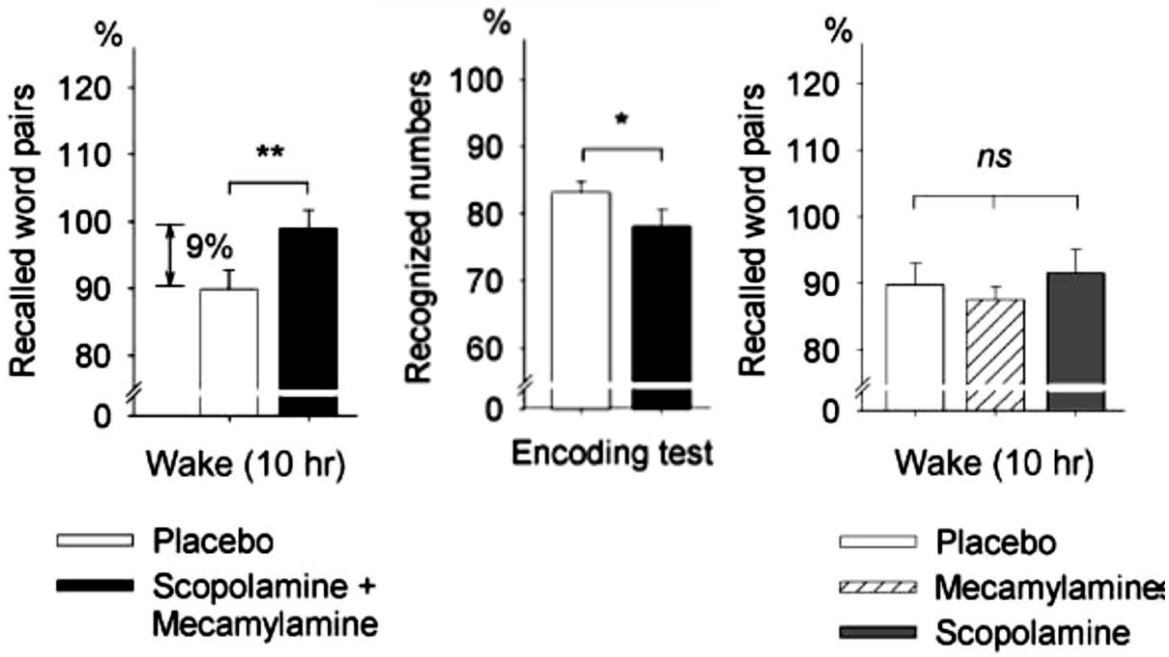

Figure 5 Effects of manipulating cholinergic activity on memory. Left: declarative memory consolidation was enhanced after combined cholinergic blockade with scopolamine and mecamylamine during a 10-hr retention interval of wakefulness. Middle: encoding of a list of numbers (assessed by recognition 1 min after presentation) was impaired under combined nicotinic and muscarinic blockade. Right: selective administration of muscarinic or nicotinic blockade during wakefulness did not have a significant effect on declarative memory consolidation. From: Rasch et al. (2006)

Reduced suppression of glutamatergic receptors by decreasing acetylcholine levels has crucial consequences for the memory consolidation process. Only an indirect benefit of the naturally occurring nadir in acetylcholine levels during SWS has been proven so far, but this change in acetylcholine level might be very useful for consolidation. A significant dip in the acetylcholine level can also be observed during quiet waking as compared to during active waking (Marrosu et al. 1995). However, the levels of acetylcholine are at their very lowest during SWS (Marrosu et al. 1995).
Especially the finding that elevating acetylcholine levels has proven to reduce the benefit for consolidation ónly during sleep (Gais & Born 2004), is of importance in the discussion of a potentially active role of sleep in the consolidation process. The extreme dip in acetylcholine levels during SWS is an interesting unique property of sleep and seems to be critical for declarative memory consolidation.

Interestingly, REM sleep, during which acetylcholine levels are at their highest (Marrosu et al. 1995), is also often discussed for its role in memory formation. According to Hasselmo and McGaughy (2004), high levels of acetylcholine are mainly important for the encoding phase of memories, whereas low acetylcholine levels set dynamics for consolidation. More research should be done on the relevance of fluctuations in acetylcholine levels during sleep on the consolidation process to provide better insight in the discussion of a potentially active role of sleep in memory consolidation.

Noradrenalin

Another neuromodulator that is of interest in the discussion of a potentially active role of sleep in memory consolidation is noradrenalin. The noradrenergic neuromodulatory system is known to modulate the fluctuations in sleep states during the sleep cycle (Sara 2009; Aston-Jones & Bloom 1981), and is often discussed for its role in memory consolidation (reviewed by Sara (2009)). The locus coeruleus (LC) is the source of noradrenalin in the neocortex and hippocampus (Aston-Jones 2004). During quiet wakefulness, the LC fires tonically and shows stimulus-related bursts during activity (Aston-Jones & Cohen 2005). During non-REM sleep, the tonic activity of the LC decreases gradually with sleep depth and during REM sleep, LC neurons stop firing altogether (Aston-Jones & Bloom 1981). There is a long-standing assumption that low noradrenergic activity during sleep, therefore, reflects mainly the low arousal during this brain state (Gais et al. 2011). However, during sleep spindles and slow oscillations, which are specific patterns of electrical field potentials of SWS, LC neurons show bursts of activity (Aston-Jones & Bloom 1981). This was shown by Aston-Jones and Bloom in 1981 by an early EEG study. They noted that noradrenergic LC neurons often discharged during EEG spindles, following a consistent pattern: discharge was reduced for the second preceding spindle onset, substantially increased during spindles and then decreased for the second following spindle offset.

Sleep spindles and slow oscillations have often been linked to memory consolidation and reprocessing during sleep (Marshall et al. 2006; Ji & Wilson 2007; Gais et al. 2002). Furthermore, there is an increase of LC activity during post-learning SWS around 2 h after the end of a learning session (Eschenko & Sara 2008). These bursts of activity of the LC noradrenergic system during SWS might, therefore, play a specific role in the sleep-related consolidation of recently acquired memories. Before the role of noradrenaline in consolidation during sleep can be further discussed, it needs to be discussed what is currently known about the role of noradrenaline on memory consolidation in general.

At the systems level, the hippocampus and the amygdala appear to be the two regions especially sensitive to noradrenaline (Tully et al. 2007; Roozendaal et al. 2004). The interaction of these two regions seems to be particularly important for the modulation of synaptic plasticity (Vouimba et al. 2007). During emotional arousal, stress hormones are released from the adrenal medulla and adrenal cortex and activate the release of noradrenaline in the basolateral amygdala (McGaugh 2000). This effect is critical for enabling modulation of consolidation. The amygdala modulates memory consolidation by influencing neuroplasticity in other brain regions, of which the hippocampus is a crucial one in the discussion of memory (McGaugh 2000; McGaugh 2004). Specifically the glucocorticoid receptors and beta-adrenoceptors in the basolateral amygdala (BLA) are crucial for the modulation of the synaptic plasticity in the dendate gyrus (DG; Figure 7; Vouimba et al. 2007).

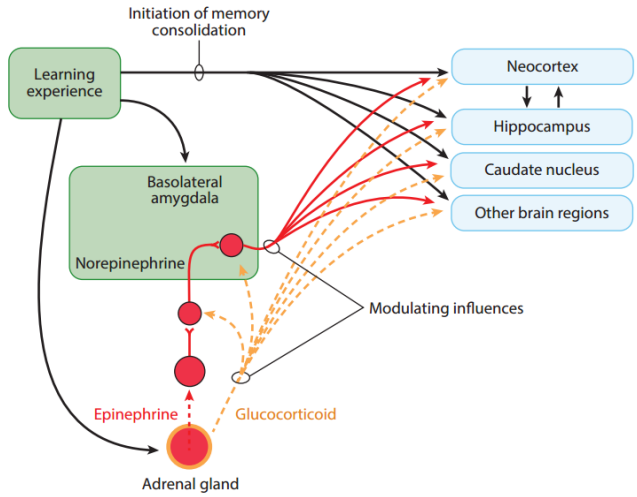

Figure 6 The modulating influence of the arousal-activated stress hormones, noradrenaline (norepinephrine) and glucocorticoid, in memory consolidation through the interaction with the basolateral amygdala and other brain systems. A learning experience activates time-sensitive storage systems in several brain regions. If the experience is emotionally arousing, the release of stress hormones from the adrenal gland and norepinephrine in the basolateral amygdala is also activated. The basolateral amygdala modulates memory consolidation through its projections to brain systems involved in memory. From: McGaugh (2000).

It is hypothesized that BLA modulation of LTP in the DG requires a cooperation of both the noradrenergic and glucocorticoid system (Quirarte et al. 1997; McGaugh & Roozendaal 2002). Adrenergic effects on memory can be altered by manipulation of glucocorticoid levels (Borrell et al. 1984; Roozendaal et al. 1996) and the BLA is a critical locus of interaction of glucocorticoids with the noradrenergic system (McGaugh 2000; McGaugh & Roozendaal 2002). The injection of the β-adrenoceptor antagonist propranolol into the BLA 10 min before tetanus impaired LTP in the DG, suggesting that amygdala β-noradrenergic activity is important for glucocorticoid modulation of memory consolidation (Vouimba et al. 2007).

Recently, Maity et al. (2016) showed that binding of noradrenaline to β-adrenergic receptors, together with activation of the glutamatergic AMPA and NMDA receptors, can even initiate epigenetic modifications like histone acetylation and phosphorylation, and DNA methylation. These modifications were shown to boost the longevity of hippocampal LTP (Maity et al. 2016; Figure 8).

Maity et al. (2016) measured the longevity of LTP in the hippocampus after administration of noradrenaline and high frequency stimulation. They showed that noradrenaline enhanced LTP, and that this enhancement was attenuated by β1 and β2 antagonists (betaxolol hydrochloride and ICI118,551 hydrochloride respectively), but not by α1 and α2 antagonists (prazosin hydrochloride and yohimbine hydrochloride respectively). These findings support the notion that the enhancing effects of NA on LTP are primarily effected by β-adrenergic receptors (Maity et al. 2016).

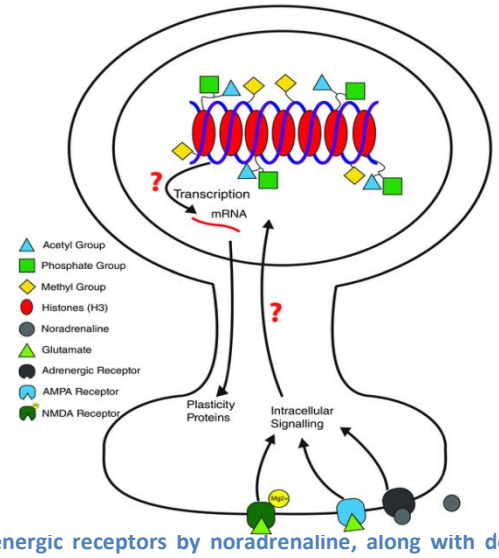

Figure 7 Activation of β-Adrenergic receptors by noradrenaline, along with depolarization-triggered activation of NMDA and AMPA receptors, promote epigenetic modifications in the nucleus. These modifications include DNA methylation by DNA methyltransferases, histone acetylation, and histone phosphorylation. The cytosolic signalling cascades that link β-adrenergic receptors to the nucleus are not clearly defined, but the epigenetic modifications ultimately lead to the longevity of LTP by production of plasticity proteins. From: Maity et al. (2016).

The exact genes that are transcribed due to these epigenetic changes are currently unknown. However, Maity et al. (2015) showed an increase in the translation rates for specific mRNAs encoding GluA1 and GluA2 subunits of AMPA receptors following priming of LTP metaplasticity by noradrenaline. Boosting transcription and translation of these AMPA receptor subunits can facilitate their supply and insertion at synaptic sites to help maintain synaptic potentiation (Figure 2; Huganir & Nicoll 2013).

Maity et al. (2016) argue a main role of the β-adrenergic receptors in the regulation of memory consolidation by noradrenaline. However, Gais et al. (2011), who studied the role of noradrenaline on memory consolidation specifically during sleep, found a crucial role of α_2-adrenergic receptors.

They performed an odour recognition experiment in a wake and a sleep group and manipulated noradrenergic availability. The latter was done through administration of clonidine, which is known to activate LC α2-autoreceptors, resulting in a blockade of noradrenergic activity. Subjects learned an odour recognition task on the first evening. Before sleep or sleep deprivation, they received clonidine or placebo. Recall was tested later after the effects of the substances had ended. They found an increase in the correctly recognized odours in the sleep group compared to the wake group, and this sleep-related improvement was impaired by administration of clonidine (Figure 9; Gais et al. 2011).

The participants in the sleep group in the study of Gais et al. (2011) slept an entire night, and the administered drug was active throughout the whole sleep period. However, because there is no noradrenergic activity during REM sleep at all and administration of clonidine during wakefulness has no effect, it can be inferred that clonidine affects odour memory consolidation during non-REM sleep (Gais et al. 2011).

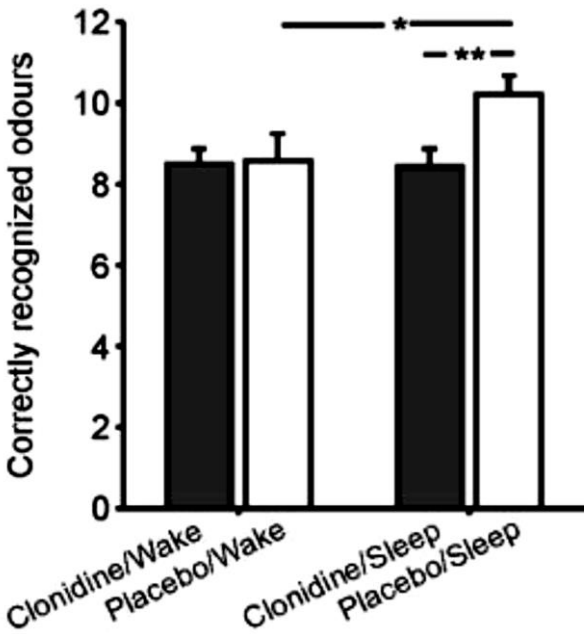

Figure 9 Number of correctly recognized odours in the placebo conditions (*white*) and after administration of the α2-autoreceptor agonist clonidine (*black*). Clonidine impaired memory consolidation only when administered during sleep but not during wakefulness. Subjects receiving clonidine during sleep displayed memory recall comparable with subjects from the wake group. This implicates that clonidine interferes with memory consolidation processes that occur specifically during sleep. From: Gais et al. (2011) .

Odour recognition is known to recruit the amygdala (Savic et al. 2000). The sensitivity of odour memory consolidation to manipulation of noradrenergic activity implicates that the noradrenaline bursts during SWS preferentially impact amygdala-dependent memories (Gais et al. 2011). The α_2-autoreceptors that were impacted in this study, would therefore be mainly important in the consolidation of emotionally arousing memories. The precise mechanisms that occur in this process remain to be identified.

Thus, the noradrenergic bursts during SWS might enhance memory consolidation (Gais et al. 2011). The global reduction of noradrenaline during SWS might have the opposite function, namely synaptic downscaling (Tononi & Cirelli 2006). Downscaling refers to a proportional reduction in the strength of all synapses converging onto the same neuron: if all synapses shed the same proportion of their weight, total synaptic weight can be reduced while preserving relative differences in synaptic strength and thereby memory traces.

The relevance of the overall low noradrenergic activity and the bursts of noradrenergic activity for memory on a molecular level have been studied by Cirelli & Tononi (2000). They have shown that the high activity of the noradrenergic system is associated with high expression of genes whose induction has been linked to the acquisition of long-term memories (phosphorylated CRE-binding protein, Arc and BDNF). The overall low tone of noradrenergic activity might therefore mainly result in synaptic downscaling (Vertes et al. 2004; Tononi & Cirelli 2006). However, the burst of noradrenergic activity during SWS might support the stabilization of newly formed memory representations during sleep. The expression of these plasticity-related genes due to noradrenergic activity occurs both during wakefulness and SWS, so this is not an unique property of sleep contributing to memory consolidation.

The fact that reduced noradrenergic availability only impaired consolidation of amygdala-dependent memories when administered during sleep, and not during wakefulness (Gais et al. 2011), indicates the occurrence of unique consolidation processes during SWS. This finding, therefore, supports the hypothesis of an active role of sleep in (at least one form of) memory consolidation. The mechanisms through which this phenomenon occurs are not completely understood, so future research has to point out what the exact role of noradrenergic activity is in memory consolidation and how relevant the fluctuations in noradrenaline levels during sleep are in this process.

Conclusion

To be able to prove a potential active role of sleep in the memory consolidation process, a specific form of memory consolidation must be shown to crucially depend on a brain property that is unique to sleep. Both acetylcholine and noradrenaline fulfil relevant roles in the memory consolidation process, although the exact mechanisms that occur in this interaction remain to be identified. By manipulating naturally occurring fluctuations in acetylcholine and noradrenaline levels during sleep, it has been shown that the level of both of these neuromodulators during sleep are crucial in the consolidation of memory. The observed fluctuations in acetylcholine and noradrenaline levels during sleep are, therefore, very relevant in the discussion of a potentially active role of sleep in memory consolidation. Specifying the precise interactions that occur between these neuromodulators and neuronal circuits during wakefulness and sleep needs to be a goal of future research in order to determine whether sleep plays an active or permissive role in memory consolidation.

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