Table of Contents

Sleep and Memory Consolidation

Articles
Hennevin, E., Hars, B., and Maho, C. Memory Processing in Paradoxical Sleep 44
Smith, C. Sleep and Memory 50
Fishbein, W. Sleep and Memory: A Look Back, A Look Forward 53
Kavanau, J.L. Sleep and Memory: Evolutionary Perspectives 59

News and Comments
Club Hypnos
Will Meet During Society for Neuroscience Meeting, 65
Tuesday 11/14, 5:30PM

APSS Researchers From Indian Subcontinent
Gather for Dinner in Front of Registration Desk, June 2nd, 6 PM
National Sleep Foundation Dinner
May 31, 7:30 PM (During APSS Annual Meeting)
Postdoctoral Position Available 66
Behavioral studies have made it clear that lasting memory is not formed at the moment that new information is acquired. It takes time to create permanent memories, and memories can be subject to further elaboration far beyond their initial storage. Thus, rather than a simple fixation process, memory processing is a dynamic and evolving process which involves gradual transformation in the organization of the memory in addition to an increase in its strength or stability. We have long been interested in the idea that active events taking place during sleep, more particularly during paradoxical sleep (PS), may participate in the elaboration of memories (Hennevin and Leconte, 1971).

That sleep can aid in the maintenance of information acquired during wakefulness is an old idea. It was first advanced for experimental test at the beginning of the present century by psychologists who found that recall of an episode, such as a set of verbal units, benefited from interpolated sleep. However, this beneficial effect of sleep on retention could as easily been attributed to reduction in interference-induced forgetting (sleep protects what has been learned from interfering waking activities) as to enhancement in memory storage. When PS was discovered, several decades later, its physiological and phenomenological characteristics suggested that active functional processes occur during this state of sleep and facilitate cognitive activities and adaptive behavior in wakefulness. This hypothesis was primarily based on the observation that i) PS is frequently associated with dreaming in humans; ii) widespread areas of the brain exhibit high mean rates of spontaneous firing in PS; iii) the amount of PS is greater during the early life, which is a critical time for basic learning; iii) severe mental retardates have lower PS values than normal subjects. In the early 1970s, the possible relationship between PS and learning/memory became the subject of extensive experimental investigation, in both humans and animals. The most largely used strategy was PS deprivation (PSD), based upon the rationale that if PS is functionally related to memory processes, its loss should impair memorization. These early PSD studies led to some disappointment because their results were not as clear cut as it could be expected, especially in humans. In addition, methodological problems inherent in the PSD procedure, and particularly the water-tank technique widely used in animals, were pointed out, leading to the impression that PSD involved so many non-specific factors (such as stress effects or disturbance in biological rhythms) that it could provide no valid data about PS function. Lastly, the hypothesis of memory processing in sleep has always had to face skepticism both from people working in the field of sleep, who predominately consider that sleeping serves more basic biological functions, and from people working in the field of learning and memory, who do not easily accept the idea that information processing can take place in a non-conscious state. For all these reasons, from the early 1980s, the relationships between sleep and memory became a somewhat neglected area. Yet, as we will show, evidence for the involvement of PS in memory processing has continued to accumulate.

Before going ahead, the following points deserve consideration. First, assuming an involvement of PS in memory does not imply that it is the only function of PS. One can reasonably assume that, through its different physiological correlates, PS can influence a broad range of brain functions, and also that one type of physiological event occurring in PS may subserve different processes (for example, brain maturation in early life and memory elaboration).

Second, assuming an involvement of PS in memory does not imply either that PS is a necessary requirement for memorization. We rather consider that what occurs in PS plays a modulatory role which aids in the elaboration of memories. Third, there are different types of learning and different forms of memory and, even for a given task, the content, the organization and the strength of the memory vary as a function of the nature and amount of information acquired during the training episode. Consequently, the kind and time course of mnemonic processes taking place after training are likely to vary, as well as the degree of sleep involvement in these processes. This could account, at least partially, for some puzzling results obtained in PSD studies. Converging evidences supporting the notion that information acquired in wakefulness can be reprocessed during PS come from studies using various experimental approaches, including PS deprivation, analysis of the characteristics of sleep following learning, evaluation of information-processing abilities in PS, direct intervention during post-learning PS. We will concentrate on animal data obtained in our laboratory, without considering arguments coming from PSD studies which are presented in other papers of this issue (see also Smith, 1985, for a review).
Learning Induces Increase of Subsequent Paradoxical Sleep

If sleep is functionally related to learning processes, some covariation between the two phenomena may be expected. Thus, one of the first approaches we used to assess the potential link between sleep and learning processes was to study the effects of training on the characteristics of subsequent sleep (see, for review, Henneman and Leconte, 1977).

The experiments were performed in free behaving rats prepared for electroencephalographic (EEG) and electromyographic (EMG) recordings. The general procedure included 1) a 6-10 day period of adaptation to the recording cables; 2) pre-training baseline recording for 2-3 days; 3) post-training recording. The states of vigilance were recorded for 3-6 hours each day according to the experiments, always at the same time of the day for each animal. Among the experiments varied the type of learning task (both appetitive and aversive trainings were used), the number of training days and the number of trials per daily session; the duration of a training session varied from 90 minutes to 2 minutes. We consistently found that in the hours following training, animals spent increased time in PS with respect both to their pre-training baseline level and to control animals exposed to the same training circumstances but without learning. Slow-wave sleep (SWS) duration was unchanged. Post-learning PS elevation did result from learning and not from some non-specific effects, such as stress or fatigue induced by the training conditions, since 1) it was not observed in pseudoconditioned animals, 2) it was not observed either in unsuccessful animals, 3) it was manifested even when only one daily training trial was given, 4) it was related to the degree of learning achieved. In the course of distributed training, the greatest PS increase never occurred after the first trials (when the situation was yet the most stressful for the animal); it occurred later, when learning approached asymptote. After that, when the task was mastered, PS returned to baseline level. But if the animal had to face a new situation, such as a stimulus differentiation in an avoidance task or a modification of the run in a maze, subsequent PS re-increased. Lastly, post-training PS increase was also observed in mice who displayed reminiscence, that is a time-dependent spontaneous improvement of performance which develops after incomplete training and which is interpreted as reflecting a maturation process of the memory. More important, we found a striking parallelism between the time course of post-learning PS increase and the development of reminiscence phenomenon (Destrade et al., 1978). Altogether, these results strongly suggest that post-training PS elevation is truly related to acquisition processes and reflects on-going information processing which contributes to memory elaboration.

Information Can be Processed in Paradoxical Sleep

A first implication of the hypothesis that information acquired in wakefulness is reprocessed during PS is that brain mechanisms which allow information processing are operational during this state of sleep. The ability of the sleeping brain to process information is quite controversial. Yet, with regard to PS, neuronal functioning shares many characteristics with that in wakefulness. Unlike SWS, PS is as wakefulness a brain activated state, which implies a tonic readiness of cerebral networks (Steriade, 1991). For example, in PS as in wakefulness, thalamo-cortical neurons have their membrane potential relatively depolarized, they display tonic discharge and short periods of inhibition, synaptic responsiveness is increased. This leads to the consideration that "from the standpoint of the thalamo-cortical system, the overall functional states present in PS and in wakefulness are fundamentally equivalent" (Linhas and Paré, 1991). At the level of the hippocampus also, similarities exist between PS and waking: rhythmical, slow EEG activity (theta rhythm) is present throughout PS and, as judged by the induction of long-term potentiation (LTP), synaptic plasticity is preserved during PS, whereas it is suppressed during SWS (Bramham and Srebro, 1989). Taken together, these cerebral conditions suggest that the PS state is suitable for information processing to take place.

One of the most potent ways to assess whether information-processing abilities exist in a vigilance state is to test if new associations can be formed during this state. For this, we designed a classical conditioning paradigm (Maho and Bloch, 1982) in which two non-awakening intra-cerebral stimulations were paired: the conditioned stimulus (CS) was an electrical stimulation of the auditory thalamus; the unconditioned stimulus (US), delivered at the end of the CS, was an electrical stimulation of the central grey (an area the stimulation of which is known to be aversive). An increase in hippocampal multunit activity to CS presentation was taken as the conditioned response. CS-US pairing trials were given either in wakefulness or in SWS or in PS according to the groups. Before pairing, CS presentation had no effect on hippocampal discharges in any state. Pairing in SWS failed to induce any CS-evoked response. In contrast, pairing in PS as pairing in wakefulness induced a marked increase of hippocampal activity at CS presentation. In addition, after conditioning had been established in PS, presentation of the CS alone in wakefulness elicited the hippocampal conditioned response. These results are important for two reasons: first, by...
showing that pairing during PS allows the development of a cellular conditioned response, they indicate that mechanisms underlying neuronal plasticity are efficient during this state; second, they demonstrate that plastic changes induced during PS can be expressed in the awake state.

These findings were expanded at the behavioral level in an other experiment using pairing of 2 external stimuli (Hennevin and Hars, 1992). A neutral tone was paired, during waking or during sleep, with low-level electrocutaneous stimulations applied to the pinna (ETSs); these ETSs had been previously paired with a footshock during the awake state for all the animals. Acquisition of tone-ETSs association was subsequently tested by presenting the tone alone to the awake animals while they were licking for water. Animals which had received tone-ETSs pairing in the awake state exhibited strong lick suppression to the tone, as if the tone had been paired to footshock. Tone-elicited suppression was also observed in animals that had received tone-ETSs pairing during PS or during SWS. This response was less pronounced than that of rats for which pairing trials had been given in waking, but it was strong enough to be maintained over several test sessions, which attested to its reliability. Thus, the finding that behavioral reactivity to the tone was changed after pairing in PS indicates that information has been processed during PS and that what is experienced during PS can find behavioral expression in wakefulness.

**Learned Information Can be Expressed in Paradoxical Sleep**

The hypothesis that information acquired in wakefulness is reprocessed during PS also implies that neuronal changes induced by waking experience are maintained and can be expressed in subsequent PS. We addressed this issue by comparing neuronal responsiveness to a tone presented in PS before and after that tone had acquired significance by conditioning in wakefulness. Multunit cellular activity was recorded in the dorsal hippocampus (Mahe et al., 1991) and in the medial aspects of the auditory thalamus (Hennevin et al., 1993). Because considerable evidence points to the amygdala as an essential component of the emotional-learning circuitry, in a more recent experiment (unpublished data) recordings were also made in the lateral nucleus of the amygdala which constitutes the amygdaloid recipient of auditory projections.

After one session of habituation to a tone, awake rats underwent classical fear conditioning in 3 sessions during which the tone was paired with a footshock. Control animals received unpaired presentations of tone and footshock. After the habituation and conditioning or pseudoconditioning sessions, the tone was presented during PS phases. Multiunit activity was recorded at each tone presentation in waking and in PS. During conditioning in wakefulness, neurons of the hippocampus, the auditory thalamus and the amygdala rapidly exhibited increased tone-evoked discharges compared with habituation level. During PS neuronal responses evoked by the tone in the 3 structures were also much higher after conditioning than they were before conditioning. This enhanced responsiveness to the tone presented in PS cannot be attributed to arousal from sleep since no change was detected in EEG and EMG activities. It developed quickly since it was observed in PS following the first 10 trials of conditioning. It was reliable since it was present after each of the 3 conditioning sessions. It was associative in nature since it did not exist after pseudoconditioning. Therefore, it did result from neuronal plasticity induced by learning in the awake state.

Most recently, in order to evaluate whether an autonomic conditioned emotional response can be evoked during PS, we used the same protocol as described above and recorded the electrocardiogram at each tone presentation in both waking and PS. Tone-conditioned tachycardia developed during wakefulness. Significant changes in heart rate were also manifested during PS following conditioning (unpublished data).

Thus, by showing that cellular and autonomic conditioned responses acquired in wakefulness can be expressed in subsequent PS, this set of results suggests that the neuronal networks involved in learning are in a functional state close to that in wakefulness and can be reactivated during PS.

**A Memory Can be Modified During Paradoxical Sleep**

We have shown that information-processing abilities exist and that learned information can be expressed during PS. But is there some evidence that learned information can be reprocessed during PS? To address this issue we tested the possibility that non-awakening treatments applied during post-learning PS can modify retention performance in subsequent wakefulness.

We first applied a cuing treatment during PS (Hars et al., 1985). Cuing typically consists of exposing the subject to some aspects of a previously learned episode without submitting it to complete training trial. It has widely been demonstrated that such a treatment applied in wakefulness facilitates subsequent memory retrieval, and a number of arguments suggest that cuing acts by inducing memory reactivation (Spear, 1978). Awake rats were submitted to an active avoidance task during which slight electrotactile stimulations to the pinna (ETSs)
were used to signal a footshock. They received the same ETSs as cues during PS phases following conditioning. When tested the next day, they showed better avoidance performance than control animals which had received no ETSs during PS. In contrast, retention performance was impaired in animals which had received ETSs during post-training SWS (Hars and Hennevin, 1987). Control experiments, in which a tone was used instead of ETSs to signal the footshock during training, showed that ETSs delivered during PS or SWS were ineffective when they had not been associated with the learning task.

In an other series of experiments, we applied a physiological treatment during PS. It has been shown that low-intensity stimulation of the mesencephalic reticular formation (MRF) enhances retention performance in a variety of learning situations when it is applied in the very first minutes following training, during what has been called the phase of memory consolidation (references in Hennevin et al., 1989). We had found in previous studies (Bloch et al., 1977) that post-trial MRF stimulation i) alleviated most of the performance decrement produced by PS deprivation and ii) decreased the post-trial PS elevation. This suggested that some functional similarity exists between events occurring in wakefulness just after registration of information and events occurring in post-learning PS. To further assess this hypothesis, MRF stimulation was delivered during post-learning PS (Hennevin et al., 1989). Rats were trained to run in a maze for food reward with one trial a day. After each trial, one group of rats received non-awakening MRF stimulation in PS phases. Two other groups received the stimulation either in SWS or in waking, at the same time intervals after training. Control animals received no stimulation. Animals for which MRF stimulation was given during PS exhibited better learning performance than any of the other groups. Stimulation in SWS failed to have any effect.

Thus, the efficiency of both cuing and MRF stimulation in PS forces to assume that 1) access to a newly acquired memory is possible during post-learning PS; 2) learned information can be reprocessed during PS; and 3) the effects of information processed during PS can be expressed in waking behavior.

What Role for Paradoxical Sleep in Memory Processing?
Collectively, the data we have reported, along with those showing that PS deprivation can impair retention, largely support the view that PS contributes to the processing of memories. Such a proposal obviously gives rise to many questions.

What is the nature of the memory processing that takes place in PS? What are the PS processes that might perform this function? What neural systems might PS processes influence? Admittedly, any discussion about how PS activity can contribute to memory is highly speculative at the present time, as must be any discussion about the physiological mechanisms that underly learning and memory processes. Indeed, we are far from being able to specify the multiple mechanisms involved in the formation, the storage and the retrieval of memories, and most of the questions that can be raised for PS can similarly be raised for the awake state.

It is common to consider that there are two possible states for a particular memory: a dynamic state (active memory), which would correspond to the same type of neural activity as that during the initial learning episode, and a dormant state (inactive memory), which would correspond to the storage form (Lewis, 1979). A memory in a presumed active state is labile, accessible and susceptible of further processing, as opposed to inactive memories. Thus, immediately after registration of information, application of various treatments can alter subsequent retention performance, which indicates that the memory is at that time in a labile form. When the same treatments are delivered at longer delays after training, they lose their effectiveness, indicating that the memory is no longer accessible. But the state of the memory does not merely depend upon the time interval that has elapsed after initial storage. For example, even long after training, exposure to external or internal physiological events associated with the training episode not only facilitates subsequent retrieval of that episode, but also reinstates the lability of the memory, as attested by the effectiveness of various manipulations following a cuing treatment (for a review, see Spear, 1978). The fact that treatments applied during post-learning PS were able to modify subsequent retention performance indicated that memory sensitivity was then reinstalled. This led us to hypothesize (Hennevin and Hars, 1985) that a newly acquired memory may go back into an active form during PS following learning, and that such a reactivation allows some reprocessing of the memory, resulting in its better expression in wakefulness.

Admittedly, evidences to support the view that specific networks may be reactivated during post-learning PS are, at least, indirect. It was reported (Pavlidis and Winson, 1989) that hippocampal place cells that had fired extensively during awake exposure to their place fields exhibited increased firing during the subsequent episodes of sleep (SWS and PS). Also, we showed that neurons, from the sensory level up to structures involved in mediating emotional conditioned responses, could

SRS Bulletin, Vol 1, 1995, page 47
express in PS learning-induced discharge changes. From the above it may be assumed that the neural circuits most active in wakefulness, in particular those involved in learning, present heightened excitability in PS following a training episode. The widespread neural activation, originating from the brainstem, which naturally occurs during PS could help to trigger neuronal firing within these circuits. In other words, a non-specific factor (diffuse neural activation in PS) might have a specific functional action (reactivation of relevant networks).

Concerning the issue of how memory reactivation in PS could have beneficial effect, two, non-exclusive, possibilities may be considered. First, memory reactivation in PS might be by itself sufficient to promote retrieval processes in wakefulness, in the same way as presentation of a reactivating treatment (cuing) to awake subjects leads to subsequent better expression of learning. Second, it is possible that certain physiological events occurring during PS complement what has been initiated during the awake state, by allowing some strengthening or stabilization of learning-induced plastic changes within the reactivated networks. For example, the reactivated networks could benefit from high amount of acetylcholine release which characterizes PS and which has been shown to promote neural plasticity (e.g., see Dykes, 1990). As noted previously, neuronal functioning in PS shares many characteristics with the awake state. Many of our results also stress the similarity between what happens in PS and in wakefulness. Parsimony would thus suggest that comparable functional processes, underlain by common mechanisms, are implemented during PS and during wakefulness. However, there are not yet enough data, whether for PS or for the waking state, to pronounce on this question which remains open.

The role we envision for PS in memory processing differs from other authors' proposals. Crick and Mitchinson (1983) postulated that a clearing-up mechanism, they called reverse learning, operates during PS in order to prevent the brain being overloaded by considerable amounts of information stored in the waking state. It must be mentioned first that, according to the authors themselves, the net result of such a process would be less confused recall, because spurious memories would be suppressed while the well-established ones would be just damped down slightly. However, the occurrence of a clearing-up mechanism in PS is inconsistent with the findings that i) new associations can be established in PS and that ii) presentation of a cue stimulus in PS improves retention performance. At variance with Crick and Mitchinson, Winson (1993) proposed a positive role for PS events in memory processing. His hypothesis is essentially based on speculation about the role of hippocampal theta rhythm which, according to the author, would be the normal, physiological means by which synaptic plasticity underlying memory storage develops in the hippocampus. During waking behaviors, theta rhythm would act to parcel information and would allow its storage in memory via the activation of NMDA receptors in the hippocampus. The re-occurrence of theta rhythm during PS would allow experience gained during waking to be reaccessed and integrated into the animal's behavioral strategy. Such an hypothesis, entirely focused on the hippocampus, reflects a dominant tendency. Within the last two decades, memory research has almost exclusively been devoted to one structure, the hippocampus, and to one mechanism, LTP.

Consequently, each time one questions about the contribution of any process to memory, one examines first how this process relates to the hippocampus and LTP. However, mnemonic information processing is most likely a matter of multiple interacting systems and it probably involves different mechanisms. With regard to the hippocampus, even if there is ample evidence that it plays a critical role in processing of certain kind of information, it is also obvious that it is not involved in all aspects or types of memory (see, for example, Delacour, 1994). If memory processing in PS was limited to the hippocampus, it should exist a clear parallelism between the effects of PS deprivation and the effects of hippocampal lesion. This is not the case: for example, while performance of PS deprived rats is impaired in both place learning and active avoidance tasks, performance of hippocampus-lesioned rats is impaired in place learning tasks but it is improved in active avoidance tasks. So far, there is no indication that what occurs in PS is limited to a particular neural system. Our view is rather to consider that PS processes exert a broad influence on plastic neurons located in widely distributed networks; such networks may be different according to the type of learning.

Our proposal, in its present state, says nothing about SWS. Behavioral data supporting the view that SWS might be involved in memory processing are few. Ten years ago, Giuditta and colleagues proposed "the sequential hypothesis of sleep function", primarily based on the belief that SWS functions and PS functions cannot be fully independent from each other. According to this hypothesis, information acquired during the awake state undergoes a two-step sequential processing during the subsequent periods of sleep. During SWS takes place a preliminary process of identification of adaptive and non-adaptive memories which is followed by the selective weakening of the non-adaptive ones. This first step is required to implement the second processing operation which occurs during PS and which consists in the strengthening and storage of the adaptive memories.
The authors' argumentation is based upon analysis of the structure of post-training sleep in rats who displayed different learning performances (see Giuditta et al., 1995, for a review). Also, in recent years, the putative role of SWS in memory has been emphasized by some electrophysiologists who assumed that the synchronous patterns of neuronal discharges which characterize the SWS state might be well suited to strengthening synaptic connections. The hypothesis was put forward (Steriade et al., 1993) that the repetitive spike bursts occurring in the thalamo-cortical system during SWS may be used to specify/reorganize forebrain circuits for consolidation of memory traces. In the same line, it was proposed (Buzsaki, 1989) that the hippocampal sharp wave-bursts, particularly abundant in SWS, may represent a physiological mechanism for the consolidation of representations within intra and extra-hippocampal circuits as well as for memory trace transfer from the hippocampus to the neocortex. Lastly, it was found that hippocampal place cells that fired together during waking spatial activity exhibited an increased tendency to fire together during the very first minutes of SWS that followed. This led the authors to propose that "the neuronal states encoded within the hippocampus are played back during SWS as part of a consolidation process by which hippocampal information is gradually transferred to the neocortex" (Wilson and McNaughton, 1994). Obviously, the above three proposals are quite stimulating. However, behavioral data are required to assess their validity since there is, at the present time, no evidence that the physiological events they point out indeed relate to learning and memory. As noted previously, neuronal functioning in SWS is radically different from that in PS (and wakefulness). In addition, some of our results suggest that a difference in information-processing abilities exists between SWS and PS: we showed, for example, that retention performance was improved after cuing in PS while it was impaired after cuing in SWS. Therefore, if indeed SWS contributes to memory, its contribution is most likely different from that of PS. The idea that SWS and PS might subserve complementary roles is, of course, attractive but it remains short of data.

Determining how the different states of vigilance relate to memory processing is a difficult but important challenge. This may both contribute to our understanding of memory processing and provide insights about the functional meaning of the sleep states. Such work obviously requires multiple interacting approaches, necessarily grounded on behavioral analysis since memory is a psychological function that we can only infer from behavior. The new interest in the relationships between sleep and memory will certainly encourage future studies, and significant advances in this exciting area of research may be expected.

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References:
The idea of a relationship between sleep states and memory processes has been around for at least 25 years. Early studies were influenced by the ideas held concerning memory consolidation at that time. One of the basic assumptions of researchers doing studies on memory was that newly acquired material existed in the brain in a very fragile state, but within a period of a few hours, consolidated to become more stable. These memory engrams were presumably less vulnerable to such disruptive agents as electroconvulsive shock or drugs known to inhibit some metabolic activity of the cell, such as protein synthesis. Thus, it was also assumed that the sleep occurring in the first 3-4 hours after the end of training were the most important for memory processing.

There were two main approaches to the study of the relationship between sleep and memory. The first was to train animals (usually rats or mice) in the task and then to carry out EEG/EMG sleep recording in the hours after the end of training. The great majority of these studies revealed increases over normal levels of paradoxical sleep (PS) or rapid eye movement (REM) sleep. It was noted that these increases did not occur in animals that did not learn the task and were not due to such factors as stress. However, as the studies have accumulated, it has become clear that the PS increases persist for many hours and even several days rather than for just the first 3-4 hours after the end of training (Smith and Lapp, 1986; Smith et al., 1980).

The second main approach was to examine the possibility that the PS deprivation (PSD) at the vulnerable post training time would result in memory deficits. The results of many studies, using either the mechanical "swimming pool" technique or drugs for selectively preventing PS, showed memory impairment. These studies have been documented in several extensive reviews (McGrath and Cohen, 1978; Pearlman, 1979; Smith, 1985). Again, as more studies have accumulated, it has become clear that PSD is capable of impairing memory in the first 3-4 hours after training, but can, depending on the task, induce impairments at times up to 53-
Human Studies

There have been fewer human studies examining the sleep-learning hypothesis. The results of these studies have not provided very consistent support for the hypothesis. It is difficult to record from humans and be confident that the relatively short (1-2 hour) task given is the only thing reflected in the sleep of the subject. Unlike rats or mice which can be exposed only to the task of interest, humans have a variety of other things, beyond the control of the experimenter, that they are learning at the same time. However, several attempts have been made following intensive learning situations, such as intensive second language learning (DeKornik et al., 1989) and following studying for final college examinations (Smith and Lapp, 1991). Clearly there are increases in both number of minutes of REM sleep and density of REMs following intensive learning.

Total sleep or selective REM sleep deprivation (REMD), although methodologically easier, has often provided variable and seemingly contradictory results. An examination of studies that used the Train-REM-Test paradigm, suggested that the type of task might be a very important variable. Studies using simple memorization of word lists or paired associates tended not to be impaired after total sleep deprivation (TSD) or REMD. On the other hand, studies that required more complex manipulation of words or used non-verbal material tended to show deficits following TSD or REMD (McGrath and Cohen, 1978).

In our initial studies, we examined the effects of sleep deprivation on both a paired associate (PA) task and on application of a set of rules to solve problems in a complex logic task. It was observed that both TSD and selective REMD of all 5 REM periods of the night were able to impair memory for the logic task, but not the PA task. Further, it was observed that only the first 2 or the last 2 REM periods of the night were sufficient to impair memory to the same extent as REMD of all 5 REM periods. Even more surprising, TSD was found to impair memory in the 48-72 hours (2 days) after the end of training as well as in the first 24 hours (material learned the same day) (Smith, 1993). In a related study, alcohol was administered just before bed and just after acquisition of the complex logic task or 2 nights after the end of acquisition. Retest the next week showed both groups to be markedly impaired on the logic, but not the PA task compared to Controls that drank only orange juice. Examination of the sleep records showed that the alcohol had significantly reduced the amount of REM sleep in the first 2 REM periods of the night on either alcohol night 1 or alcohol night 3.

Learning theorists have recently divided learning material into declarative (or explicit) and procedural (or implicit) types of tasks. In an extensive study, we examined the possibility that procedural tasks were more vulnerable to REMD than were declarative tasks. Subjects were given training in the Tower of Hanoi, the Corsi Block-Tapping task, a word recognition task, a word fragment completion task (priming), and the Rey-Osterrieth complex figure task. REMD of the last two REM periods of the night was performed, leaving the first 3 REM periods intact. Results showed deficits in the Tower of Hanoi, priming, and the Corsi Block-Tapping task, when retesting was done one week later. Neither the word recognition or the Rey-Osterrieth task were impaired. These results were considered to support the idea that

Table 2

<table>
<thead>
<tr>
<th>Name of Task</th>
<th>Task Characteristics and Theoretical Classification</th>
<th>Type of Sleep Necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paired Associate</td>
<td>Cognitive, Verbal (D/E)</td>
<td>None</td>
</tr>
<tr>
<td>Word Recognition</td>
<td>Cognitive, Verbal (D/E)</td>
<td>None</td>
</tr>
<tr>
<td>WM Logic Test</td>
<td>Cognitive, Non-verbal (CP/I)</td>
<td>REMD</td>
</tr>
<tr>
<td>Word Priming</td>
<td>Visual, Verbal (CP/I)</td>
<td>REMD</td>
</tr>
<tr>
<td>Corsi Block-Tapping</td>
<td>Cognitive, Visuospatial, Non-verbal (CP/I)</td>
<td>REMD</td>
</tr>
<tr>
<td>Tower of Hanoi</td>
<td>Cognitive, Non-verbal (CP/I)</td>
<td>REMD</td>
</tr>
<tr>
<td>R-O Visual Task</td>
<td>Visual, Non-verbal (D/E)</td>
<td>None</td>
</tr>
<tr>
<td>Pursuit Rotar</td>
<td>Fine motor, Non-verbal (MP/I)</td>
<td>Stage 2</td>
</tr>
</tbody>
</table>

* D/E = Declarative/Explicit, CP/I = Cognitive procedural/implicit, MP/I = motor procedural/implicit

procedural/implicit material is vulnerable to REM sleep loss while declarative/explicit material is not. This interpretation fits well with previous results in which the PA task was not impaired following REMD, while memory for a complex logic task was impaired (Smith, 1993).

Memory for a Motor Task

It was decided to examine the effects of sleep deprivation on memory of a fine motor task. Subjects were trained in the pursuit rotor task using their non-preferred hand and then deprived of Total sleep either the same night, night 1, night 2 or night 3 after the acquisition. Unlike the cognitive procedural logic task, only the subjects deprived of total sleep on the same night as they were trained showed motor impairments one week later. It was at first assumed that this effect would be mainly due to the loss of REM sleep. However, in a second study where subjects were sleep monitored in the laboratory, the REMD subjects did as well as subjects in the normally rested group. However, subjects deprived of Total sleep for the last half of the sleep night were quite impaired on retest. Since the last half of the sleep night is composed almost entirely of Stage 2 and REM sleep,
Human Studies
There have been fewer human studies examining the sleep-learning hypothesis. The results of these studies have not provided very consistent support for the hypothesis. It is difficult to record from humans and be confident that the relatively short (1-2 hour) task given is the only thing reflected in the sleep of the subject. Unlike rats or mice which can be exposed only to the task of interest, humans have a variety of other things, beyond the control of the experimenter, that they are learning at the same time. However, several attempts have been made following intensive learning situations, such as intensive second language learning (DeKoninck et al., 1989) and following studying for final college examinations (Smith and Lapp, 1991). Clearly there are increases in both number of minutes of REM sleep and density of REMs following intensive learning.

Total sleep or selective REM sleep deprivation (REMD), although methodologically easier, has often provided variable and seemingly contradictory results. An examination of studies that used the Train-REMD-Repeat paradigm, suggested that the type of task might be a very important variable. Studies using simple memorization of word lists or paired associates tended not to be impaired after total sleep deprivation (TSD) or REMD. On the other hand, studies that required more complex manipulation of words or used non-verbal material tended to show deficits following TSD or REMD (McGrath and Cohen, 1978).

In our initial studies, we examined the effects of sleep deprivation on both a paired associate (PA) task and on application of a set of rules to solve problems in a complex logic task. It was observed that both TSD and selective REMD of all 5 REM periods of the night were able to impair memory for the logic task, but not the PA task. Further, it was observed that only the first 2 or the last 2 REM periods of the night were sufficient to impair memory to the same extent as REMD of all 5 REM periods. Even more surprising, TSD was found to impair memory in the 48-72 hours (2 days) after the end of training as well as in the first 24 hours (material learned the same day) (Smith, 1993). In a related study, alcohol was administered just before bed and just after acquisition of the complex logic task or 2 nights after the end of acquisition. Retest the next week showed both groups to be markedly impaired on the logic, but not the PA task compared to Controls that drank only orange juice. Examination of the sleep records showed that the alcohol had significantly reduced the amount of REM sleep in the first 2 REM periods of the night on either alcohol night 1 or alcohol night 3.

Learning theorists have recently divided learning material into declarative (or explicit) and procedural (or implicit) types of tasks. In an extensive study, we examined the possibility that procedural tasks were more vulnerable to REMD than were declarative tasks. Subjects were given training in the Tower of Hanoi, the Corsi Block-Tapping task, a word recognition task, a word fragment completion task (priming), and the Rey-Osterrieth complex figure task. REMD of the last two REM periods of the night was performed, leaving the first 3 REM periods intact. Results showed deficits in the Tower of Hanoi, priming, and the Corsi Block-Tapping task, when retesting was done one week later. Neither the word recognition nor the Rey-Osterrieth task were impaired. These results were considered to support the idea that procedural/implicit material is vulnerable to REM sleep loss while declarative/explicit material is not. This interpretation fits well with previous results which in which the PA task was not impaired following REMD, while memory for a complex logic task was impaired (Smith, 1993).

Memory for a Motor Task
It was decided to examine the effects of sleep deprivation on memory of a fine motor task. Subjects were trained in the pursuit rotor task using their non-preferred hand and then deprived of Total sleep either the same night, night 1, night 2 or night 3 after the acquisition. Unlike the cognitive procedural logic task, only the subjects deprived of total sleep on the same night as they were trained showed motor impairments one week later. It was at first assumed that this effect would be mainly due to the loss of REM sleep. However, in a second study where subjects were sleep monitored in the laboratory, the REMD subjects did as well as subjects in the normally rested group. However, subjects deprived of Total sleep for the last half of the sleep night were quite impaired on retest. Since the last half of the sleep night is composed almost entirely of Stage 2 and REM sleep,
it was concluded that it was the loss of Stage 2 sleep that was
inducing the impairment of motor memory. Further, it would
seem that the best learning occurs if the Stage 2 is continuous,
as an awakening control group with a number of arousals in
Stage 2 showed deficits on the task also (Smith and MacNeil,
1994). A summary of the human studies can be seen in Table
2.

**Enhanced Memory in Humans**

In an attempt to see if the enhanced memory phenomena in
rats could be observed in humans, subjects were placed in one
of four groups. The experimental group was trained in the
complex logic task with an audible ticking noise of about 70
dB in the background (a loud ticking clock). Then during the
night, 70 dB "clicks" were again delivered to the left ear of the
subjects whenever the size of the actual rapid eye movements
(REMs) of REM sleep were of sufficient amplitude to trigger
them. Thus, clicks were delivered to the subjects via mini-
earphones coincident with the REMs. There were several
control groups. One group was identical to the experimental
group except that no clicks were present during acquisition. A
second group was given clicks during acquisition, but the
clicks during REM sleep were delivered only when there were
no actual REMs. That is, a number of clicks equal to the
number delivered to the experimental group were presented
during the "REM quiet" segments of the REM periods. A
third control group was not given any clicks during training or
during the night.

Results showed the experimental group to be 23% better
than normally rested controls when retested one week later.
The other two groups were not significantly better than the
normally rested controls. The results support the idea that the
click (cue) presented during REM sleep serves to initiate
"recall" of recently learned material to the REM sleep state
for further processing (Smith and Weeden, 1990).

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**SLEEP AND MEMORY: A LOOK BACK, A LOOK FORWARD.**

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**Sleep and memory research -- looking back:**

Twenty-eight years ago I was a graduate student in
Biopsychology at the University of Colorado. Basic research
in two separate fields -- sleep and memory -- was in the midst
of thrilling breakthroughs, but at the time I was immersed in
graduate courses. One course was a seminar in Experimental
Psychology taught by behavior geneticist and biochemist Kurt
Schlessinger. For the term paper, Kurt required everyone to
write a theoretical paper about the biological bases of
memory. Many of us cowered at his brusque style, but
everyone turned in something.

I had come to graduate school from Eliot Weitzman's sleep
laboratory at Albert Einstein College of Medicine in the
Bronx. Before Eliot, I worked in Hy Witkin's and Arthur
Shapiro's sleep laboratories at Downstate Medical Center in
Brooklyn. I was their research assistant. I knew a little about
sleep, nothing about memory and a smidgen about
neuroscience, and yet I had the ominous task of having to

write a theoretical paper about a complex matter I knew little about. I wrote the paper with considerable fear that I would be hideously humiliated. It was about sleep, and I tried to draw some wild connections between the unique neurochemical and electrophysiological characteristics occurring during sleep and what we knew at the time about the biological bases of memory. I titled the paper "Sleep, wakefulness, dreams and memory: A theory of long-term information storage." After reviewing the literature, I had the thought that because sleep occupies such a large fraction of the 24-hour day — and REM sleep a significant portion of that — the ability to remember may have something to do with the brain activity occurring during sleep. As I reread the paper today, I’ve kept it all these years — I see that I wrote in the preface "my theoretical notions borrow heavily, consciously and perhaps unconsciousness from many others. It [the paper] probably derives much of whatever value it has from those borrowings. Where conscious borrowing has occurred," I said, "the source has been identified, but failure to mention a source is not to be construed as a claim to originality." To be sure I was being very cautious; I wanted to tread lightly in Kurt’s presence.

From what I knew, two others before me had the idea that something going on during REM sleep may play a role in fortifying memories, and there is no doubt that I borrowed from them. Michel Jouvet hinted about the possible connection between REM sleep and memory in a paper published in 1965; Arthur Shapiro had a similar idea in an unpublished paper presented at a meeting in 1966. Yet at the time I wrote my paper — it was 35 pages long — I could not imagine that it would become, off and on, a central focus of my research career for the next 28 years.

To my surprise, Kurt liked the paper and although he made no secret of the fact that he had no interest in sleep, other than what he got of it when he wasn’t working, and at most really had only a passing interest in memory research, he asked me if I would like to pursue my ideas in his laboratory.

Kurt had a mouse laboratory. I had never touched a mouse (or a rat for that matter) before, nor did I know anything about them except for the wild mice my dad caught, generally behind the refrigerator, when I was a kid growing up. If I was going to write a doctoral dissertation, however, I was about to become an expert in the life and ways of those little buggers.

First I needed a polygraph and as luck would have it, Kurt found one in a back storage room under a ton of boxes and lot of other unwanted paraphernalia. It had vacuum tubes and two working channels. I was ecstatic; I was in business. Next I had to figure out how to record mouse brain waves to get sleep recordings. As far as I knew no one had yet developed a technique for performing long-term EEG recordings in mice. Solving this problem turned out to be a matter of miniaturizing the technique I had used with newborn kittens in Eliot Weitzman’s laboratory. The difficulty was figuring out how to anchor the electrodes without them tearing out.

There were numerous failures but then I got the idea of making inverted Ts out of stiff electrode wire so that the electrodes could be anchored between the skull and the brain. That worked out well. Over the years I improved the technique until it became a standard procedure in my laboratory.

The next problem was figuring out how to deprive mice of REM sleep. I knew of Jouvet’s inverted flower pot technique. All I had to do was miniaturize the procedure to the size of mice, and get Kurt’s permission to glue large and small toadstool pedestals inside his acrylic cages. He wasn’t too happy about that, but I was on a roll. The only thing I didn’t anticipate was that I would eventually find myself having to hand wash 50 to 100 cages daily for the next two years of my life. Nor could I have anticipated all the slack I received, in the years to come, about the “stress factor” produced by the mouse-on-a-pedestal technique. I spent a great deal of time trying to prove that there was no stress factor. Despite my efforts to design experiments in a way that the training and retention testing were not confounded by the pedestal procedure, it became clear that no matter what control experiment I did, I was never going to convince everyone. Eventually, this controversy led me to completely abandon the REM deprivation procedure and look instead at the effects of learning on REM enhancement.

Finally, I needed a behavioral task, one that would provide a memory trace that I could assay for after the animals had been REM deprived. Kurt suggested a jump-box based on some phosphorylation inhibition memory studies he had been tangentially involved with some years before, so off to the shop I went. There was no technician: this was a do-it-yourself operation. Frankly, I did not know one task from another; they all seemed the same to me: so why not Kurt’s idea? The task I built was an active conditioned avoidance apparatus. A light and buzzer signaled that the grid floor of the box would be electrified. The animal’s job was to jump to a shelf to escape, or preferably jump to the shelf before the grid was electrified. It was with this apparatus that I performed my first REM deprivation — memory experiment: it was the Fall of 1967. After training mice to jump to the shelf, I deprived them of REM sleep for three days by my toadstool technique, and then tested the animals for retention. To my utter amazement, the REM deprived animals’ retention performance was substantially poorer than the large pedestal controls. I couldn’t believe it. Was it really true? I really thought my Experimental Psychology paper was a lark. I really hadn’t believed what I had written.

The active avoidance task, however, was a forerunner of a subsequent task. The jump-box had all sorts of problems. The mice were so jumpy after the first training trial, it was often impossible to put them back on the grid floor to train them for a second trial. Chasing mice who had leapt out of the apparatus and trying to catch them on the laboratory floor just wasn’t proving to be an effective way to carry on an experiment, so I got another idea: one-trial passive avoidance.
Back to the shop I went and built a step-through, one trial, conditioned avoidance task. I built it so that the mice could be placed in an enclosed alleyway with a bright light shining on them. Naturally the mice will make their way down the alleyway to escape the bright light; upon entering a darkened chamber, they receive a footshock from the grid floor. The animals are then removed from the apparatus. One trial: simple, straightforward, no fuss, no muss. The retention measure is the time it takes to walk down the alleyway on the retest trial. Long walk-through latencies are interpreted as good retention because the animals have to actively inhibit the natural response of moving away from a bright light. Behavior is inhibited because the electrified grid floor is more aversive than the bright light. The apparatus was wonderful, not only because I could obtain reliable measures of entry latencies, but a control group of animals could be employed that received the footshock on the training trial by placing them directly into the darkened chamber. In this way I was able separate the effects of footshock alone from the combined behavior of walking down the alleyway and receiving footshock.

So, holding my breath, I repeated the first experiment with this new apparatus: Trained the mice, deprived them of REM sleep for three days, then tested them for retention. The results were the same! Retention in the REM deprived animals was substantially poorer than the mice from large pedestals. I had the makings of a doctoral dissertation. I was jumping up and down.

From there, it took almost two years to perform, analyze and describe the half dozen experiments that comprised my dissertation; and this was only the beginning. Of course Kurt made me do all kinds of other experiments and data analyses unrelated to my hypotheses. Remember, he is a behavior geneticist. Consequently I did strain difference studies, backcrossing, footshock intensity, open field, etc. I also performed biochemical assays (norepinephrine, dopamine, serotonin) that never panned out.

There were many questions to be answered and clearly not all could be in a half dozen experiments:
1. How much REM deprivation is necessary to produce memory impairment?
2. Does memory recover after the animals make up lost REM sleep?
3. If the memory recovers, might there be a way to make the amnesia permanent?
4. To what extent does living on a pedestal in the midst of a pool of water produce stress?
5. Are there strain differences in the ability to REM deprivation to produce impairment?
6. Are mice with naturally high levels of REM sleep better learners than mice with low levels?
7. How long can mice live without REM sleep?
8. What is the effect of REM deprivation before learning?
9. Will alternative means of producing REM deprivation, say with REM suppressing pharmacological agents, produce similar effects?
10. If REM deprivation produces amnesia, does enhanced REM sleep produce memory facilitation?
11. Is there a relation between the amount of learning achieved and the amount of REM sleep?
12. How much learning is necessary to produce an enhancement of REM sleep?
13. Are there sex differences in the amount of REM sleep? Do any differences manifest themselves in memory ability.
14. Can the amount of REM sleep be a predictor of memory decline in senescence?
15. Is the REM deprivation effect task specific or is it a universal effect?
16. Does REM sleep differentially facilitate automatic memories (skills, habits, etc.) compared to memories that we think and talk about (facts, events or specific stimuli)?
17. What about the effects of early development? Does enriched rearing augment REM sleep and impoverished rearing reduce it?
18. Is REM sleep solely involved in consolidation of new memories or might it be involved in sustaining memories for a lifetime, or possibly both?
19. What are the anatomical structures, brain and cellular mechanisms involved in REM sleep facilitating the consolidation, storage and retrieval of memories?
20. And finally, how much of all this is related to human sleep?

To be clear, I understood that empirically derived affirmative answers to these questions would raise an alternative theoretical view of the function of dreams, compared to classic psychoanalytic thinking in which Freud (1900) tried to make sense out of the seeming chaos, or meaninglessness of the dream by suggesting that it is a disguised representation of childhood wishes. By the time I completed my dissertation, I had evidence that REM sleep may be part of a complex system of processes involving the unusual adaptive function of transforming newly acquired experiences into life-long memories.

REM sleep and the consolidation of long-term memory -- some early findings:
Early on, the majority of memory research concentrated on the behavioral parameters of the fixation process of memory consolidation. Nowadays, the major body of memory research concentrates on the cellular and synaptic events of memory formation because it is now generally recognized that an experience physically changes the synaptic configuration of the nervous system, altering neural circuits that participate in perceiving, performing, thinking, and planning. We refer to these neural changes as memories. Nevertheless, knowing the behavioral parameters of an experience-dependent neural change is the first step in understanding the nature of memory processes.
Therefore, a crucial first step in sleep-memory research was to ask whether REM sleep participates in the neural modifications of the brain that ultimately lead to consolidation of a long-term memory trace. To answer this question, it was necessary to demonstrate that animals learn normally and remember normally, at least for a short period of time before amnesia sets in. Otherwise, subsequent experiments would be difficult to interpret since there would be no way of distinguishing poor acquisition from retention impairments. I accomplished this in two separate experiments. In the first (for review see Fisher & Gutwein, 1977), separate groups of mice were deprived of REM sleep for three days, trained, and then tested for short-term memory retention (up to 1 hour), and long-term memory (1 to 7 days). The results were very clear. REM deprivation had no effect on acquisition; mice learn normally and remember normally up to an hour after training. Consequently, it seemed fair to conclude that REM sleep plays no visible role in the acquisition and immediate retrieval of a learned task. On the other hand, animals tested for retention seven days later or even the next day, are completely amnestic of the learned behavior (anterograde amnesia). The results led me to the idea that the neural events occurring during REM sleep may play a vital role in the conversion of a labile working memory trace into a stable, long-term memory -- but has no role to play in acquisition and immediate recall (working memory).

Therefore, if REM sleep provides an important milieu for long-term memory fixation, the second question is in what way does it further the consolidation process? One universally agreed upon finding about memory formation is that it takes time for experience-dependent processes to consolidate. Consolidation is not an instant event; at the very least it takes a few minutes. Any procedure slowing the consolidation process would leave the developing neural changes subject to other interfering events. Therefore, a way of getting at this question was to study the gradient of the memory consolidation phase. It would be strong evidence that the role of REM sleep is to accelerate (fortify) the memory stabilization process, if REM deprivation slows the time course of the consolidation gradient. To see whether this was the case (for review see Fisher & Gutwein, 1977), I REM deprived separate groups of animals for three days, trained them, and then administered electroconvulsive shock (ECS) at various intervals after training (from immediately afterward up to 6 hours later). The animals were tested for retention 3 days later. Again, the results were clear-cut. Extension of the susceptibility to disruption gradient (anterograde amnesia) was far beyond -- more than three hours -- the expected normal limit of a minute or two.

Still other evidence added to the idea that REM sleep plays a role in the formation of a permanent memory trace. This work comes from experiments in which REM deprivation is administered after an activity-dependent neural change has been initiated (learning). Again, remember, amnesic agents such as ECS have their effect only when administered within minutes after training, while the trace is still in its working form. Yet in one experiment (for review see Fisher & Gutwein, 1977), mice trained in the one trial task and immediately deprived of REM sleep, are made permanently amnesic when ECS is administered after two days of REM deprivation. In animals allowed to recover the lost REM sleep (no ECS), retention is normal. From this experiment I formulated the idea that REM deprivation prevents the solidification of the memory trace by sustaining it in its labile -- working memory -- form long after learning takes place. Consequently, an experience-dependent neural change encoded during waking can be held in suspension until some later time -- during sleep -- when it is replayed, strengthened and finally transformed into a long-term trace.

Finally, there was another possible way of examining the existence of the consolidation process: the enhancement of REM sleep after learning. Whether under conditions of massed learning or distributed learning, REM sleep is augmented (Fishbein & Gutwein, 1977; Dujardin et al., 1990). Two aspects of these studies provide signs that a delayed consolidation process is in evidence. In a massed learning experiment REM augmentation does not occur immediately, but is delayed for six hours, and then lasts for at least eighteen hours afterwards. Although circumstantial, the findings signal that after a learning experience, an "off-line reactivating" sleep process comes into operation. More directly, the REM sleep increases are observed primarily in animals that have not yet achieved the asymptote of the learning curve (distributed learning), or are slow learners (massed learning). Taken together, it seemed reasonable to conclude that insufficiently stimulated activity-dependent neural changes taking place during wakefulness, are etched into permanent form by the subsequent occurrence of REM sleep. Then, when learning has been achieved (consolidation), the delayed reactivating process no longer is necessary and as such REM augmentation no longer occurs.

In humans it had always been assumed that memories form and are retrievable without sleep -- just as it is the case in mice -- but with these new findings a fundamental shift in memory consolidation theory was emerging. It appears that sleep and in particular REM sleep has an important role to play in transforming newly acquired experiences into more efficient and enduring memory traces. It remains an open question whether memory forming processes during waking and sleep have a shared basis at the cellular level. The finding of Pavlidis & Winson (1989) that hippocampal place cells firing in the CA1 region during the wake state -- presumably encoding a neural representation of space -- subsequently discharge during sleep, suggests this may be the case. These researchers also conjecture that dreaming during REM sleep may be a reflection of a delayed integrative memory process. At the very least, sleep serves to fixate working memory traces, making them less susceptible to disruption by other interfering events.
It has taken the students in my laboratory, and three other research groups led by Chester Pearlman in Boston, Carlyle Smith in Canada, and Vincent Bloch, Elizabeth Hennevin and Pierre Leconte in France, more than two decades to provide much of the knowledge we now have about the behavioral parameters of the REM sleep role in the consolidation process. Of special interest are the intriguing data provided by Smith and his colleagues (1982), of delayed REM sleep "windows" of time after the training session, when consolidation processes are conceivably active. REM deprivation during these selected periods is effective in retarding learning.

The new findings of Avi Karmi, Dov Sagi and their colleagues in Israel (1994) bridge the animal findings to sleep in human subjects, and extend the human (explicit or declarative memory) studies performed by Eppson and colleagues (for review see Karmi et al, 1994) to implicit, (procedural) nondeclarative memory. It has been generally assumed that procedural knowledge -- repetitive tasks, like learning to type, roller skate, or play a musical instrument -- is formed solely by repetition of the task. Yet in an unequivocal way Karmi and his colleagues employing a visual discrimination task, demonstrate that enhanced remembrance of procedural knowledge depends on the occurrence of REM sleep.

Most intriguing of all is the recent findings of Wilson and McNaughton (1994) who provide direct, unequivocal evidence of an off-line sleep-memory process. Their findings build on those of Pavlides and Winson (1989). In rats, after recording from an ensemble of hippocampal place cells, firing together when the animals occupy particular locations in spatial working-memory tasks, they found that the hippocampal neurons replay the same neural discharge patterns off-line during the subsequent sleep periods, seemingly transferring the recently acquired information from the hippocampus to the neocortex. The only contradiction between their work and the REM deprivation and REM enhancement research is that they found the reactivating process occurring during non-REM, slow-wave sleep. These findings broaden the idea that off-line activation processes operate in other phases of sleep besides REM sleep.

To summarize, there is now an accumulation of experimental findings asserting the idea that sleep and in particular REM sleep, has an important role in transforming newly acquired experiences into long-term memories. Most importantly, the strength of the idea comes from supportive evidence from many different techniques and approaches to the question.

REM sleep and the reactivation of remote memories -- looking forward:
Perhaps one of the most important behaviors in higher cognitive functions is the ability to remember events for long periods of time, indeed for a lifetime; obviously, without this ability humans could never have evolved as they have. We need only look at Alzheimer's patients to see how devastating the loss of this ability can be. Therefore, another important question centers on the process of remote neurobiological memories, how they are sustained, and whether REM sleep has a role to play in this process.

One approach to this problem are the studies performed by Witkin and Lewis (1965). Thirty years ago, in a series of studies, they showed highly anxiety-arousing films -- a particularly gruesome circumcision rite performed with stone knives by members of a remote Australian aboriginal tribe, or a very dramatic teaching film, showing the delivery of a baby by a vacuum extraction method -- to subjects just before sleep onset. They found that the content of the film can be easily teased out of the subjects' REM dream reports upon waking that night and in subsequent nights. Actually, the very occurrence of earlier memories reappearing in human dreaming, in itself is presumptive evidence of a naturally occurring reactivating process. Such observations would suggest -- but are at best only presumptive evidence -- that a neuronal reactivating process is operative in the brain during sleep.

Unfortunately, direct evidence of a reactivating process is technically not easy to demonstrate by empirical research. It is profoundly difficult to design experiments, free of alternative interpretations, showing that REM sleep provides the milieu for an endogenous long-term reactivating process. Not to be dissuaded, however, one approach to the question would be the use of subject groups displaying distinctly different amounts of REM sleep. Presumably subjects with higher levels of REM sleep should remember better than subjects showing lower levels. This may be the case. Mice reared in enriched environments have more REM sleep and perform better in learning tasks compared to mice reared in impoverished environments (Gutwein & Fishbein, 1980a, 1980b). Even human studies show that reared children engage in less REM sleep than normal children, and intellectually gifted children engage in more REM sleep (For review see Dujardin et al., 1990). However, like the Witkin and Lewis studies, it is conjecture at best to conclude that these REM sleep differences represent greater (or lesser) availability of a reactivating process, lending itself to better retention in these subjects.

Another way of examining the question of a reactivating process might involve biological manipulation of the REM brainstem trigger zone. Employing techniques that have no direct action on memorial processes, it is possible to selectively raise or lower levels of REM sleep for protracted periods of time. Possibly memory ability may follow the increase or decrease of REM sleep.

In a series of studies that we recently completed, my students and I have made some progress in this direction. Some years ago we discovered that the occurrence of REM sleep is sexually dimorphic; female mice have more REM sleep than males (Bright & Fishbein, 1987) (interestingly, the sexual dimorphism is just the opposite in rats (Pang & Fishbein, submitted for publication)). Furthermore, if the animals are
subjected to prenatal stress (Fishbein & Bright, 1987), or the males are gonadectomized within 24 hours of birth (Yang & Fishbein, 1995), the sleep of males can be converted into female sleep patterns, with significantly more REM sleep.

We performed a parallel memory experiment (Yang et al., 1993) in which normal males, females, and perinatally orchidectomized mice were trained daily in a brightness discrimination, Y-maze shock avoidance task for 25 days. As we suspected, based on our prediction from the sleep studies, the females learn, and reverse learn faster and better than the normal males. On the other hand, castrated males' significantly outperform normal males; the castrated males are in fact indistinguishable from the females. In other studies, it has been found that male rats generally outperform females in spatial learning tasks (Beatty, 1984). This is consistent with our finding that male rats have more REM sleep than females. Although we see these findings as consistent with a reactivating process, we also recognize that this study falls short, too. The study certainly provides more evidence for an augmented consolidation process, but at best circumstantial evidence for a remote reactivating process. Nevertheless, we see the work as a step forward in determining whether the REM sleep reactivation process has a role in preventing experience-dependent neural changes from weakening over time.

Perhaps the model experiment to directly test whether REM sleep is a natural, endogenous process for sustaining memories would be along the lines of the work accomplished by Pavlides and Winson, and more recently performed by Wilson and McNaughton. Evidence of an ensemble of hippocampal or neocortical cells discharging during a learning experience and then shown to spontaneously discharge in the same configuration during sleep, days or preferably weeks or months after the original orchestrated pattern had been acquired, would be very strong evidence of a remote reactivating process.

Clearly, far more resourceful experiments will have to be done before it would be possible to conclude that REM sleep provides a natural brain reactivating process for sustaining memories from the remote past.


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Summary: The origin of both sleep and memory appears to be closely tied to the evolution of mechanisms of enhancement and maintenance of synaptic efficacy. The development of use-dependent synaptic plasticity apparently was the first step in the evolution of nervous systems beyond a capacity to respond to environmental stimuli by mere reflexive actions. Each activation of a synapse with use-dependent plasticity results in a transient enhancement of efficacy. Repetitive activation of synapses, referred to as “dynamic stabilization” (DS), induced either in the course of frequent functional use or by spontaneous neural oscillatory activity, is the likely primate mechanism by which synaptic efficacy enhancements were maintained more lengthily by serially inducing the individual transient enhancements.

One source of selective pressure for the evolutionary origin of neurons with oscillatory firing capacities may have been the need for frequent spontaneous activations to maintain synaptic efficacy in infrequently used circuits, referred to as ‘non-utilitarian’ DS. In many ‘primitive’ invertebrates DS occurs primarily in the course of frequent functional use. But in more advanced cold-blooded, locomoting animals, synaptic enhancements are thought to be maintained both by frequent functional use and by ‘non-utilitarian’ DS that occurs primarily during rest.

As non-sleeping, cold-blooded animals evolved increasingly complex brains, ever greater numbers of synapses in infrequently used circuits required to be reinforced. The selective pressure for the evolution of sleep may have been the need to depress perception and processing of sensory inputs to minimize interference with ‘non-utilitarian’ DS of these circuits.

As warm-bloodedness evolved, with higher body temperatures and metabolic rates, mere muscle hypotonia during sleep apparently was insufficient to prevent sleep-disrupting skeletal muscle contractions in the course of DS of infrequently used motor circuits. Selection against sleep disruption may have led to further decreases in muscle tone during a fraction of non-REM sleep, culminating in the postural atonia of REM sleep. Phasic variations in heart and respiratory rates during adult REM sleep may result from superposition of activations accompanying ‘non-utilitarian’ DS of synapses in redundant and modulatory motor circuits on the rhythmic autonomic control mechanisms. In the course of DS during sleep, some of the information stored in the circuitry being reinforced achieves the level of unconscious awareness as dreams and other sleep mentation.

INTRODUCTION

The year 1966 was marked by two important conceptual advances in neurophysiology: Reffarg, Massion, and Dement conjectured that the main function of the spontaneous, repetitive excitations of neural circuits during REM sleep in the human embryo is to facilitate circuit development and maintenance. They further suggested that circuits are maintained throughout life by such excitations during REM sleep. Guided by studies of human retrograde amnesia, Milner proposed, in effect, that human declarative memories become established in the neocortex through repetitive hippocampal "replay." Both concepts have proved highly fruitful, with further elaborations and experimental support from many investigators.

The first concept provided the seeds for the paradigm of “dynamic stabilization” (DS) of neural circuitry (reviewed in Kavanau, 1994; see also Krueger and Obal, 1993). According to this paradigm, synaptic efficacy in neural circuits storing inherited information ("phylogenetic memories") and information acquired through experience ("ontogenetic memories") is enhanced by frequent synaptic activation. This occurs either in the course of frequent functional use or through spontaneous oscillatory neural activity. Since the spontaneous activations serve only to enhance synaptic efficacy, and usually do not trigger the performance of circuit functions (usually inhibited by increased activation thresholds), the activations are referred to as being ‘non-utilitarian.’ Unless functional DS is referred to specifically in the following, ‘non-utilitarian’ DS is implied.

Pursuing implications and consequences of the phenomenon of DS, has led to the formulation of a chain of causal evolutionary neural links, from primitive synaptic adaptations of cold-blooded animals to the adaptations represented by REM sleep. In this pursuit, causal factors for phasic events of REM sleep and poor memory of dreams, may have been identified.

DS of synapses in infrequently used neural circuits may be the main function of spontaneous oscillations in brain regions during sleep. The efficacy enhancing activations appear to originate in networks of brain neurons whose oscillatory capacities are conferred by intrinsic membrane properties (Llinás and Paré, 1991). One source of selective pressure for the evolutionary origin of neurons with oscillatory firing capacities may have been the need for spontaneous activations to effect DS of infrequently used synapses. In support of this conjecture, single neurons with endogenous oscillatory properties are widely in invertebrates—even in organisms with the most ‘primitive’ nervous systems (for example, jellyfish). Such a need probably is of very ancient origin because, as Bullock has noted, "coordinated spontaneous activity...is a fundamental feature of the most primitive nervous systems."

DS is required for circuit development, maturation, fine-tuning, and maintenance in the embryos of warm-blooded animals. Almost all DS of human fetal circuitry occurs during sleep states, mostly during REM sleep (reviewed in Kavanau, 1994). The situation is extreme in fetal sheep—no wakeful
state exists; all fetal movements appear to represent phasic REM events.

Non-REM (NREM) sleep accounts for 36-50% of human sleep at birth and becomes increasingly dominant in the next 8 months. In the infant and child, intense new learning and highly active growth, synaptogenesis, cerebral development, and organization of the central nervous system are accompanied by large amounts of sleep and extensive self-activations in brain circuitry. Considering these circumstances and the large body of evidence for information processing by the brain during sleep (reviewed in Kavouzian, 1994) leads to a strong presumption that DS during sleep states greatly supports the consolidation and maintenance of phylogenetic and ontogenetic memories in the infant and child. There is no reason to doubt a similar accomplishment of these functions in the adult.

In non-sleeping animals with complex, highly-developed brains and extensive ontogenetic memories, for example, many cold-blooded vertebrates, most DS probably occurs during rest. I have proposed that (a) as brains of ever increasing complexity evolved, DSs of the expanding circuitry became increasingly incompatible with neural activities of rest, and (b) the selective pressure for the evolution of sleep was the need to ameliorate this conflict. The principal activities of the brain during rest, that seem not to be fully compatible with DS, are the processing of sensory inputs.

Just as sleep probably evolved from rest, REM sleep may have evolved by further adaptations of a fraction of NREM sleep. These adaptations may have accompanied the evolution of warm-bloodedness, through selection for more powerful mechanisms of skeletal muscle inhibition during sleep than more hypotonia. In the absence of a more powerful inhibition, skeletal muscle contractions during DS of motor circuitry would have severely disrupted sleep, as in the essentially equivalent pathological "REM sleep behavior disorder," in which dream and executed motor activities—punching, kicking, pounding on walls—closely parallel one another.

A pathway for the origin of mechanisms reinforcing (maintaining) ontogenetic memories also was suggested. Primitive planktonic and largely sedentary invertebrates that inhabit relatively uniform aquatic environments—for example, many coelenterates (sea anemones, corals, jellyfish)—are exposed many times per day to environmental conditions that induce specific patterns of synaptic stimulation in ontogenetic memory circuits. Since the corresponding altered synaptic efficacies would be enhanced repetitively by experience, virtually around-the-clock, there would be neither need nor selection for their lengthy persistence.

As advanced locomotor mechanisms evolved and widely distributed food sources became exploited, the possession of lengthy ontogenetic memories of diverse locales, predatory and escape tactics, utilizable food, etc., became increasingly adaptive. To meet these needs, it is reasonable to assume that DS, the already existing mechanism reinforcing phylogenetic memory circuits, was preempted to maintain the ontogenetic memory circuits as well. In agreement with this proposal, both phylogenetic and ontogenetic memory circuits are equally susceptible to remodelling and other alterations.

MECHANISMS FOR PROLONGING SYNAPTIC EFFICACY ENHANCEMENTS

Temporary, use-dependent enhancements of synaptic efficacy could be prolonged indefinitely with sufficiently frequent activations of DS. However, supplemental mechanisms of later evolutionary origin have provided greater flexibility, whereby, in some circumstances, efficacy enhancements induced by single activations are prolonged more lengthily and can be maintained by DS employing less frequent serial activations.

Long-term potentiation (LTP) appears to be one such mechanism. It is distinguished from most other forms of synaptic plasticity, in that a very brief stimulus may induce alterations of efficacy that are sustained for days to weeks. In a mechanism leading to even longer prolongation, genes that normally are unexpressed, that mediate the synthesis of new messenger ribonucleic acids and proteins, become activated—within a very narrow time window during learning—leading to alterations of synaptic efficacy that last for a few weeks to a month or more.

HIPPOCAMPAL REPLAY

Neuroscientists and psychologists distinguish between two kinds of memory. Declarative memory involves conscious recollection and explicit remembering of facts and events. Non-declarative memory concerns behavioral changes acquired implicitly after many repetitions, such as occurs in skill learning, perceptual learning, conditioning, etc. (Squire, 1992).

Guided mainly by findings on human retrograde amnesia, Eccles expressed the current widely accepted view derived from Milner's original paradigm of hippocampal replay, as follows: in order to effect a 'permanent' consolidation of declarative memory, hippocampal input to the neocortex must be "replayed" for 1 to 3 years, in so-called "recall episodes," much as in the initial experience. Failure of hippocampal replay results in the ordinary process of forgetting, but after 1 to 3 years of replay, the memory circuits in the neocortex usually have become consolidated.

Although Eccles proposed that recall episodes reproduce excitations much as in the initial experience, such specificity may be unnecessary. Evidence supporting this latter suggestion is exemplified by positron emission tomographic findings: as certain motor skills are learned, initial contributions by non-motor regions in the cerebral cortex drop out.

Whereas the hippocampus may be essential for consolidating new declarative memories, it is not a long-term storage site. It temporarily stores incoming information and aids in its retrieval, for example, temporal order of recent events. As indicated above, together with adjacent structures in the medial temporal lobe, it also is thought to direct repetitive interactions with selected, distributed neocortical storage sites that together represent the memory of an event.
These repetitive interactions seemingly bind the storage sites together, eventually leading to their 'permanent' establishment in the neocortex. Within the framework of the DS paradigm, 'permanent' establishment signifies that, after the initial period of dependence on hippocampal replay, encoding synapses in the neocortex are reinforced spontaneously on a 'permanent' basis.

**ELECTROENCEPHALOGRAPHIC CORRELATES**

Rhythmic activity in the adult neocortex, as revealed by EEGs, is pervasive at all times. Human EEGs represent potential differences arising from currents generated by billions of synaptically coupled thalamocortical neurons. In highly aroused and attentive waking states, the EEG consists of low amplitude fast waves (14–30 Hz), the beta rhythm.

In a quiet room, at rest, on closing the eyes, the beta rhythm gives way to primarily high amplitude, synchronized slow waves (8–13 Hz) – the alpha rhythm. This rhythm is blocked by sudden sensory stimuli or mental activity (Winson, 1985). During putative sleep, occurrence of the alpha rhythm usually indicates arousal. Alpha activity increases during early stages of meditation, that have been compared to states of sleep or relaxation.

The major synchronized EEG waves of NREM sleep stages 2–4 are delta waves, spindle oscillations, and the slow sleep oscillation. As a NREM sleep bout progresses, spindles become reduced and progressively overwhelmed by lower frequency (1–4 Hz), high voltage, thalamocortical delta waves. The latter, comprising stages 3 and 4, are also known as slow-wave sleep.

A marked increase in the excitability of the brain’s internal communication systems occurs during REM sleep (Hobson, 1990; McCarley, 1994). The accompanying remarkably complex EEG rhythms lack low-frequency components. Synaptic excitability in thalamic and cortical regions surpasses waking values. Frequent transitory, usually unremembered, arousals during REM sleep often terminate a dream and sometimes initiate lucid dreaming.

Dramatically increased internally generated signals, the ponto-geniculo-occipital (PGO) spikes, occur widely in warm-blooded animals. They are not easily recorded in humans; largely inhibited during waking, they occur only in response to external unexpected stimuli, such as the startle response (Hobson, 1990). PGO spikes are the pacemaker for phasic events of brain activity in REM sleep. Besides heralding onset of rapid eye movements (REMs) and also influencing the movements, PGO spikes indicate a brain arousal state resembling alert wakefulness (McCarley, 1994).

Whereas the neocortical EEG is desynchronized during REM sleep, all marsupial and subprimate terrestrial placental mammals evidence a highly synchronized, almost sinusoidal, high-voltage hippocampal EEG oscillation – the theta rhythm. Infrequent to rare in waking human adults, the rhythm plays an important role in waking infancy and childhood, and during adult drowsiness and sleep. It normally occurs continually during REM sleep. In some animals, for example rodents, it also occurs during movement-related species-specific activities important for survival (Winson, 1985).

Several studies suggest that the theta rhythm facilitates and gates flow of information through the hippocampus to target structures, facilitates synaptic enhancements in these targets, as in the consolidation of declarative memories, and facilitates or induces LTP in hippocampal circuits. Its involvement in learning is attested to the finding of Berry and Thompson that its proportional representation in the hippocampal EEG is highly predictive of learning rates in classical conditioning. The rhythm also occurs during conditioning stimuli in aversive conditioning paradigms.

The hippocampal pyramidal cell firing pattern changes substantially on cessation of exploratory activity and the theta rhythm in the rat. Whereas the majority of hippocampal cells are silent during theta-associated exploratory activity, certain groups of cells begin to fire in synchronous volleys associated with EEG bursts of field irregular sharp spikes (SPWs), which also occur in primates, including humans.

During NREM sleep, immobility, and consummatory behaviors, the population discharge synchrony of hippocampal pyramidal cells and bursts of SPWs are maximal, most frequently during NREM sleep and least frequently during consummatory behaviors. A powerful depolarizing effect of SPW-associated population bursts on postsynaptic neocortical targets, suggests to Chrobak and Buzsáki that the bursts mediate hippocampal replay to the neocortex.

**THE SELECTIVE PRESSURE FOR SLEEP**

The selective pressure for the evolutionary origin of sleep may have been the need to achieve a more profound state of unresponsiveness of the brain to environmental input during DS of memories than during restful waking. Increasing complexity of brains was accompanied by greatly increasing needs for DS of memory stores, which probably led to conflicts with the neural activities of restful waking. If, under selective pressure, voluntary activity ceased, and the brain were relieved of extensive needs to process environmental input, as during sleep, DS could have proceeded unimpededly.

**Sensory pathways**

Sensory input in waking mammals is modified at all levels of incoming pathways. For each sensory mode except olfaction, peripheral information ascends from the thalamus to separate unimodal sensory neocortical systems. Each primary unimodal cortical area relays the information to associated areas, sometimes with convergence of several sensory modalities. Thence the information converges on the entorhinal cortex, where it receives its most refined analysis (Winson, 1983), as well as back to appropriate thalamic neurons. Each sensory system also sends inputs to separate parts of the amygdala, which interprets incoming sensory information and integrates neuromodulatory influences on the storage and strengths of long-term memories, particularly those that are emotionally influenced.
From the amygdala and entorhinal cortex information is relayed to the hippocampus (Hobson, 1989). Thus, if a single perceptual event is formed by the roughly simultaneous receipt of ensembles of sensory inputs, the highest order of perceptual abstraction of these sensory inputs, together with an emotional association, are presented to the hippocampus for processing (Winson, 1985). From the hippocampus, information is relayed to other limbic structures and thence directly and indirectly back to the neocortex.

Interference with information processing

Relaying of higher order sensory information from the amygdala and entorhinal cortex to the hippocampus during active waking very likely is not fully compatible with a simultaneous performance of the latter's relay role and roles of other brain structures in memory processing, as incoming sensory information interacts with the brain's self-generated activities. For example, neuronal activity circulating through cortical and thalamic networks is modified by incoming sensory information. A classical example of sensory interference is alpha blocking by alerting stimuli.

Sleep states and depression of sensory perception

During much of sleep, the perception and arousal value of most sensory inputs are depressed; the degree of depression varies phasically in concert with PGO spikes. Although EEG reactivity to environmental stimuli is increased during NREM sleep, and the amplitude of most primary evoked cortical responses to sensory input during REM sleep is equal to or greater than in waking, one is not awakened by stimuli perceivable during waking.

In effect, the brain is in a modified attentive state, with its attention largely turned away from sensory inputs toward the functions of its internally generated signals (Hobson, 1989), namely, from the present perspectives, toward enhancing synaptic efficacy in labile new circuits and maintaining existing stable circuits. Accordingly, with great depression of sensory perception (and absence of proprioceptive input during REM sleep), circuit consolidation and reinforcing functions of the hippocampus and information processing by other brain structures can proceed unimpededly.

The first step in the evolution of sleep from restful waking

The essence of waking brain function appears to be the processing of sensory input, an enormous amount of which is required by vision (Llimás and Paré, 1991). Viewing this enormous requirement from the perspectives outlined above, the first step in sleep's evolution from restful waking doubtless consisted in closing the eyes (or occluding the iris). For humans, at least, this obviates needs for very extensive processing of visual input and initiates the alpha rhythm. By this tactic we achieve some of the benefits of sleep. [Except for a few sharks, fishes lack eyelids and nictitating membranes, but they are able to occlude the iris by rotating the eyeball.]

Evolution of REM Sleep

Most lines of evidence point to NREM sleep as the primitive sleep state. Sleeping cold-blooded animals, such as reptiles, do not exhibit unambiguous REM sleep, which exists only in warm-blooded animals, and correlates with a highly developed forebrain and cortex. Both sleep states exist in birds, and in all studied marsupial and terrestrial placental mammals.

Motor circuit activation and REM sleep atonia

During NREM sleep, skeletal muscle tone merely is reduced, whereas during REM sleep it is absent (Hobson, 1989). REM sleep atonia is interrupted briefly by the excitatory inputs that produce REMs and other characteristic muscle-driven phasic events. Brainstem phenomena associated intrinsically with REM sleep involve activations in both cortical and subcortical motor areas (Mccarley, 1994). Since the cortex is incapable of making a motor response without marginal departure from REM sleep, the few outbursts of gross movement tend to occur at the beginning or end of REM sleep bouts.

Selection for the evolution of REM sleep

A reduction in skeletal muscle tone during rest or sleep in cold-blooded vertebrates apparently suffices to prevent sleep-disruptive movements during motor circuit reinforcement. But the evolution of warm-bloodedness entailed progressive, very appreciable increases in body temperature and metabolic rate. As metabolic rates increased, mere reduction in muscle tone apparently could not prevent sleep-disruptive movements during DS of motor circuits. Accordingly, evolution of more powerful inhibitory mechanisms was favored.

This circumstance apparently led to adaptive changes in a fraction of NREM sleep, in which skeletal muscle tone merely was suppressed, to produce REM sleep, in which skeletal muscle tone is absent and even sympathetic muscle tone is depressed. In this way, DS of infrequently used motor pathways could have occurred largely during REM sleep without disrupting it.

"Inconsequential Phasic Events"

Numerous minor muscle movements occur during REM sleep. These include rapid eye movements, fine movements of the digits, tongue, small facial (e.g., chin) and middle ear muscles, and muscles of the nape of the neck, resulting from strikingly potent motor excitatory drives that phasically overcome motoneuronal inhibition. In the words of Chase and Morales, "...the underlying motor control landscape is actually ravished by storms of inhibition and brief whirlwinds of excitation directed toward the final common pathway, the somatic motoneuron."

Additionally, strong phasic variations occur in muscle-driven autonomic activities, influencing, most notably, heart rate and respiratory rate and amplitude but also affecting arterial blood pressure. These phasic occurrences in the adult are referred to as "inconsequential phasic events." During ontogeny, on the other hand, the phasic muscle contractions
or tremors that accompany DS of the developing motor system are indispensable for maturation of neuromuscular junctions and muscles.

Neural networks and multiple interactive neural systems

I have been referring to a need to reinforce circuits in infrequent functional use, as if fixed one-to-one relationships exist between functions and neural substrates. The existing relationships are pursued in greater depth here. Pertinent data concern the extensive redundancy of neural circuitry, and the presence of extensive modulatory circuitry.

In the last two decades it has been established that neural networks can serve several functions. Different types of neurons in a network may belong to different systems, assemblies, and subassemblies, each contributing to the work of the whole. Complex functions may be supported by several circuits, the 'multiple interactive neural systems' approach.

Consistent with these views, recent studies indicate that the cortical memory trace is widely distributed, that multiple, parallel, and widely dispersed cortical areas are dedicated to single sensory functions and modalities, and that motor control involves distributed storage sites in multiple cortical areas. Moreover, mosaics of neural substrates for given functions occur in both cortical and subcortical regions.

The respiratory system provides the best example of a widespread existence of redundant control and modulatory circuitry. As detailed by Orem, structures that can control brainstem and spinal respiratory neurons exist at all levels of the CNS. In addition to concentrations of respiratory neurons in the medulla, neurons related to respiration are found in the amygdala, the anterior cingulate gyrus, the orbital frontal cortex, and the mesencephalic central gray matter. Influences also can be achieved by stimulation of cerebellar and other subcortical and limbic structures. Awake, attentive humans can breathe rhythmically despite severe damage to medullary regions that once were believed to be indispensable, implying the existence of a corticospinal respiratory projection that can drive breathing via a neural complex causal to the medulla.

Redundancy of neural circuitry

Circuitry redundancy is well illustrated by lesion studies. Cats retain certain skilled pattern discriminations despite 98% complete bilateral optic tract lesions. Patient recovery is possible following 97% pyramidal tract destruction. People over age 65 remain intellectually well preserved after cerebral lesions that temporarily reduce or cut off blood flow to as much as 50 ml of tissue. Auditory thresholds are not altered significantly after extensive bilateral ablation of the temporal cortices of dogs and cats. Recovery of auditory language comprehension is possible after lesions of less than 50% of Wernicke's cortical area. Lesions of structures in the basal ganglia and connecting fibers of rats must exceed 60% before behavioral impairments become detectable.

Need to reinforce ancillary circuitry

In view of extensive redundancy of brain circuitry, one cannot conclude that circuitry associated with frequently occurring functions requires no reinforcement by DS during sleep. Much ancillary circuitry associated with a frequently occurring function may be unused much of the time that the function occurs. The existence of redundancy even in flatworm brains, and of spontaneous activity in the most 'primitive' nervous systems, support the view that DS may have been the primordial means of serially prolonging otherwise transient use-dependent enhancements of synaptic efficacy.

Fulfillment of the requirements for DS of extensive ancillary circuitry for motor functions in the brains of warm-blooded animals may underlie the occurrence of inconsequential phasic events of REM sleep. These probably occur as activations of DS phasically overcome motoneuronal inhibition.

Chase and Morales describe the situation being attributed here to the consequences of DS of ancillary motor circuitry, as follows. "Thus, from time to time for reasons as yet unknown, excitatory drives overpower inhibitory drives, motoneurons discharge, and the muscle fibers that they innervate contract.... When motoneurons do discharge during the REM periods of active sleep, their activity, as well as the resultant contraction of the muscles that they innervate, is unlike that which occurs during any other state. Movements are abrupt, twitchy and jerky, and without apparent purpose." In Parmeggiani's words, "[r]emarkable in REM sleep is...the difficulty in establishing any physiological rationale for the [autonomic] changes... which are] difficult to explain in terms of homeostasis."

Though otherwise perplexing, these unusual movement characteristics and other inconsequential phasic events of REM sleep, including phasic variations in heartbeat and involuntary respiration, could be explained by random contractions and antagonistic sympathetic and parasympathetic influences, such as might be expected from largely 'functionally uncorrelated' activations of DS of redundant and modulatory motor circuitry.

DREAMING AND POOR DREAM RECALL

Within the context of the preceding analyses, a few tentative steps can be taken toward elucidating the origin and evanescence nature of dreams. The view championed by Hobson and McCarley and also espoused by Greenberg and Antrobus is that dreaming, though it may be influenced by preceding events and pre-sleep emotional states, is a byproduct of and tightly linked to, mental activities normally occurring during REM sleep. Based on the non-visual dreams of the blind and those of patients with certain brain damage (for example, faceless people populate the dreams of prosopagnosic patients), one also can conclude that dream mentation and waking perception operate on the same neuroanatomical substrates (Linds and Paré, 1991). This analysis supports the above cited views, specifying the "mental activities" as the consolidating and reinforcing of circuits storing memories, but not restricting the activities to REM sleep. In adopting these views, one does not deny that dreaming may serve ancillary or secondary functions.
A long-standing puzzle of dreaming has been, why dreams are remembered poorly. Responding from the present perspectives, dreaming is a very short-term unconscious awareness of manifestations of processes of activating selected ensembles of labile ontogenetic memory circuits (say, younger than 3 years) to render them stable, and of stable phylogenetic and ontogenetic memory circuits (say, older than 3 years) to maintain them.

But no mechanism exists, nor would it be adaptive, to make new records of manifestations of the process of reinforcing or consolidating ensembles of old records. That would be the equivalent of keeping a record of manifestations of each night's record keeping. Included in the record of one night's record keeping would be a record of the record keeping of the previous night, which itself would include a record of the record keeping two nights earlier, etc. Keeping such redundant records, which would tend to increase exponentially, would overwhelm our brains with tremendous amounts of useless new information (records of record keeping).

The tendency of dreams to favor current events, the "day residue" of Freud, and of these dreams to be lengthy coordinated and, sometimes not far short of authentic recall, may owe to the integrative role of the hippocampus in replaying only relatively recent events to the neocortex. The fact that a vividly recalled dream can repeat with fidelity over a period of many years suggests that the hippocampus also can integrate and replay memory circuits established through dream recall. On each repetition and recall of a salient dream, it apparently can again achieve the status of a recent event, thereby entering again into hippocampal replay.

SUMMARY OF PROPOSED EVOLUTION OF NEURAL ADAPTATIONS

On the basis of the foregoing treatments, one can suggest the following chain of causal evolutionary links, from the most primitive neural adaptation of cold-blooded animals to the neural adaptations represented by REM sleep in warm-blooded animals.

DISCUSSION

Most of the different brain waves characteristic of sleep, and some of those of waking, probably reflect relatively non-specific requirements for reinforcing fairly broad categories of synaptic efficacies. Also represented among the waves during sleep, though, must be the activations whose primary function is to maintain sleep states and to allow DS to proceed with maximum interference.

There is no reason to believe that the 'non-utilitarian' excitatory regimens of DS need closely reproduce (replay) those of the initial experience of an event. Nor is there any reason to believe that, after sleep evolved, any type of circuit reinforcement occurred only during sleep. The evolution of sleep in response to the proposed selective pressure would be consistent with sleep's independent origin in different taxa, as is suggested by its somewhat discontinuous taxonomic distribution.

With spontaneous, endogenous activations of the sleeping brain being primarily for the purposes of extending and maintaining its functional capacities—regardless of whether normal or impaired—it would be evident why EEG sleep studies have been unable to provide sound diagnostic criteria for psychiatric disorders, and why deprivation studies to elucidate sleep functions have produced little or no evidence of deterioration of mental function. A few night's lack of circuit reinforcement need not impact seriously on brain performance; to a certain degree functional capacities can be extended and maintained by synaptic enhancements during waking, as in animals that do not sleep.

REM sleep deprivation, alone, would be expected to be even less impacting, as redundant mechanisms of the phylogenetically older NREM state probably can compensate partially in maintaining synaptic efficacies normally reinforced during REM sleep. Thus, REM sleep deprivation can lead to an increase in NREM dreaming, increased heart-rate variability, and increased incidence of PGO spikes. The most significant losses during limited periods of sleep deprivation probably occur in the realm of ancillary physiological imperatives, such as bodily rest and rejuvenation.

The proposal that the waking processing of sensory input is not fully compatible with simultaneous neural activities that serve to establish and maintain long-term memory is not meant to imply that brain function is ill adapted. Rather, it suggests that some or many of the circuits employed in sensory reception and processing also are employed in the establishment and maintenance of memory, and that a full implementation of both functions cannot be achieved simultaneously. Rest or sleep accompaniments circumvent this limitation, yielding overall adaptedness.

This treatment has dealt only with apparent manifestations of 'non-utilitarian' DS of motor, cognitive, and sensory circuitry (inconsequential phasic events and dreaming) largely during REM sleep. Manifestations of DS of ancillary non-motor circuitry regulating physiological processes (e.g., hormone secretion) also may occur but be largely undetected.

In contemplating the likelihood that 'non-utilitarian' circuit reinforcement in the CNS occurs largely during sleep, we come close to regarding activations of these circuits in sleeping and active waking brains as differing primarily in sources and consequences of input to the higher centers. In active waking brains, most maintenance and extension of neural capacities are accomplished by functional reinforcements brought about by unprogrammed external stimuli, and accompanied by waking experiences. In sleeping brains, most maintenance and extension of neural capacities are accomplished by 'non-utilitarian' reinforcements brought about by programmed internal stimuli, and accompanied by NREM sleep mentation and dreaming.
<table>
<thead>
<tr>
<th>State of Life</th>
<th>Selective Pressure</th>
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<tr>
<td>Highly active or demanding at home</td>
<td>for short-term memory (synapses that learn)</td>
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<td>Current environments</td>
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<tr>
<td>Overactive, highly diverse environments</td>
<td>for more lengthy maintenance of synaptic efficacy enhancements</td>
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<tr>
<td>Advanced lifestyles and senses, including highly developed vision; cold-blooded</td>
<td>for DS of vast memory stores without interference from sensory perception and processing</td>
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<tr>
<td>Warm-blooded</td>
<td>for sleep undisturbed by DS of motor circuitry</td>
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REFERENCES

News and Comments

Club Hypnos

Members who will be attending the Society for Neuroscience meeting this fall should plan to attend the first annual reception held by Club Hypnos on Tuesday, 11/14 from 5:30 to 7:30. The Board authorized Adrian Morrison and Michael Chase to organize this SRS-sponsored event as a way to publicize opportunities in sleep research. We are especially eager to have uncommitted students get to know our field. Look for more details in the final meeting program.

Sleep Researchers From The Indian Subcontinent

Sleep researchers who are from the Indian subcontinent (India, Pakistan, Bangladesh and Sri Lanka) are invited to gather in front of the registration desk on Friday, June 2nd at 6PM. We can then go out for dinner. In past APSS meetings we have done this and it has been very enjoyable.
The National Sleep Foundation Dinner

“The National Sleep Foundation is proud to announce the first Annual Research Dinner at the 1995 APSS annual meeting in Nashville on Wednesday, May 31 at 7:30 p.m. This event is organized by the Pickwick Club of the National Sleep Foundation and the evening’s entertainment features noted Dickens scholar and speaker, Professor Elliot Engel and includes a full course dinner with wine, music, and an auction.

Building on the excitement and enthusiasm generated by last year’s Pickwick Club reception, the Organizing Committee, chaired by William C. Orr, Ph.D., is planning an evening of camaraderie among associates dedicated to furthering the field of sleep medicine. Last year a tradition was born when a first edition manuscript of Charles Dickens’ *The Pickwick Papers* was auctioned for a tidy sum and graciously donated back to the NSF for future contributions.

The Foundation believes that funding scientific research in sleep medicine and promoting the work of young sleep investigators is critical. We invite everyone with an interest in the field of sleep to join us in supporting this important cause.

Individual seats for the research dinner are $150.00, however group tables of ten identifying your sleep center or geographic region can be reserved for $1,000. In addition, various levels of corporate sponsorship are available for this event. All proceeds will go to support sleep research by funding fellowships on an annual basis. For reservations or more information on corporate sponsorship, please call Reid Blank at (202) 785-2300. Seating is limited, so please make your reservations early.

The World Federation Of Sleep Research Societies 2nd International Congress: The Mystery Of Sleep

The World Federation of Sleep Research Societies will be having its 2nd International Congress on September 12-16, 1995, at the Crystal Palace in Nassau, the Bahamas.

For further information, please contact:

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POSTDOCTORAL RESEARCH POSITION

The Biological Rhythms Research Lab at Rush-Presbyterian-St. Luke’s Medical Center, Chicago, Illinois is seeking an individual who is interested in research on light, melatonin or exercise for shifting human circadian rhythms in simulated night shift studics. Participation in a winter depression treatment study may also be possible.

Fax to (312) 942-6050 or write.

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