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Review

Interaction of REM and non-REM sleep with memory

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ABSTRACT

Numerous studies on the function of sleep have been conducted, getting a great deal of information. One of them is the effect of sleep on memory. Investigations have been performed to see how sleep and wakefulness affect the outcome of memory-related tasks such as learning and skill development, and it has been observed that the sleep state yields better results. After identifying rapid-eye movement (REM) sleep and separating sleep into REM and non-rapid-eye movement (NREM), the memory interaction of sleep in these two stages began to be examined separately. Because there are neurochemical, electrophysiological, and neurobiological differences between these two stages of sleep, and these differences influence showing the effect of sleep on memory in different ways and at different times. To prove this idea, research and hypotheses dealing with these two stages separately were conducted, and the interaction of sleep and memory was tried to be explained. The findings revealed that sleep is an important factor in memory consolidation and that different periods of sleep have a beneficial effect on different types of memory.

Keywords: Memory consolidation, memory, non-rapid-eye movement sleep, rapid-eye movement sleep, sleep, slow-wave sleep.

Sleep is a behavior that is characterized by reduced response to the environment and temporary unconsciousness. The two-process model of sleep, defined by Alexander Borbély, explains sleep and wakefulness as a cycle that occurs through a circadian and homeostatic process. The homeostatic process can be explained as the need for sleep increases as the amount of time spent awake increases, and this needs closing when we sleep. Likewise, the circadian process is the process that determines when we will sleep and wake.[1] In mammals, sleep is divided into two stages: rapid eye movement (REM) and non-rapid-eye movement (NREM). The reason for this is that sleep is not homogeneous, with differences in neurochemical, electrophysiological, and neurobiological aspects between these two stages. Non-rapid-eye movement and REM sleep repeat each other throughout the night. Each repetition, beginning with NREM and ending with REM, is referred to as a sleep cycle.[2] Although the length of this cycle varies by individual, it is repeated 4-6 times during sleep.

Non-rapid-eye-movement sleep is the stage that begins earlier and it lasts longer than REM. At this stage, electroencephalography (EEG) activity begins to slow. It is divided into four stages as a result of the formation of various EEG activities within itself. The first two stages (N1 and N2) are referred to as shallow sleep, while the last two (N3 and N4) are referred to as slow-wave sleep (SWS). Physical rest is achieved at this stage since there is a decrease and improvement in heart rate and respiratory rate in general. Growth hormone is also known to be secreted during the NREM process. This is particularly important during childhood, as children who do not get enough sleep may experience growth retardation.[1]

Rapid-eye-movement sleep is shorter in duration than NREM sleep and occurs after that. In the case of narcolepsy, sleep may begin with REM. Electroencephalography activity rises again during this phase, similar to the waking state.

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The periodic eye movements that characterize REM sleep give it its name. Outside of the REM phase of sleep, periodic eye movements are not visible, and they occur and disappear in this phase. Rapid-eye movement sleep is also referred to as paradoxical sleep. This is due to the fact that the muscles lose tone at this stage and the brain performs a function similar to waking even though the body is asleep.

Memory is formed in general by the activity of the medial temporal lobes and hippocampus, and long-term memory and short-term memory are classified under headings. Long-term memory is classified as explicit (declarative) memory and implicit (non-declarative) memory.

Implicit memory can be defined as spontaneous, unconscious memory. This memory is defined as automatic events such as habits and skills. There are four types of implicit memory, including priming, procedural, associative, and non-associative. Explicit memory is the memory that is consciously learned and recalled. It includes episodic memories that are easily learned and forgotten in a spatial context, as well as stored facts, i.e. semantic memories that are independent of contextual information.[3]

Memory formation consists primarily of the steps of encoding, combining, and retrieval. Memory is divided into three major subprocesses: encoding, consolidation, and retrieval. Memory consolidation means the process of stabilizing the memory trace and connecting it to old information. This is basically what we call combining. After that, the processed memory is accessed and recalled. Studies have shown that memory traces are not consolidated all at once, but are reconsolidated to ensure long-term persistence with factors such as remember and recall.[3]

The brain is optimally engaged in encoding and recalling during the waking period, stabilizing and combining processes are thought to provide more suitable conditions for the sleeping brain. Furthermore, they are thought to be separated from each other because the coding and consolidation processes occur in overlapping neuronal sources.[3]

When memory formation is considered at the neuronal level, it is based on changes in the synaptic connections in the memory network. The neuronal effect of coding is that it induces long-term potentiation (LTP) and long-term depression (LTD). It is thought that the consolidation that takes place after coding occurs in two different ways: synaptic consolidation, which leads to a permanent synaptic change by the formation of the synapses and dendrites of the neurons representing the memory, and system consolidation, which occurs when the neuronal activity resulting from synaptic consolidation is distributed to other systems to become more permanent.[3,4]

SLEEP AND MEMORY INTERACTION

Sleep has been shown to help memory consolidation in both animals and humans for over a century. Jenkins and Dallenbach's 1924 study was one of the first to demonstrate the effect of sleep on memory.[5] It was attempted in this study to compare the subjects' recall levels after sleep and wakefulness. According to the data, recall after sleep was higher than recall after waking. Studies have been conducted to elaborate and better explain this relationship by considering memory as explicit and implicit memory, sleep as REM, and NREM.[6]

Initially, studies on REM sleep were emphasized. This is due to the fact that REM sleep has higher cortical activation than other parts of sleep. With this feature, it was thought to be a better time for consolidation.[7] Although some studies on the changes in REM sleep after training revealed an increase in REM sleep after various tasks, this was not observed in all studies. This caused the focus to shift from REM sleep to NREM sleep.

Sleep-memory consolidation hypotheses

The dual-process hypothesis postulated that the consolidation of different types of memory is supported by different stages of sleep. Slow-wave sleep has been shown in studies to have an effect on implicit memory, while REM sleep has an effect on implicit memory. The results supporting this hypothesis were generally obtained from studies using the split-night paradigm.[8] The split-night paradigm is basically subjecting the person to the first SWS-dominated midnight sleep or the second REM-dominated midnight sleep after learning. Slow-wave sleep was found to support hippocampus-dependent

explicit memory, while REM sleep was found to support implicit memory in these studies. Studies on the effect of sleep stage deprivation on memory consolidation have also produced results that support this hypothesis.

In a study, it was observed that 40 minutes of sleep with no interruptions other than restarts was insufficient to support memory consolidation, but 40 minutes of sleep with odor-marked restarts was similar to and sufficient to a 90-minute sleep without odor cues.[9] The fact that 90 minutes of sleep was more supportive of memory consolidation than 40 minutes of sleep was attributed to the time spent in SWS. According to the findings of this study, depending on SWS density, sleep has a beneficial effect on memory consolidation due to the hippocampus. While this effect lasts 90 minutes in the natural sleep course, it can be accelerated with odor cues.

Procedural memory, which is a part of implicit memory in the dual-process hypothesis, is also mentioned. Procedural memories are more skill-based. Therefore, visual-motor-based learning styles are used in their research. In comparison to explicit memory, the hippocampal area plays a minor role in procedural memory. Although it is thought that REM sleep supports this memory in the dual-process hypothesis, the results of the studies are insufficient to support this.[10] In a study that supported this hypothesis, the effect of sleep on the development of manual dexterity was examined.[11] The study results revealed that sleep outperformed wakefulness in memory formation for motor skills. It has also been demonstrated to have a significant correlation with the amount of time spent in REM sleep. However, in some studies, the effects of NREM sleep rather than REM sleep on combining procedural memory have been found to be noteworthy. This has raised questions about whether the effects of REM sleep are confused with the effects of stress caused by sleep deprivation.[10] Another hypothesis developed to describe the relationship between sleep and memory is the sequential hypothesis, which states that the cycle of NREM and REM sleep aids in memory formation and explains this as follows: The first step is attenuation of maladaptive memories and reinforcement of congruent memories during SWS; the second step is the storage of compatible memories that were previously reinforced during REM by integrating them with already existing information. This hypothesis is supported by studies that show it is more beneficial not to disrupt the NREM-REM sleep cycle when keeping words throughout the night.[12] However, this hypothesis was unsatisfactory to distinguish between the effects of NREM and REM sleep on memory.

The active system consolidation hypothesis also combines the dual-process and sequential hypothesis.[13] It emphasizes the importance of the unity of NREM and REM sleep in memory processes and examines the neuronal mechanism that provides consolidation. According to this hypothesis, in the SWS phase of NREM sleep of the hippocampal neuronal repeats, hippocampal-neocortical information flow, and cortico-cortical through strengthening the connection are reinforced memory.[14] It is also thought that the slow waves that occur during this phase of sleep facilitate this reactivation. The effect of REM sleep is explained as the stabilization of these changes.

Another hypothesis proposes that the increase in protein synthesis caused by slow-wave activity in NREM sleep is necessary for late LTP, implying that SWS sleep plays an important role in converting early LTP to late LTP.[15] Due to the ponto-geniculo-occipital (PGO) waves, theta synchronization, increased acetylcholine, and the increase in transcription in genes associated with plasticity in neurons that are characteristic of REM sleep, it has been thought that it provides a suitable environment for LTP and LTD, synaptic plasticity necessary for learning and memory formation in the hippocampal complex.

Sleep and synaptic plasticity

Synaptic plasticity refers to changes in synapses. These changes may include synaptic strengthening and weakening, the number of synapses between neurons, and the distribution of receptors. Although synaptic plasticity is most intense during the ontogenetic period, it persists until the end of life. It is also the foundation of learning and long-term memory.

Synaptic plasticity develops in response to synaptic activity, and the Hebbian synapse is a

key model for it.[16] In this model, it is assumed that learning properties can occur in neural networks by strengthening only the synaptic inputs that provide the activity of the postsynaptic neuron and weakening the others. This argues that the neurotransmitter secreted from the presynaptic neuron should be effective as long as it activates the postsynaptic neuron. In other words, it should contribute to the strengthening or weakening of the synapse. Synaptic potentiation and depression are defined by the size of the postsynaptic neuron's potential (PSP-postsynaptic potential) induced by the presynaptic neuron. This potentiation and depression last for hours to weeks. For this reason, they are referred to as long-term potentiation and long-term depression. Long-term potentiation occurs in the hippocampus as a result of short-term and high-frequency stimuli, and this stimulus should be excitatory and high-frequency. Long-term potentiation can emerge in various ways in different regions, even in the same synapse. This is important in memory storage and the formation of special neuron teams.[1] In animal studies, cells with different firing patterns were observed in certain parts of the CA1 and CA3 regions of the hippocampus, and these cells were termed place cells. These are hippocampal pyramidal neurons that form LTP during the spatial learning period, showing that spatial memory is formed in the hippocampus depending on LTP.[1] This idea has also been supported by research showing that LTP suppression impairs spatial memory.

Although it is known that LTP has important effects on memory, if synaptic connections were only increased and strengthened, after a point they would eventually be unable to grow any more. At this point, the necessity of LTD emerges. LTD is basically the suppression of stimuli in the cell that do not provide an ignition. Unlike LTP, it requires long-term and low-frequency stimuli to form. Although the behavioral role of this event, which is defined in the cerebellum and hippocampus, is unknown, it is thought to prevent LTP saturation and play an important role in memory storage.[1]

Several studies have been conducted to investigate the relationship between sleep and synaptic plasticity. These studies prove that sleep is an important factor in synaptic plasticity.[17] In a study on cats, it was found that sleep causes an increase in cortical synaptic plasticity during a period known to be critical for visual development in cats.[18] In another study, REM sleep deprivation resulted in a prolonged postnatal period for the production of a developmentally important form of LTP in rats.[19]

As a result of studies examining the relationship between sleep and memory, the relationship between synaptic plasticity and sleep has also been tried to be explained. Furthermore, enriched environments that support synaptic plasticity are formed with an increase in the amount of sleep, especially REM sleep, after learning, and it has been concluded that sleep deprivation after learning impairs task acquisition.[16]

NREM SLEEP AND MEMORY

The effect of NREM sleep on memory has been proven in studies, with positive effects on tasks such as remembering learned faces and words and negative effects on visual-motor tasks due to SWS sleep suppression.

An experimental technique known as targeted memory reactivation is used to demonstrate the contribution of NREM sleep memory reactivation.[14] In a study they conducted to test the idea that newly encoded memory traces are reactivated and consolidated during sleep using this technique, Rasch et al.[20] found that slow-wave sleep has an effect here. Their work is basically the use of the scent of roses given during learning as a clue to the person during sleep.

As a result of the studies, it was observed that administering the scent during any period of REM sleep had no effect. During the SWS period of NREM sleep, an improvement was observed in the consolidation of hippocampus-dependent implicit memory, while no effect was observed in non-hippocampus-dependent implicit memory. Studies have also been conducted to examine the effect of inhibiting slow waves in sleep as well as the sharp waves and ripples seen in the hippocampus.[21] In a study, rapid oscillations, known as ripples were observed in the CA1 region of the hippocampus during slow-wave sleep and were prevented by training.[22] As a result, performance impairment was found in rats trained for this study. This supported the idea that the ripples in the SWS are responsible for transferring memory traces from

the hippocampus to the neocortex for long-term storage.

It is also possible to examine the effect of NREM sleep on memory at the cellular level. When the cholinergic activity occurring during SWS was applied lower than normal conditions, gene expression related to plasticity could not occur, limiting the induction of LTP, which is associated with memory consolidation.[14] Sleep is also known to contribute to the formation of dendritic spines in neurons following motor learning. These dendritic spines form in response to different learning tasks. They prevent extra knowledge from being eliminated when more than one thing is learned. When deprived of NREM sleep after motor learning, specific spine formations of neurons were prevented, and deterioration in neural activity began to occur. These results indicate that NREM sleep plays an important role in the formation of synapses, which are responsible for memory storage, as well as in the protection of these synapses.[4]

REM SLEEP AND MEMORY

Since the definition of REM sleep, which is characterized by periodic eye movements, and the division of sleep into REM and NREM, the interaction between sleep and memory has been associated with sleep stages. At first, the idea that newly formed memory during REM sleep was reactivated while dreaming predominated.[23] The results of studies that tested this idea were not as expected.

Discussions arose that the results of the REM sleep deprivation technique, which was applied to differentiate the effect of REM sleep, were not very efficient due to the stress factor created in the studies. Among the antidepressants used to suppress the REM sleep, monoamine oxidase inhibitors (MAOIs) are suppressed almost completely, but tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) caused a decrease in the range of 40-85%. As a result, there was no significant decrease in memory consolidation.[24]

In another study, night sleep was divided into two groups: early and late-night sleep.[25] This helped in distinguishing between the results of SWS, which was intense in the first half, and REM sleep, which was intense in the second half. Explicit memory was examined using a word list task consisting of related pairings, and the development of procedural memory, i.e. implicit memory, was tested using a mirror tracking task. The results showed that the first half, the SWS-intensive period, provided significant support in consolidation to explicit memory in the word list task, and the second half, which was intense from REM sleep, to procedural memory in the mirror-viewing task. In addition, this study supports the dual-process hypothesis by demonstrating that the effects of different sleep periods on different areas of memory are distinct from one another. However, similar to the logic of this study, other studies focusing on different memory types and tasks have also been conducted and have yielded interesting results.

In one of these examples, the contributions of SWS in early sleep and REM sleep in late sleep to the retention of two neutral and emotional texts were examined.[26] The results were supported by REM sleep when high emotional material was present in a task where other studies have shown slow-wave sleep in light to be more effective. This led to the idea of REM sleep is more effective at reinforcing emotional memories.

When we looked at animal studies with sleep deprivation after learning, it was observed that memory consolidation was impaired when insomnia was applied during certain periods of REM sleep.[27] These are post-training periods with an increase in REM and are called paradoxical sleep windows (PSW) or REM windows. Delays in PSW onset are observed within a few hours or days of training.

The complexity of the task is effective in the degree of deterioration in REM sleep deprivation after training.[27] REM sleep deprivation does not pose a major obstacle in behaviors that can be considered as simple as simple maze learning and passive avoidance. However, challenging tasks such as complex maze learning, conditioning, and discriminant learning are more susceptible to REM sleep deficiency. It has also been observed that when the animal reaches a certain level of learning, the lack of REM sleep affects it.

In some rodent species, REM activity includes PGO activity, which creates waves (P waves) that spread from the pons to other of the brain.[28]

Several studies have suggested that these waves have an effect on memory consolidation. Datta et al.[29] found that in REM sleep, different parts of the brain stem are activated to produce different signals in conjunction with P waves.[30] P waves generated with the help of a P wave generator have been shown to improve learning even in REM sleep deprivation. These results were thought to support the hypothesis that P waves have a role in memory consolidation due to REM sleep.

Sleep is a physiological event that is known to be very important in the lives of all living things, but there are many unknowns about how it works and its effects. There have been numerous studies on the unknowns of sleep. Sleep has been observed to have a beneficial effect on memory consolidation, and this effect is being tried to be detailed. In these studies, various tasks and methods are used to examine different aspects of sleep and memory. For example, SWS and REM sleep compared was possible using the split-night paradigm. In the sleep deprivation method, data were obtained by focusing on a certain sleep period. It was tried to observe how different types of memory were affected by sleep based on the characteristics of the given tasks. Despite all of the work that has been done, there are still many points that have not been clarified. This is due to the fact that the interaction of sleep with memory performance varies depending on the task and experimental design, and that cannot be explained. It is well known that different stages of sleep have a supportive effect on some steps in the development of different types of memory, and examining the effects of these stages separately is a complex process. This has a negative impact on research and the development of the subject. The method of the study is another factor that contributes to inconsistencies in studies. In studies conducted by deprivation of selected stages of sleep, the stimuli used to cause deprivation cause changes in the person's sleep patterns, attention disorders, stress, decrease in motivation, and deterioration in biological rhythm, and these non-specific effects can affect the results of insomnia by affecting the behavioral potential. When the effect of sleep on memory was examined at the neuronal level, synaptic plasticity, or changes in synapses, drew attention.

In conclusion, it is known that synaptic reinforcement (LTP-reinforcement) occurs in neurons in response to learning. Although the effects of LTD, or synaptic depression, are not fully explained, it has been observed that it plays a role in balancing LTP and memory storage. Studies have shown that sleep supports memory by increasing synaptic plasticity. It is thought that new studies will aid to understand the uncertainties of sleep, which will help to answer questions about memory.

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