Sleep and Brain Plasticity
Maquet Smith Stickgold
(2003)

Foreword.
Howard Eichenbaum – Boston University

"Poets and physicians have pondered the function of sleep, and neuroscientists have weighed in on this issue for some time as well. However, despite considerable and continuing efforts, no clear and compelling role for sleep has been identified. Yet, we spend so much of our time asleep, and the motivation to sleep is so powerful, it mush have some very important physiological function, right? ..... Within a broad range of experimental programs there is ... strongly suggestive evidence that sleep plays some role in neural plasticity, including that which underlies at least some forms of memory." pg i

While reading:
- as you consider the effects of sleep deprivation, pay at least as much attentions to the controls for memory as to the measures for memory loss.
- chapters that describe neural activity patterns during sleep following learning, consider to what extent the experiment determines whether these patterns reflect the consolidation or persistence of memories.
- About the notion of memory replay during sleep, consider the contents of dreams versus those of memories.
- Consider the kinds of memory for which the relationship between sleep and the neural plasticity associated with experience related changes in behavioral performance we call memory.

Sleep dependent memories are often not declarative memory, but memories that involve perceptual learning and the acquisition of perception-motor routines that are mediated by cortical and motor systems.

Introduction.
Piere Maquet, Carlyle Smith, and Robert Stickgold.

"The function of sleep remains unknown despite our rapidly increasing understanding of the processes generating and maintaining sleep. A number of non-mutually exclusive hypothesis have been proposed for sleep function: energy conservation, brain thermo-regulation, brain detoxification, tissue restoration and that sleep is favorable for brain plasticity." pg 1.

Brain plasticity may relate to brain maturation, maintenance of infrequently used cerebral networks, or retention of hereditary and novel behavioral traits, dynamic stabilization thru reactivation.

In 1914 Heine reported that nonsense syllables learned just before going to be were better recalled after 24h than those with a waking period interpolated between learning and sleep. Further works along these lines has revealed the fundamental effects of sleep on memory and various experimental difficulties such as circadian rhythms.

The discovery of REM sleep in the 1950's establishes that sleep was not a homogeneous state of passive rest but an active condition of intense cerebral activity. Ontogenetic development is characterized by large amounts of REM sleep in neonatal and infants.

The role in adults remains less clear. "First it was suggested that tasks which rely on pre-existing species-specific skills were insensitive to post-training sleep deprivation. ..... Second, different species were used. Tasks that were insensitive to sleep deprivation in one species were not necessarily so in other species. ..... [indicating] the importance of genetic background in learning, memory and sleep ..... Third, the temporal organization of the experiment is critical ... Fourth, the validity of the method for REM sleep deprivation was questioned..... Finally, it was argued that deleterious effects of sleep deprivation on learning was due to non specific effects, and especially to the associated stress response." pg 4

"In humans, the influence of sleep on memory remained uncertain because the respective role of NREM sleep and REM sleep in memory processing was, and still is, unclear. .... In the same time, increases in REM sleep have been reported following training in various experiments...." pg 5

"More recently, the positive effects of sleep on recent memory traces were confirmed by an increasing number of publications using refined experimental designs and new techniques of investigations, at several levels of description." pg 6

Stress modifies sleep/wakefulness cycles and stress hormones regulate the processing of memory traces. It is usually considered that while persistent stress has a deleterious effect on memory, acute stress enhances the formation of new memories and glucocorticoids have have been involved in the consolidation of recent emotional memories." pg 9

Conclusions. "The role of sleep in memory trace processing remains to be confirmed. The characterization of task-dependent regionally specific brain activities during post-training sleep should be pursued, at different levels of cerebral

organization. They should be shown to be related to long-lasting behavioral adaptation. The specific role of sleep (i.e. sleep discharge patterns) in memory processing should be disentangled from other effects like experimentally induced stress or circadian modifications. Finally, the respective influence of SWS and REM sleep on the memory trace should be specified. " pg 9

Section 1 Human Behaviour

Chapter 1 Memory, Cognition and Dreams.
Robert Stickgold

Research across a range of disciplines and animals indicate a fundamental role of sleep in reprocessing memories. This includes changes in the wakeful state such as consolidation of procedural learning, coping with emotional stress, changes in neurophysiological functioning during sleep, and changes in cognitive and emotional processing during sleep.

A single definition of dreaming is most likely impossible but in this book sleep is defined as any mental activity during sleep.

One approach to the study of cognition during sleep is to measure cognitive performance during the first 2-5 min after awakenings from REM sleep and NREM sleep when "sleep inertia" (Lubin et al. 1976), allows one to study the brain in a condition where cognitive performance hopefully reflects the behavior of the brain in its pre-awakening sleep state (Dinges 1990). Three separate studies using this approach to investigate cognitive functioning during sleep point toward more flexible associative memory processing during REM sleep.

1. Semantic priming after REM sleep and NREM sleep awakenings suggests that the brain is functionally reorganized during REM sleep to preferentially activate weak associative links. (hyperassociative)
2. Subjects can solve 32% more anagrams after awakenings from REM sleep than NREM sleep (unclear if it is an different or improved process)
3. Identification of emotional faces is more flexible and less predictable during REM sleep than in NREM sleep.

While sleep is implicated in functional memory processing, the role of dreaming is unclear.

1. The occurrence of hallucinations in dreams stands in a reciprocal relationship to the tendency to reflect and think in a logical or directed way.
2. 98-99% of dream elements related to waking thoughts and events appear to result from the priming of neocortical memory systems, in much the same way as implicit memory tasks provide access to often consciously inaccessible cortical memories. Thus we dream *about* what happened, but not what actually occurred.
3. Dreaming can incorporate both specific and loosely associated images and themes from traumatic events in waking life, and that the form can predict the long term waking response to the trauma. This has been difficult to resolve due to the difficulty in incorporating waking events into dreams and in characterizing their nature when incorporated.

Hypnagogic dreaming enables experimental manipulation of dream content. Experienced, novice and densely amnesic subjects played Tetris for 7-9hrs a day for 3-4 days and reliably dreamed about it. Comparing novices and experts:

1. Similar imagery across subjects related to the nature of Tetris
2. 24hr delay of Tetris dreams for novice players
3. Tetris imagery is associated with poorer game performance
4. experienced players sometimes report imagery from earlier games

The densely amnesic subjects reported dreams with the same frequency but with no recollection of playing the game on the prior day (ie dreams do not depend materially on the declarative memory system)

Subsequent studies with the "Alpine racer" game resulted in more dreams on the first night for novices and similar inclusion of salient features. After 2hrs of uninterrupted sleep the imagery represented more weakly related concepts: "I felt I was falling downhill".

Hypnogogic dreaming involves a high rate of image incorporation, includes older memories, salient material, but without high dream affect or hippocampal or medial temporal lobe involvement.

"It is our belief that dreaming merely represents one of numerous mechanisms of off-line memory reprocessing occurring during sleep." pg 31

- We are currently unable to even properly phrase a question concerning a specific function of dreaming qua dreaming
- the neurophysiological basis of dreaming is in its infancy.
- A neurocognitive model is presented of how the brain activity during REM sleep might orchestrate a high level, functional reprocessing of existing memories and associations, accompanied by the phenomenon of dreaming.

Chapter 2 Human Studies of Sleep and Off-line Memory Reprocessing.
Robert Stickgold.

Recent evidence strengthens the hypothesis that sleep plays a role in learning and memory processing at many levels including visual, problem solving and cognitive performance. This chapter focuses on human behavioral studies of sleep learning and memory, while ignoring mechanistic questions. This still includes a very broad range of questions including timing of sleep relative to training (before after), the aspects of learning or memory, the stages of sleep, the time period (day(s), night(s), the types of memory (declarative, procedural) and many more sub questions.

The research involved a texture discrimination task TDT.

Pure procedural learning tasks can be successfully accomplished by amnesic patients for whom damage to medial temporal lobe structures has made the acquisition of for whom damage to medial temporal lobe structures has made the acquisition of declarative knowledge impossible.

Two groups have reported specific, localized activation increases in regions of visual cortex following training.

Improvement on the TDT develops slowly after training with no improvement when retesting occurs on the same day as training. Instead, improvement is only observed after a night of sleep.

The slow improvement in TDT performance has been shown to be (i) eye-dependent, not transferring from one eye to the other, (ii) retinotopically specific, not transferring to other quadrants of visual space, and (iii) orientation-specific, not transferring to stimuli in which the background bar are rotated from their horizontal orientation to a vertical orientation.

The amount and timing of training beyond a single session does not affect the final level of performance reached either 24 or 72 hours after the first training session.

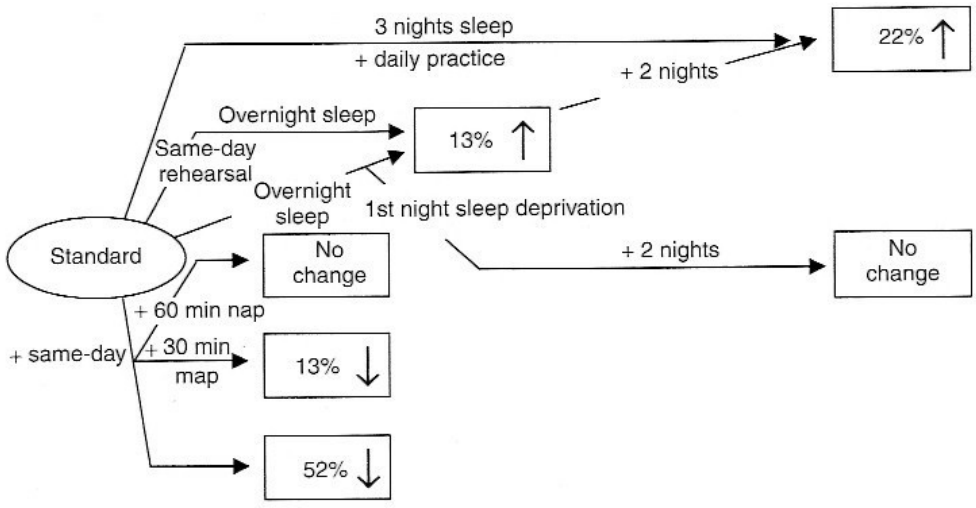


Figure 2.8 Interaction of training and sleep on TDT performance. Boxes show results from actual experiments described above.

declarative memory, emotional memories, and complex cognitive learning. Of the various sleep stages, evidence is undoubtedly the strongest for a role of REM sleep, and of the various forms of learning and memory, there is more convincing evidence for sleep's role in procedural and complex cognitive learning.

Repeated, same day testing on the TDT leads to an actual deterioration in performance. However, a brief 30min nap can halt the continued deterioration with further practice, and a 60min nap can actually reverse the observed deterioration. Furthermore, the deterioration is not due to generalised fatigue.

Improved performance on the TDT appears to require not only training, but subsequent events occurring during SWS early the following night and REM sleep later that same night.

The performance increase due to sleep for the TDT is unusual compared to other studies that indicate that sleep simply prevents deterioration. However, motor task learning (finger tapping task FTT) also shows an increase in performance with sleep.

Early studies found relatively little evidence for sleep, or REM sleep in particular, playing a role in declarative memory consolidation. More recently, these findings have been challenged and there is the suggestion that SWS may mediate declarative memory consolidation. It has also been argued that while early sleep is overall better for simple declarative memory retention, REM sleep augments recall of emotionally charged memories.

It has been proposed that habitual reagtions, which are closely linked with survival, are REN sleep independent; but activities involving assimilation information require REM sleep for optimal consolidation.

Findings from human studies, reviewed in this chapter, suggest distinct roles for SWS, stage 2 NREM sleep, and REM sleep in these processes, and suggest that sleep may help to consolidate both perceptual and motor skill learning, simple

Chapter 3. Roles of Early and Late Nocturnal Sleep for the Consolidation of Human Memories.

Because sleep comprises a highly complex array of neurotransmitter and neuroendocrine changes, any attempt to associate the assumed memory function with the classically defined sleep stages, which represent only the phenotype of this dynamic pattern, might be misleading.

Stickgold established that sleep was necessary to establish a persistent performance improvement in a basic textural discrimination task

Consolidation of procedural motor skills (finger tapping), though strongly benefiting from sleep, appears not to occur solely during sleep.

The acquisition of declarative memories can take place after a single salient event, and is initially critically dependent on the hippocampus formation but over the long term memories become independent of the hippocampus due to the development of more distant neuronal interconnections in the neocortex.

Evidence that sleep is obligatory for consolidation of long-term memories has been provided so far for procedural material only. However, a distinctly facilitating influence of sleep on the consolidation has been established for hippocampus-dependent declarative memories as well. This picture clearly implies a functional advantage of sleep over the wake state for memory preserving processes.

Smith (1995) concluded from a review predominantly from animal studies that REM sleep might be critical in the consolidation of procedural skills, but not of declarative memory.

More resent result in humans indicate a selective facilitation of declarative memory consolidation by early, SWS-rich periods of sleep, and conversely, a selective facilitation of consolidation of non-declarative procedural types of memory during late, REM sleep-rich periods of sleep.

Convergent evidence exists that within the declarative memory system, processing of emotional materials involves neurophysiological mechanisms and structures seperable from those involved in the processing of neural stimul, Specifically, in addition to the hippocampal formation, declarative memory for emotional material essentially relies on the integrity of the amygdala.

Investigations by the authors points to an aggravating influence of REM sleep on the valiance of emotional stimuli in conjunction with improved emotional memory formation during REM-sleep-rich part of the night, and argue against an emotionally cathartic function of sleep.

The comparison of retention rates over periods of early, SWS-rich sleep and late, REM-rich sleep indicates specific facilitating effects of late sleep for procedural skill memory and of early sleep for declarative memories, if emotionally neutral. Although declarative and procedural memory, as well as emotional memory are conceptualized as separate memory systems they mutually interact and probably all procedural or declarative memory is also more or less emotional.

It is assumed that the consolidation of memories during sleep is based on some kind of reactivation of neuronal networks that are involved in the prior encoding of the experience. This is supported by two types of evidence. Firstly, during human sleep, the DC potential shifts strongly towards negative polarity at the transition from stage 3 to SWS, and the period of steepest negative DC potential shift coincided with a maximum in spindle activity. This may well correspond to strong depolarisation in the apical dendrites of the pyramidal cells and hyperpolarisation of their somata, which by triggering strong calcium influx prepares the pyramidal cells for subsequent memory consolidation. Secondly, each slow wave oscillation represents a systematic variation of excitability of thalamo-neocortical circuits, which, depending on the phase, allows for or prevents the occurrence of fast activity.

SWS and REM sleep are characterised by a specific regulation of neurochemical processes including neurotransmitter and neuroendocrine activity.

Collectively the available data justify several conclusions. (i) There are tasks of procedural learning which require sleep as a necessary condition for their long-term consolidation. Declarative memory consolidation also benefits from sleep, although sleep has not been shown to be critical for this type of memory. (ii) Although both SWS and REM sleep may normally act cooperatively on memory consolidation, the strength of the influence of each of these sleep stages depends on the type of memory. Declarative memory benefits more from SWS, predominant during early sleep, while procedural memory as well as emotional declarative memory receives great benefit from REM sleep, predominant during late nocturnal sleep. (iii) Electrophysiological evidence has been provided, that neocortical reprocessing of memory representations assumed to underlie the consolidation process, can take place not only during REM sleep but also during SWS in humans.

(iv) Neurotransmitter (glutamatergic) and neuroendocrine (cortisol) processes have been identified in humans, which do not appear to be strictly linked to one of the classically defined sleep stages, but essentially contribute to memory consolidation during sleep.

Chapter 4. A Role for Stage 2 Sleep in Memory Processing.
Rebecca Nader and Carlyle Smith.

"Stage 2 sleep is the classification given to approximately 50 percent of the night of sleep in humans. It is recognized as having very salient features that distinguish it from other sleep stages. Traditionally, stage 2 sleep has been defined as having background EEG frequencies in the 5-8 Hz range, with intermittent 12-14 Hz spindle activity and K-complex slow wave activity (Rechtschaffen and Kales 1968). It occurs mainly in the last two-thirds of the night. Despite the presence of this stage in larger amounts than any other stage of sleep, the functions of stage 2 remain obscure. " pg 87

After total sleep deprivation, state 3 and stage 4 (SWS) recover before stage 2. The 12-14Hz spindle activity differentiates state 2 sleep from REM where it is absent. The K-complex is composed of a well delineated negative sharp wave immediately followed by a positive component. Sleep spindles last from 0.5-2sec and occur between 2-8 times per minute. It is likely that there are several spindle generators in the brain. The sleep spindle is well developed in all mammalian species.

"During spindling, cortical pyramidal cells receive strong dendritic excitation from the thalamus. Simultaneously, these same cortical cells are inhibited from firing by inhibitory thalamic input to the cell bodies. The depolarization of these cortical cells coupled with inhibition to prevent the cells from firing results in a physiological state ideal for the influx of Ca++ ions, without excessive cell firing. It is suggested that this influx may serve to prime the synapses for permanent changes, since Ca++ mechanisms are clearly involved with synaptic plasticity..... This calcium influx may also be involved with the gene expression which occurs during synaptic plasticity..... Thus, the sleep spindle provides a physiological brain state which is theoretically ideal for synaptic plasticity. " pg 89

The differences in sleep spindle activity between younger and older children could be used as an indicator of neural maturation. The changes in spindle activity continue with age and frontal and parietal spindles appear to follow a different developmental path. Individuals vary considerably in their spindle activity but the native number of spindles, the power of those spindles and possibly the peak frequency are all quite stable within an individual.

Spindles do not inhibit sensory input and might occur in periods of increased central nervous system excitability. Repetition of information during stage 2 could enhance memory storage processes that presumably are already occurring.

Post training stage 2 would appear to be important for the efficient memory consolidation of procedural motor or skills tasks. Memory for these skills tasks would appear to be completely unaffected by the amount of REM sleep that occurred.

Memory for a simple finger taping task is improved by 20% if subjects are allowed a nights sleep between training and retesting and there is a very high correlation with the performance and the amount of stage 2 sleep in the last quarter of the sleep night.

The increased time spent in stage 2 sleep and the increased number of spindles following task acquisition support the idea that spindly activity might reflect brain activity involved in memory processing of motor procedural material.

"A higher level of spindle activity (as assessed by total number of spindles and sigma power) is related to a greater ability to perform tasks which require perceptual, analytical and reasoning abilities." pg 94

"While stage 2 probably has a number of functions, there is evidence that this state of sleep is involved with the consolidation of procedural motor tasks. Although much remains to be done, minutes of stage 2 and number of spindles within stage 2 have both been related to memory for skills tasks.
From the developmental perspective, there is evidence to suggest that the native number of spindles exhibited by each individual is a biological marker for ability to learn certain kinds of tasks. " pg 95

Chapter 5. Expression and Modulation of Memory Traces During Paradoxical Sleep.
Elizabeth Hennevin

“This beneficial effect of sleep on memory was replicated many times and has given rise to three interpretations, each deriving from a theory about memory and forgetting: the decay theory (memory traces are subjected to a time-dependent decay process, and the decay rate would be slower during sleep than during wakefulness); the interference theory (forgetting results from interfering learning, and sleep would prevent activities that interfere with what has been learned); the consolidation theory (new memories consolidate over time, and sleep would facilitate the consolidation process).”

Paradoxical sleep is associated with dreaming, is a state of intense cerebral activity, and its amount is greater during early life, a critical time for basic learning.

The interest in sleep and memory waned in the 80's for various reasons but was reinvigorated in 1994 by Karni who demonstrated that overnight improvement in perceptual skill depended on PS and Wilson and McNaughton who showed that place cells in rats were also active in subsequent quiet time ans SWS.

Some events taking place during post-learning PS actively contribute to facilitate memory consolidation but this does not imply that PS is an absolute requisite for memory formation, but that PS optimise's the formation of some types of memory.

It has long been proposed that a particular memory can be in either a dynamic state (accessible and susceptible to disruption) or a dormant state.

Exposing subjects to cues prior to a retention test enhances memory retrieval.

Weak electrical stimulation of the MRF (mesencephalic reticular formation) applied during wakefulness or PS is able to improve a newly acquired or a newly reactivated memory.

Post learning PS constitutes a special period for reactivation of new memories which allows further processing or reinforcing of the neural circuits underlying the learning, that it, a further consolidation process similar to the effect or reactivation cues in wakefulness.

Because memory is a psychological function, it can only be inferred from performance expressed at a behavioural level.

There is supporting evidence from functional imaging.

The mechanisms allowing the development of associative plasticity are operative during PS, at least in the hippocampus, whereas they do not sem to be during SWS. Associative plastic changes induced during the PS state are maintained and can be expressed in the awake state.

The amygdala plays a pivitol role in the acquisition and expression of conditioned fear.

Memory traces during fear conditioning can be reactivated and expressed during PS.

The amygdala is also involved in positive reinforced tasks.

The mechanisms underlying physiological plasticity are operative during th PS state and some aspects of sensory processing are preserved during PS.

Testing neuronal plasticity during PS allows the dissociation of thalamic and amygdalar plasticity.

Wheras MGB neurons behave similarly in PS after fear conditioning and appetitive conditioning, exhibiting increased responses to the acoustic CS regardless of its affective value, LA neurons behave differently.

Beyond its potential role in memory, the possibility for memory traces to be reactivated and expressed during PS has a basic survival function.

PS is not exclusively devoted to memory, and there is memory without PS. In the field of behavioral neurosciences, to be simplistic can catch the attention but is never heuristic.

Chapter 6. The REM Sleep Window and Memory Processing
Carlyle Smith.

The REM sleep window (RSW) is the relatively short period where REM deprivation (REMD) (3-4h) can induce memory impairment. RSW varies with respect to: I) th strain and type of organism learning the task, ii) the type of task being trained, and iii) the number of training trials per session during training.

Studying a male Sprague-Dawley rat using the two way shuttle shock avoidance task:
- 100 trails in a single session resulted in the most dramatic increases in REM sleep.
- Rats that did not learn showed REM sleep similar to non-learning controls.
- The more training trials that were given at one session, the more subsequent REM sleep occurred in those animals that were successful in learning the avoidance task.

In similar trials exploring REMD, varying only the number of training trials per day resulted in large variations in the times and durations of increases in REM sleep. Also, the times when increased REM sleep occurred coincided with the RSW's for the taks for that strain.

The idea that the stress resulting from the task induces above normal levels of REM sleep appears unlikely. RSW is a far better explanation.

Investigations into the mechanisms of action during the REM sleep windows suggested:
- that protein synthesis inhibition during the RSW was devastating to memory consolidation in these animals
- that an ACh transmitter inhibitor active during the RSW impaired memory consolidation.

It seems likely that there is a close relationship between amount of REM sleep and levels of the ACh transmitter.

After rats are exposed to the informal learning situation of exposure to a variety of novel stimuli, they have thicker, heavier cortices, greater dendritic branching, greater cortical AChE activity and experience more REM sleep.

The interaction of brainstem and hippocampal structures during the RSW are very likely part of the consolidation process following training in th MWM.

The lateral amygdala is likely most active durinf RSW for the CCP task and that one of the transmitters is ACh.

RSW is well established in rats and mice but has not often been seen in humans but there is some similar evidence

Alcohol impairs normal REM sleep and memory in humans.

Thoughts
- “Rats that did not learn showed REM sleep similar to non-learning controls.” This indicates that that REM sleep increased as a result of learning rather than as a component of learning.

Chapter 7. Activation of Phasic Pontine Wave (P-wave): A Mechanism of Learning and Memory Processing.
Subimal Datta and Elissa H. Patterson.

Introduction.

"...animal studies suggest that memory consolidation following task training requires processes selectively active during REM sleep and that the organism homestatically adjusts it's REM sleep in response to memory consolidation demands." pg 135

Human "results suggest that REM sleep plays a larger role in the consolidation of procedural memories while SWS is more critical for declarative memory consolidation." pg 136

"The goal of this chapter is to present arguments and supporting data for the hypothesis that the activation of phasic pontine-wave (P-wave) generating cells in the brainstem is critical for sleep-dependent learning and memory processing." pg 136.

P-wave: description an functional significance.

Activation of a group of neurons in the pontine tegmentum generates a prominent field potential just prior to the onset of and throughout REM sleep. The P-wave is 75-150ms in duration, has an amplitude of 100-150uV, occurs as a singlet or in clusters of 3-5 waves/burst at a frequency of 30-60 spikes/min during REM sleep.

P-wave role in the memory consolidation process.

Reactivation of the hippocampus, amygdala, parahippocampal areas, and many other sites in the forebrain is critical for sleep dependent memory processing. The reactivation stimulus is probably coming from the brainstem based on stimulation of the mesencephalis reticular formation (MRF) of rats which appeared to be a substitute for REM sleep with regard to memory.

Evidence that the brainstem P-wage generator is the triggering stimulus for consolidation processes in the forebrain.

Standard procedure to to induce Long Term Potentiation in the hippocampus, amygdala and neocortex is to apply several hundred pulses of 250-400Hz stimulation or several short bursts if >200Hz stimulation with an interburst interval of 200ms.

High frequency bursting patterns of P-wave generating cells during REM sleep support the idea that the P-wave generator may be the source of electrical stimulus for the induction of psysiological LTP.

There is evidence for monosynaptic axonal connections between P-wave generating cells and forebrain structures to transmit the P-waves to enable LTP and memory processing.

When a background clicking noise was presented during acquisition of a learned skill, presentation of the same auditory stimulus during REM sleep correlated with a 23% improvement on retest performance one week later.

The amount of REM sleep and the percentage of eyebursts during REM sleep both increased with visual learning. This and other evidence suggests a physical role of the eye movements in reviewing visual data during REM memory processing.

There is a significant relatinoship between the rate of change of P-wave generating cell activity and levels of memory retention.

Conclusions

Based on all the evidence discussed in this chapter, it is clear that P-wave generating cells are capable of inducing physiological synaptic plasticity. It is also evident that the activation of P-wave generating cells is critical for the improvement of learning. If synaptic plasticity (LTP) is the physiological substrate for learning and memory, then P-wave generating cells are the presynaptic source for the high-frequency stimulus.

To account for sleep-dependent memory processing and learning, the following hypothesis has been suggested. During wakefulness, external information is randomly input into the brain and temporarily stored in the neocortex. At the same time, this information is represented in a brief cataloged form in the amygdala, hippocampus, and parahippocampal areas. This process is called acquisition and temporary encoding of information. During subsequent SWS, the amygdala, hippocampus, and parahippocampal areas acquire the detailed information that was previously represented only by an abridged catalogue; the transmission of additional associative information from the neocortex helps to eliminate maladaptive and unnecessary information. By eliminating maladaptive and unnecessary information, the system creates a high signal.

Chapter 8. The Role of Sleep in Memory Processing: The Sequential Hypothesis.

Introduction. The discovery of REM sleep attracted a lot of attention which drastically reduced interest in SWS. SWS also has an important and active role in memory.

Theoretical Considerations. The sequential hypothesis is that "some of the initial steps in information processing occur during SWS and are required for the further processing that takes place during PS". The more specific proposal of this paper is that the interleaved SWS and PS are involved in memory clearance and retention respectively. This proposal was arrived at through analogy with other body functions, logical requirements of memory, the EEG characteristics of SWS, PS and active W, and the ontological development of SWS, PS and W.

Experimental Data. The identification of Transition Sleep TS led to the identification of four sleep sequences that started with SWS and ended with W or PS, two of them including an intervening episode of TS. The sequences were labeled: SWS→W, SWS→PS, SWS→TS→W, and SWS→TS→PS. Trained rats were assigned to a fast learning FL group, a slow learning SL group (demonstrated learning on the day after training) or to a non-learning NL group.

Prior to training FL rats had more SWS in SWS→TS→W and lengthier sequences of SWS→TS→PS than the other groups. The other two sequences SWS→W, SWS→PS were comparable I all groups.

Post training FL rats and lengthier sequences of SWS→TS→PS than the other groups.

On the whole, the sleep data suggested that SWS→TS→W, and SWS→TS→PS sequences were processing memories of the novel avoidance response, respectively by implementing the initial processing step and the last processing step.

In earlier data, prior to the identification of TS and of the SL group, training appear to have markedly modified post-training SWS (not only PS) in a selective way in the rat groups. Processing of avoidance memories appeared responsible for most modifications of post training SWS and PS in FL rats, while processing of memories of innate responses appeared responsible for most differences of post-training SWS in NL (including SL) rats. This led to the proposal that "non adaptive memory traces may be de-stabilized during SWS→W, episodes, and eventually cleared from th brain. On the other hand, adaptive memory traces may be de-stabilized during (the SWS segment of) SWS→PS episodes, to be stored again in more suitable form (better integrated with preexisting memory traces) during the ensuing PS episode)."

The above interpretation was in agreement with the results of a correlative analysis between post-training SWS and PS and radio-labeled brain DNA.

The reminiscence shown by SL rats was found to be associated with lengthening of post-training SWS episodes of the SWS→W, and SWS→PS sequences in the third, fifth and six post-training hour and an increase in PS in the sixth hour. This was not seen in the NL rats. These changes in the SL rats were similar to those of the FL rats but delayed – possibly after dissipating the additional stress.

In sleeping rats, hippocampal place cells active during a previous waking experience were shown to selectively resume their activity during SWS or PS.

Alternative views. Information flows from the neocortex to the hippocampus via the superficial layers of the entorhinal cortex, and flows back to the neocortex via the deep layers of the entorhinal cortex. There is a hippocampal inflow with theta waves of active W r PS and outflow with hippocampal sharp waves of quiet W or SWS. During the latter phases, synaptic connections are strengthened. A plausible reconciliation with the sequential hypothesis might emerge from the assumption that synaptic strengthening during hippocampal sharp waves only concerns the components of waking experiences to be retained.

Conclusions. As above and....

A plausible explanation is offered by an extension of the mosaic hypothesis of sleep to all vigilance states (Krueger et al. 1995; Nielsen 2000). Accordingly, states of SWS, PS, or W should not be viewed as including the entire set of neuronal circuits, but only a fraction of them, albeit sufficiently large to allow the correct classification of vigilance states. A well-known, extreme example regards the alternation of SWS in either brain hemisphere of dolphins, while the other hemisphere is kept awake. Hence, it may not be unreasonable that when we are awake, some brain circuits are asleep (either in SWS or PS), and conversely, that when we are asleep (either in SWS or PS), some brain circuits may be awake or in the other sleep state. In other words, local transgressions are possible and may actually be required to account for local processing needs.

Section III Sleep and Neural Development.

Chapter 9. Role of REM Sleep in Brain Development and Plasticity.

Fetal and neonatal REM sleep. Rapid Eye Movement REM sleep occupies a large proportion of time during early brain development. The time course of REM sleep development in mammals corresponds well with the period of brain maturation ranging from only the first month in a rat to the preschool years period in humans.

The intensity of phasic neuronal activity is also higher in this early developmental period with specific identifiable periods of intensity and development.

REM sleep and brain development. Rats that have been deprived of REM sleep pharmacologically during development showed changes in adulthood including: increased anxiety, reduced sexual activity and disturbed sleep, and reduced size of cerebral cortex. We hypothesize that during the homeostatic adaption of receptor sensitivity to a persistent change in the intensity of incoming neuronal stimulation, individual neurons have established "set-points" which are determined by the amount of synaptic activation in early development, most probably during REM sleep.

REM sleep and brain plasticity. Neonatal REM sleep deprivation not only impairs brain development but it also prevents further plasticity of the brain in adulthood.

REM sleep and depression. Neonatal REM sleep deprivation induces adult depression.

Concluding Remarks. REM sleep plays an important role in brain growth, connectivity, and synaptic plasticity. The use of antihypertensive drugs during human pregnancy can suppress fetal and neonatal sleep and may have behavioral and psychological consequences in adulthood.

Chapter 10. The Role of Sleep in the Development of Central Visual Pathways.

Introduction. In a variety of mammalian species, sleep amounts are much greater during periods of rapid brain development and plasticity than at any other time of life. The abundance of sleep in infancy, and the fact that adult sleep is associated with complex patterns of brain activation and the release of neuromodulators that influence neural development, suggests that sleep may play an important role in brain maturation.

The roles of endogenous activity and experience in visual system development. In the developing visual system, endogenous activity in the retina and in thalamocortical circuits helps establish initial patterns of synaptic circuitry that are elaborated and sculpted by experience during subsequent critical periods of postnatal development.

The LGN receives bilateral retinal input via the optic tracts, where it is segregated into eye-specific lamina. The LGN also receives inputs from ascending brainstem centers, as well as from primary cortex, which modulate LGN response properties. Visual information is then relayed to VI, and further segregated into several functional domains arrayed in radial columns spanning the cortical plate. In animals with binocular vision, two basic functional domains are the ocular dominance and orientation columns. The ocular dominance columns are alternating regions of VI that receive visual inputs representing one or the other eye. While most normal cortical neurons respond to stimuli seen by either eye, neurons within a specific ocular dominance column respond more strongly to visual inputs that innervate that column. Neurons in VI are also sensitive to the orientation of edges of the stimulus within their receptive fields. Cortical neurons preferentially activated by a specific stimulus orientation are arranged radially in columns. Tangentially, the preferred orientation of cortical columns changes gradually and progressively across the cortex, except at occasional discontinuities. Visual inputs relayed through the LGN terminate within these alternating cortical regions where they activate specific columns of neurons. In addition to these thalamic inputs, neurons in VI receive numerous intracortical projections from neighboring ocular dominance and orientation domains and from extra-striate visual areas, which together determine their response properties.

The role of endogenous neural activity in visual system development. LGN. The initial maturation of the LNG does not require visual experience, but is dependent upon endogenous neural activity. V1.

Similarly in V1, the segregation of LGN afferents into occular dominance columns begins well before the onset of visual experience. This is paralleled by the formation of crude long-range, horizontal connections between cortical cells that in adult animals connect columns of similar orientation preference.

The role of experience in visual system development. The maintenance and further refinement of rudimentary circuits an response properties in central visual pathways is highly dependent on visual experience during critical developmental periods.

Sleep and visual system development. REM sleep is accompanied by a tonic excitation of thalamic and cortical neurons and phasic activations in visual structures (PGO waves) and associated with increased release of a neurotransmitter that influences neuronal development and synaptic remodeling (acetylcholine). NREM sleep is also characterized by events conducive to synaptic plasticity and neural development, such as synchronized bursting and thalamocortical circuits, transient elevation of intracellular calcium and in some mammals, the release of somatotropins. Both REM and NREM sleep also appear to promote processes dependent on synaptic remodeling, such as learning and memory.

Sleep and subcortical development in central pathways. Tests based on REM sleep deprivation and the elimination of REM sleep PGO waves suggest that REM or REMD can influence certain developmental events in the LGN during critical periods of visual system development.

Sleep and developmentally regulated cortical plasticity. A role for REM sleep has also been reported in a developmentally regulated form of long term potentiation LTP elicited during the critical period for visual development.

Some further considerations. Despite the experimental support sited in this chapter it must be recognized that the manipulation of sleep structure, or lesions that damage parts of the brain active in sleep are likely to have complex effects on neural development and behavior outside of their impact in sleep. The effects of stress should also be considered as a result of sleep deprivation. A related issue that complicates the interpretation of some studies occurs when the experimental manipulation alters vigilance states in ways likely to influence both the acquisition of sensory input in wake as well as subsequent processing during REM and NREM sleep.

Theories of sleep function in developing animals. The ontogenetic hypothesis proposes that large amounts of REM sleep in early infancy provide an important source of endogenous neural activity necessary for brain maturation. However, a number of issues remain to be resolved. Another suggestion, is that NREM sleep may have functions in developing animals in addition to its role in consolidate waking experience; a process that begins during critical periods of brain development when the animal is most sensitive to waking experience, but is retained throughout life.

Summary and concluding remarks. Many phenomena strongly suggest a role for sleep in brain development and plasticity, but we currently know little about the cellular and molecular mechanisms by which sleep exerts its effects.

Section IV System Level

Chapter 11. Cerebral Correlates of Memory Consolidation During Human Sleep: Contribution of Functional Neuroimaging.

This chapter concentrates on the contributions of positron emission tomography PET and functional magnetic resonance imaging fMRI to understanding similarities in sleep between animals and humans, and the modulation of brain function during sleep by the previous waking period.

Functional neuroanatomy of human "canonical" sleep.

NREM Sleep. In mammals the decreased firing in the active structures of the brainstem tegmentum plays a permissive role in the generation of non-rapid eye movement NREM sleep. The thalamus plays a central and executive role in the generation of NREM sleep rhythms, due the the intrinsic properties of its neurons and to the intrathalamic and thalamo-cortico-thalamic connectivity. NREM sleep oscillations (spindles, theta, slow rhythms) are characterized by bursting patterns which alternate short bursts of firing with long periods of hyperpolarization.

The deactivation of the cortex is not homogeneous. The most deactivated areas are located in associative cortices of the frontal, parietal, and to a lesser extent temporal an insular, lobes. One of the most deactivated areas is the hippocampal formation and neighboring parahippocampal gyrus.

REM Sleep. The neuronal populations of the mesopontine tegmentum play a key role in the generation of REM sleep by activating the thalamic nuclei which forward this activation to the cortex. Limbic and paralimbic areas (amygdala, hippocampal formation, anterior cingulate, orbito-frontal, insular cortices) are the most active during REM sleep. Pnto-geniculo-occipital PGO waves are a distinguishing feature and fundamental process of REM sleep and have been implicated in the facilitation of brain plasticity.

Experience-dependent cerebral reactivations during human REM sleep. An implicit learning task was used which required subjects to repeatedly respond to one of six signals which were delivered either in random order or with some unexpected probabilistic sequence (enabling a response speed increase). Results showed that the bilateral cuneus and adjacent striate cortex, mesencephalon and left premotor cortex were both activated during the practice of the SRT task and during post-training REM sleep suggesting a reactivation process which may have contributed to overnight performance improvement in the SRT task. The rCBF in the left premotor cortex was significantly more correlated with the activity of the pre-supplementary area SMA and posterior parietal cortex during post training REM sleep. But the first experiment could not distinguish the simple optimization of a visuo-motor skill from high order acquisition of the probabilistic structure of the learned material (or both). Follow-up experiments showed that the reactivation of neural activity in the cuneus during post training REM sleep corresponds to the reprocessing of elaborated information about the sequential contingencies contained in the learned material.

The reprocessing of recent memories during post-training sleep only occurs if the learned material is structured, but not so complex as to be unlearnable. REM sleep percentages increase in humans after learning textbook passages, but only when they are meaningful.

It was also found that the cuneus establishes or reinforces functional connections with the caudate nucleus which suggests the involvement of the basal ganglia in the off-line reprocessing of implicitly acquired high-order sequential information.

Furthermore it was found that the cuneus regional blood flow during post-training REM sleep is modulated by the level of high-order, but not low order, learning attained prior to sleep.

Strong support for the active involvement of sleep in the processing of recent memory traces.

Influence of sleep versus sleep deprivation on recent memory traces. A pursuit task in which the target trajectory was predictable on the horizontal axis but not on the vertical axis was used to study the effects of sleep deprivation. It was found that sleep deprivation on the first post-training night disturbs the slow processes that lead to the acquisition of this procedural skill and hampers the related changes in connectivity that are usually reinforced in subjects allowed to sleep on the first post-training night.

Conclusions. Functional neuroimaging during post-training sleep provides direct evidence for experience dependent changes in regional brain activity. These changes are likely to be task dependent, and are modulated by the processing of high-level material that was learned. These changes do not involve isolated brain areas but entire macroscopic cortico-subcortical networks.

Chapter 12. Off-line Processing of recent memory and its role in memory consolidation: A Progress Report.

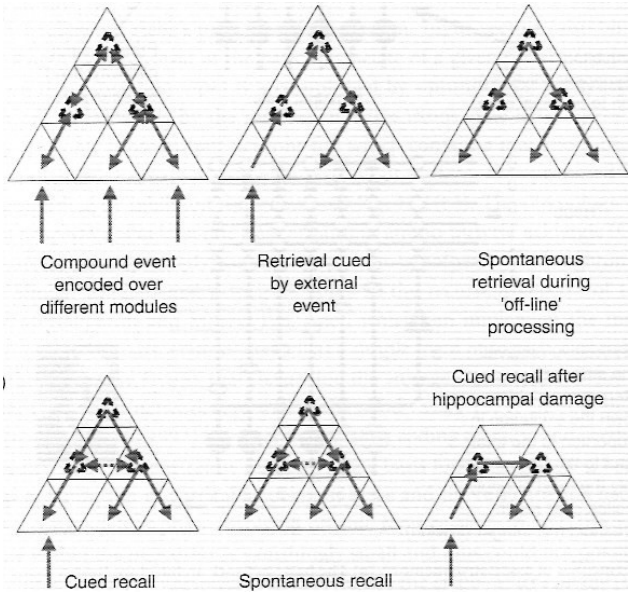
Introduction. This chapter reviews the theoretical considerations for why the brain might require an active reprocessing of memories during periods when it is relatively "disconnected" from external input.

Cortical hierarchies, indirect association, and the need for off-line reprocessing. The most basic model for associative memory, proposed by Marr, has a fundamental necessity for off-line reprocessing. The model has remarkably consistent physiological and anatomical properties with at least one type of GABAergic interneurons. The three primary factors that determine the storage capacity are connectivity density, coding sparsity and orthogonality. However, the full connectivity of the model is not supported by the cortical organization which is in the order of $1{:}10^6$. A solution to this problem is to create a modular, hierarchical cortex, in which connectivity is locally dense but the intermodular connectivity is even more sparse.

It is possible that the cortex evolved its hierarchical organization to overcome the problem of intermodular associations. The lower level modules appear to be reciprocally connected via Hebbian synapses with one or more higher level modules. The upper level may thus play the role of an index for the lower, which would enable pattern completion. This however, places high demands on the capacity of the indexing system. It would be more efficient to generate the specific inter-modular connections that are necessary to support the existing associations that are stored in the indexing system and thus free-up indexing capacity for new memories. This is, presumably, the primary purpose of off-line memory reprocessing which would allow the repeated presentation of the more often than not single unique eternal experience.

What do hippocampal neural ensembles "encode": evidence for the index theory. The optimal strategy for an indexing system would be to allocate an arbitrary, random pattern to each event. Neurophysiological studies of hippocampal neurons suggest that the system satisfies the conflicting indexing constraints of being noise tolerant (capable of pattern completion) and distinguishing between similar events. The evidence comes from the ability of the hippocampus to generate distinct (even uncorrelated) "maps" of the same physical location.

Hippocampal cells cannot be said to "represent" anything at all in the traditional sense that we understand the term. The "meaning" of a



hippocampal activity pattern can only be retrieved from the activity that it induces in lower cortical modules, which store the data, and are at east in principle decodable.

Quantification of memory trace reactivation. The "explained variance method" can be used to assess off-line memory retrieval in a set neuronal ensemble recordings made during control sleep S1, during a behavioral task T and during the subsequent period of sleep S2. The method provides a measure of how well T explains the difference in S1 and S2.

The LIA state and the role of hippocampal sharp-waves. The LIA (large irregular activity) occurs during restful waking, consummatory behaviors and SWS. It appears that the LIA state is a sufficient determinate of reactivation. In contrast, there is no evidence for reactivation during the theta state in waking animals (organized, externally directed behavior) and, on average, there is very little evidence of reactivation during REM sleep (theta) using the explained variance method on rat hippocampal assemblies, following repetitive spacial behavior.

Aging, NMDA receptor blockade, and the possible mechanism of reactivation. Observations of the hippocampus indicate that the Hebbian scheme outlines is either not the case, or not the whole story. One alternative involves non-associative plasticity mechanisms. A second possibility arises from the "continuous attractor" concept (Tsodyks and Sejnowski 1995) where the network drifts (random walk) away from the recently experienced set and may transfer to an alternate basin.

Does affect effect reactivation? Yes, positive or negative coloring definitely plays an important role in

memory. However, it is not because the affectively-colored events are reactivated more strongly. It may be because the reinforcement signal is coherently reactivated with the encoded events.

Effects of repetition and memory load on reactivation. Reactivation is reduced following experience in a large environment either because the number of target states is large or because the number of repetitions of each state in the sampling period is low.

Storage and reactivation of memory sequence "snippits". The reactivation sequence in SWS preserves the encoding sequence but on a substantially shorter timescale.

Hippocampal readout to neocortex and ventral striatum during LIA. It appears that memory trace reactivation is a widespread, although possibly not universal, phenomenon in the brain, and that when and where it occurs it is coherent across diverse structures.

The hippocampal-neocortical dialog.

Chapter 13. Maintenance and Modification of Firing Rates and Sequences in the Hippocampus: Does Sleep Play a Role?

[this chapter included extensive a clear references to a broad selection of work]

REM sleep may not be the critical stag of sleep for memory consolidation because 1) there is nothing in REM that is not in Waking 2) the link between performance gain and REM is weak 3) chronic elimination of REM with antidepressants does not cause memory problems 4) why do we "waste" 6hrs/day in SWS if REM does it all?

Two-stage model of memory trace formation. Several features of sharp waves SPW burst make it an excellent candidate for inducing neuronal plasticity. First, the time window of the SPW population burst roughly corresponds to the time constant of the NMDA receptor, through which Ca^{2+}, the key ion for the induction of synaptic plasticity, can enter. Secondly, the oscillatory network output is the ideal frequency range for initiating long term potentiation LTP. Third, during the burst there is a 3-5-fold gain of network excitability, creating an ideal condition for synaptic potentiation.

Neuronal activity during sleep may awake synaptic modifications made during in waking or alternatively repeatedly replay pathways modified during waking, perhaps at an altered temporal scale.

There is (slim) evidence that, during learning, associated with theta oscillation, task specific activation of the entorhinal input will bring about synaptic changes in the recurrent CA3 system. In the subsequent non-theta state the previously activated neurons are reactivated in a time-compressed manner during SPW bursts. As a result the behaviorally induced synaptic strengths will be maintained and the "memory representation" in the CA3 region can be transferred to neocortical targets.

Similarity of long-term firing rates and co-activation on the waking ad sleeping brain. Firing patterns observed in a well learned stereotyped behavioral task are correlated with similar patterns in the sleeping animal. Firing rates correlated not only between awake and SWS states but also between SWS and REM sleep.

Experience in a novel environment may alter firing patterns in subsequent sleep. Experience can alter the minute-scale firing rates and patterns of neurons and the changes are not all or none since some residual correlation is still present between firing patterns of the waking state and the proceeding sleep session.

Neuronal sequences correlated between waking and the subsequent sleep episode were “replayed” much faster during sleep than in the waking animal.

Homeostatic maintenance of firing rates. Cortical pyramidal cells fire single spikes and complex spike bursts. The function of bursts is unclear. We propose that bursts may be conceived as a homeostatic mechanism to maintain synaptic strength.

Downstream effects of cortical activity during sleep. We hypothesize that the strong depolarization brought about by SPW activity might be especially effective in the regulation of different autonomic and endocrine functions.

Chapter 14. Neuronal Plasticity During Sleep Oscillations in Corticothalamic Systems.

This chapter postulates that, far from being epiphenomena with little or no significance, spontaneously occurring brain rhythms during slow wave sleep SWS produce plastic changes in thalamic and neocortical neurons. We discuss the role played by augmenting responses elicited by stimuli at 10Hz, which are the experimental models of sleep spindles, in producing plastic changes in neuronal properties through the rhythmic repetition of spike-bursts and spike-trains fired by thalamic and cortical neurons.

Concluding Remarks. The above data show that naturally occurring SWS oscillations and their experimental models, such as augmenting responses that mimic sleep spindles, produce progressive depolarization in the membrane potential of neocortical neurons, their increased responsiveness that may be short-or medium-range (up to 15 min), self-sustained oscillations with the same waveform and frequencies as those of evoked responses in prior stages of stimulation, and may develop into paroxysmal activity.

Together with intracellular recordings in naturally sleeping animals, showing high discharge rates in SWS, these results suggest that neocortical neurons are the sites of processes leading to consolidation of memory traces during SWS.

It was suggested that both SWS and REM sleep are implicated in the process of network reorganization and memory consolidation, in the sense that early SWS stages favor retention of declarative memories, whereas sleep during late night, when episodes of REM sleep prevail, favors the retention of non-declarative memories. The role of REM sleep was challenged on the basis of a series of arguments, among them the stress induced in experiments with REM sleep deprivation. The role of SWS in memory consolidation is substantiated by results using ocular dominance plasticity during the critical period in cats and by potentiation of discrimination tasks in humans if the training period is followed by sleep, the enhancement correlating more closely to SWS.

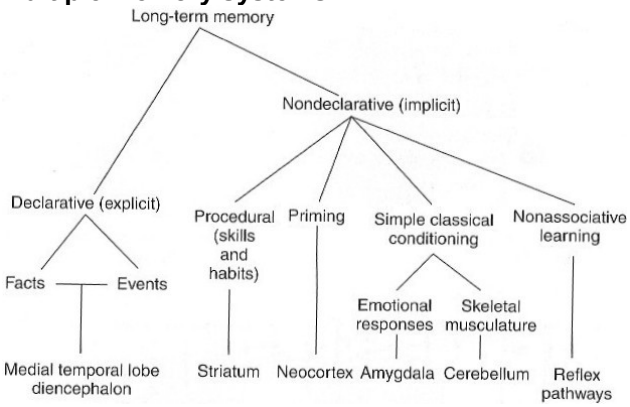
Section V. Cellular Level.

Chapter 15. Molecular Mechanisms of Memory Consolidation.

The specific molecular mechanisms that mediate certain forms of memory storage are regulated by sleep systems, suggesting that sleep and memory consolidation may involve similar molecular mechanisms. This chapter discusses these biochemical signaling pathways, focusing on REM sleep and the potential role of acetylcholine, NREM sleep, hippocampal sharp waves, glutamate, as well as the role of intracellular signaling mechanisms in memory consolidation. This chapter will focus on consolidation and on the hippocampus because 1) the hippocampus is known to be involved in consolidation, 2) there are dramatic changes in hippocampal neurons during the sleep/wake cycle 3) several components of the molecular cascade responsible for memory storage have been identified in the hippocampus.

The hippocampus and anterograde amnesia. Patient H.M. suffers severe anterograde amnesia after having his hippocampus and surrounding structures removed. Other patients have similar impairments with other damage and studies with primates allow that H.M's condition may be due to lesions in the perirhinal cortex and parahippocampal gurus as well as the hippocampus. There have also been studies with rodents involving lesions and genetic alterations.

Multiple memory systems.



The Hippocampus and retrograde amnesia. Despite the differential role of distinct brain regions in explicit and implicit memory, both types of memory undergo consolidation. Human and animal studies provide strong support that the hippocampus is crucial for memory consolidation. Destruction of the hippocampus does not destroy all long-term memories. Hence it is likely to be a location for consolidation with long-term storage elsewhere (cortex).

Sleep and memory consolidation for hippocampus-dependent tasks. What mechanisms might mediate the consolidation? Investigations utilizing sleep deprivation are challenged by the difficulty in controlling non-specific effects such as stress. Other approaches attempt to correlate sleep/wake states after leaning with the memory consolidation are better.

Acetylcholine, REM sleep, and memory consolidation. During NREM sleep, levels of norepinephrine, serotonin and Ach all decline as compared to waking but during REM sleep levels of norepinephrine, serotonin drop to near zero while Ach increases to levels comparable to waking. Neuromodulators such as Ach may not only modify synaptic transmission within the hippocampus itself, but they may alter communication between hippocampus and other regions. In this context, the low levels of Ach during NREM sleep may be as important as the high levels that occur during REM sleep and waking.

Adenosine and memory consolidation. Adenosine has a role as a sleep-promoting substance whose levels increase with extended wakefulness and slep deprivation and it has the potential to modulate memory consolidation.

NMDA receptors and memory consolidation. Long term potentiation LTP has bee especially well-characterized in hippocampal area CA1 at the synapse between Schaffer collateral axons from CA3 pyramidal cells onto CA1 neurons. In hippocampal area CA1, the induction of many forms of LTP is critically dependent on the NMDA receptor. NMDA receptors have a special role in memory because of their voltage-sensitive and ligand-dependent properties. These properties of the NMDA receptor allow for coincidence detection during memory acquisition, a property that may be especially important for associative learning as well as spacial learning. NMDA receptors are important for acquisition but any role in consolidation is unclear.

The intracellular mechanisms of memory consolidation and sleep. Many of the neurotransmitter systems that mediate memory consolidation and sleep/wake regulation alter the levels of intracellular second messengers, which in turn activate a variety of signaling cascades which ultimately result in the induction of new gene expression and the synthesis of new proteins leading to long-lasting changes in neuronal function.

Anisomycin, a protein synthesis inhibitor, interferes with memory consolidation and selectively blocks

long-term memory storage. Protein synthesis inhibitors, including anisomycin, dramatically reduce REM sleep, and possibly increases NREM sleep.

Conclusion. Neuromodulators and electrophysical phenomena in the hippocampus during NREM and REM sleep affect intracellular signaling pathways that are know to mediate memory consolidation. The hippocampus appears to be a locus for consolidation during sleep. During sleep replay of activity occurs in the hippocampus in oscillations that have the ability to alter synaptic plasticity, perhaps via molecular cascades involved in LTP. More research required.

Chapter 16. Recent Evidence of Memory Processing in Sleep.

Introduction. His chapter will briefly review recent experimental evidence with particular detail on molecular studies. A model of how sleep may act to consolidate acquired memories will be presented.

Behavioral Studies. Sleep deprivation impairs short term or declarative memory and perceptual learning (in humans). Training and rich environments increases REM. Short naps after training reduces human performance fatigue on perceptual tasks. Memory consolidation occurs during critical sleep windows 4-8 hours after training.

Electrophysiological studies. Behavioral gating refers to modulation of the neuronal transmission through the hippocampal trisynaptic circuit by the behavioral state of the animal – with enhanced transmission during SWS and variable during theta depending on synchronization with the theta rhythm. Theta rhythm are present in all mammals but during waking when animals perform ecologically relevant species specific behavior (predatory behavior in a cat, prey in the rabbit, exploration in the rat). Theta rhythms are important for memory consolidation during waking and their occurrence during REM are suggestive. Hippocampal neuronal activity during sleep recapitulates waking activity.

Molecular Studies. Laying down of long-term memories requires the modification of neuronal connections, most likely through the activation of gene expression programs that lead to neuronal plasticity. There is a high rate of protein synthesis during SWS sleep.

A particularly interesting candidate for mediating the long-term effects of experience on the brain is the immediate early gene IEG zif-268, whose expression in mature neurons is triggered by sustained membrane depolarization, NMDA channel opening and calcium influx.

Research with rats exposed to a caged environment C and an enhanced environment EE found that zif-268 expression decreased from the W to the SWS group and that there was a clear rise from the SWS to the REM sleep group. The effect was particularly noticeable in the cerebral cortex and hippocampus where zif-268 expression in EE animals was significantly higher in the REM group than in the SWS group. Zif-268 levels during REM slep were higher for EE than C animals. This is the first demonstration that brain gene expression during REM sleep depends on prior waking experience.

The experiments were extended to use unilateral

high frequency stimulation HFS leading to hippocampal LTP for the EE exposure to explore the mechanisms involved. The results indicated that zif-268 expression is reinduced in the brain during REM sleep that follows HFS of the hippocampus during W. Furthermore, hippocampal activity during early REM sleep that follows HFS is essential for REM seep-associated zif-268 reinduction in the cerebral cortex and the amygdala. The observations also provide evidence for the sequential activation of the cortex and amygdala during REM sleep that follows induction of hippocampal LTP. It also shows that cortical and amygdalar activation during REM sleep is strongly dependent on concurrent hippocampal activity.

We suggest that REM sleep constitutes a privileged window for hippocampus-driven cortical activation, free from waking interference and, in principle, capable of playing an instructive role in the communication of memory traces from the hippocampus to the cortex.

A Model of Memory Consolidation During Sleep. We propose a model for how sleep contributes to memory consolidation in warm-blooded amniotes (REM sleep is thought to be absent in reptiles, with the possible exception of crocodilians). When animals are habituated to stimulus, no new memories are acquired, much less consolidated.

The presentation of a novel/rich stimulus to an awake animal produces a marked increase in cellular calcium influx, monoaminergic/chlinergic neuromodulation, and activity dependent gene expression. Presumably, this chain of plasticity-related events carves novel memory traces in the brain by potentiating specific synapses, triggering protein synthesis and eventually determining morphological synaptic changes such as synaptic sprouting.

Upon entering SWS, the large amplitude oscillations that characterize this state will generate long alternating transients of high and low calcium dependent second messenger cascades, such as the phosphorylation of CaMKII, PKA and CREB. Still, SWS does not seem to be concomitant with plasticity related gene expression capable of consolidating the newly acquired synaptic changes, which reappears in association with REM sleep. Given the natural alternation of SWS and REM sleep, and the intrinsic temporal delay between mRNA synthesis and protein translation, it is easy to conceive how increased gene expression during REM sleep leads to an augmentation of protein synthesis during SWS.

Based on the existing evidence, we propose two separate but related functions for REM sleep: First, it propagates synaptic changes within the hippocampus to downstream cortical and amygdalar neurons, via the activation of calcium-dependent signaling cascades. We suggest that this process binds together, in the appropriate temporal sequence, short memory traces stored in the hippocampus and cerebral cortex as increased firing correlations among neuronal ensembles. Second, REM sleep triggers plasticity-related gene expression along the activated circuit, leading to the addition (and removal) of synapses, and therefore to the effective consolidation in extra-hippocampal regions of the new memory traces acquired during W, REM sleep).

According to this view, the ultimate role of REM sleep in memory processing would be to transcriptionally "freeze" the pre-genomic changes in synaptic efficacies evolved locally during SWS and then globally during REM sleep, so as to convert biochemical changes into morphological ones. Such a mechanism for the consolidation of synaptic changes during REM sleep predicts a homeostatic renormalization of synaptic efficacies through the brain after a certain number of sleep-wake cycles (in computational neuroscience jargon, "network renormalization"), at the expense of the addition and removal of synapses. Also implicit in the model is the idea that the repetition of the SWS/REM sleep cycle and the proportional increase of the latter as the subjective night progresses should allow for the evolution of longer and longer correlated firing chains across the neuronal matrix, that is, for the evolution of increasingly more complex memory traces as the sleep-wake cycle recurs.

Chapter 17. Sleep Modulation of the Expression of Plasticity Markers.

Introduction. Sleep must have very robust adaptive value. The sleep function is not localized in any one portion of the brain, the whole of the brain sleeps. Sleep is a fundamental property of neuronal networks. Connections between neurons in a network are strengthened with use and vice versa. The whole brain is in a state of constant flux.

Brain Organization and Sleep. There ar well known thalamic and anterior hypothalamic-basal forebrain circuits involved in NREM sleep regulation and the pontine REM sleep mechanisms. There are several arousal systems which are influenced by the sleep regulatory networks. The fundamental paradigm is that sleep is actively regulated by these networks and is dependent upon prior duration of wakefulness.

We proposed a fundamental modification to the paradigm which remains consistent with the evidence. We posited that sleep is an inherent property of small groups of highly interconnected neurons (neuronal groups), and further that sleep is targeted to neuronal groups based on the degree of their prior activity rather than on the duration of prior wakefulness. We envisioned that the role of the sleep regulatory and arousal networks was one of annealing the sleep of individual neuronal groups into a co-ordinated niche-adapted sleep for the organism.

Birds and whales are capable of unihemespheric sleep. Clinical observations indicate that sleep and wakefulness are simultaneously possible in different parts of the brain. Metabolic and electrical activity in the brain is neither uniform or constant. If one half of a dolphins brain is deprived of sleep then only that half demonstrates sleep rebound. Additional stimulation of a body part results in greater SWS activity in the corresponding motor cortex.

Sleep Function. The hypothesis is that sleep serves to stimulate, and thereby preserve, adaptive functional networks sculpted by genetics and prior experience and simultaneously serves to integrate new network firing patterns into existing networks. The biochemical networks responsible are the same as and inseperable from sleep mechanisms.

Neural activation induces growth factor production which act as autocrines and paracrins to alter the input-output relationships of nearby neurons.

Biochemical Regulation of Sleep. Several gene families are involved in the regulation of sleep and each has multiple biological activities and most are either directly or indirectly involved in synaptic plasticity. Many of the sleep regulatory substances are released or produced in response to neural activity, and act in autocrine or paracrin fashion suggesting that sleep will be targetted to those brain areas with higher prior activity.

Examples of sleep and molecules involved in plasticity. The neurotrophins, NGF and BDNF and the activity regulated cytoskeleton associated protein (arc) are thought to be involved in plasticity. Cell adhesion molecules CAMs are cell membrane macromolecules essential in controlling cell-to-cell adhesion during development by influencing neurite outgrowth, neural migration and adhesion, synaptogenesis, and intracellular signaling. In addition, CAMs regulate cell-to-extracellular matrix adhesion that appears to be critical to the process of learning and memory.