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NEUROPSYCHOLOGICAL STUDY OF THE SLEEP-LEARNING RELATIONSHIP

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Summary

The objective of this study is to describe the relationship between sleeping and learning. The hippocampal neuron possesses an outstanding plastic capacity needed for learning. The so-called long-term potentiation is produced in them as a selective mechanism for strengthening the synapses activated during learning. We can objectivise this potentiation thanks to the description of the theta rhythm that appears when learning occurs. However, this rhythm also appears during sleep, so we ask, "Does a relationship between sleep and learning exist?" And if so, in which sleep phases? The existence of neuronal activation during sleep similar to that produced during learning tasks has been demonstrated both in experiments with sleep deprivation techniques and with new imaging techniques. Based on recent experiments with selective deprivation of the different sleep stages we can suggest that the processes related to memory and learning that occur during sleep begin in the deep phases of slow sleep and are consolidated during REM. The question that arises is how the different sleep phases influence the synaptic plasticity that underlies all learning processes. It has recently been demonstrated that a relationship between sleep and the neuronal growth factor exists. This means, as a final conclusion, that there is also a relationship between sleep-neurotrophic factors-brain circuits-learning.

Key Words: Learning, Sleep, Neuronal Growth Factor, Memory, Plasticity, Theta Rhythm, Long-term potentiation.

Discussion

From the neuropsychological point of view, we understand learning to be the process by which we acquire new knowledge; the process by which we retain this knowledge throughout time is called memory. The forms of learning that require a conscious register are called explicit learning. In humans the so-called temporal lobe (especially the hippocampus), among other cerebral structures, must function perfectly for explicit learning. The hippocampus, which received this name because of its likeness to the seahorse, processes the information recently acquired for a period of weeks or months; it is later transferred to other nerve structures for a longer storage.

In 1973 Bliss and Lomo (1973) demonstrated that hippocampus neurons posses a significant plastic capacity of the type needed for learning. They reported that brief trains of high frequency stimulation to monosynaptic excitatory connections in an isolated slice of hippocampal tissue caused an abrupt and sustained increase in the efficacy of synaptic transmission. This increase was specifically reflected by increases in the amplitude of excitatory postsynaptic potentials. The effect occurs within milliseconds of stimulation and can persist for hours and sometimes days. The effect (long-term potentiation, LTP) has been considered to be a physiological base of memory (Uchida et al. 2001). They observed that a brief series of high-frequency action potentials in one of the hippocampal neural pathways intensified the synaptic strength in that pathway. This strengthening has been shown to last for hours in an anaesthetised animal, and even days in an awake animal that can move freely. Bliss and Lomo (1973) called this strengthening "Long-term Potentiation" (LTP). The principal neuronal paths of the hippocampus use the amino acid glutamate for transmission. This produces LTP when it joins the glutamate receptors of the target cells. There are two types of glutamate receptors: NMDA (N-methyl-D-aspartate) and non-NMDA. Non-NMDA dominate most of the synaptic transmission because the ion channel associated with the NMDA receptor is usually blocked by Mg. This block disappears when the postsynaptic cell is depolarised. For NMDA channel activation to be optimal, two signals are needed simultaneously: glutamate positioned in the receptor and postsynaptic cell depolarisation. Thus, the NMDA receptor has associative or detector properties of this simultaneous situation.

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The affluence of calcium towards the inside of the postsynaptic cell through the NMDA receptor channel is decisive for long-term potentiation. Calcium initiates LTP, activating at least three different types of kinase proteins. LTP induction seems to depend on the postsynaptic depolarisation that induces calcium flow and subsequent kinase activation, while LTP maintenance is due to an increase in the transmitter that leaves the presynaptic terminal.

If LTP induction requires a postsynaptic episode (which makes calcium flow into the NMDA receptor channels) and LTP maintenance implies a presynaptic event (greater transmitter liberation), then some message must be sent from the postsynaptic to the presynaptic neurons. Calcium activates the pathways of the second messenger, or perhaps the direct intervention of calcium liberates a factor of retrograde plasticity from the active postsynaptic cell. This retrograde factor then reaches the presynaptic terminals to activate one or various messengers that promote transmitter liberation and thus maintain LTP.

These LTP have been proposed as a selective mechanism for strengthening synapses activated during learning episodes. This would result in a stabilization of the network that codifies the information. When NMDA receptors of the hippocampus are blocked, animals cannot learn a task set for them.

Having briefly considered the mechanisms by which learning can produce changes in the neurons, from the neuroanatomic point of view, a new question emerges: How can we objectivise the fact that the basic cerebral mechanisms underlying learning are taking place?

In physiological studies of the hippocampus, a theta range (4-7 Hz) rhythmic oscillation known as the hippocampal theta oscillation or rhythmic slow activity (RSA) has been observed in many kinds of animals. This has drawn the attention of neurobiologists because of its possible functional role in memory.

The hippocampal theta oscillation was first described by Jung and Kornmueller (1938), who found a 5-6 Hz regular rhythmic oscillation in the non-anesthetized rabbit hippocampus. Later, Green and Arduini (1954) reported hippocampal theta in both rabbits and cats in the wake state. This rhythm appeared on animals when they felt uneasy due to stimuli from outside. Individuals who are awake seem to show this rhythm when they assume behaviour crucial for survival. That is to say, theta rhythm appears when individuals use behaviour not determined genetically, but rather constituting a response to information from a changing environment.

A sleep researcher reported the next notable discovery of the hippocampal theta oscillation. Jouvet et al. (1959) reported that in cats theta rhythm was a prominent feature of hippocampal activity during paradoxical (rapid eye movement (REM)) sleep. Almost simultaneously, Shimazono (1960) independently reported the same findings in dogs. Theta EEG activity has become one of the criteria for scoring sleep stages in animals. Since the medial temporal lobe was known to play an important role in mnemic functions after the case report of HM (Scoville and Milner 1957), these finds were soon combined to support a possible hippocampal function in memory (Uchida et al. 2001) As, specially, the theta rhythm was registered in the hippocampus during this sleep phase and the hippocampus intervenes in mnemic processes, presence of theta rhythm during REM sleep in this brain region could be related to another activity, was thus proposed that theta rhythm reflected a nerve function by which information vital for species survival accumulated during the day was reprocessed in memory and during REM sleep.

Theta rhythm constitutes the natural method through which the NMDA receptor in hippocampus neurons is activated. During REM sleep, although no information entry or movement exists in this sleep phase, the network formed by the neocortex and the hippocampus is covered by the theta rhythm. This is then capable of provoking some modification of the long-term memory.

But has the existence of this rhythm been demonstrated in humans?

Using electrocorticogram (ECoG) recordings of epileptic patients, Uchida et al. (2001) have demonstrated during wakefulness signals from the human medial temporal lobe of two distinct frequency oscillations, beta-1 (10-20 Hz) and gamma (30-150 Hz) (Hirai et al. 1999a, b). Since the hippocampal theta rhythm in non-human animals changes between NREM and REM sleep, they have examined how these frequencies change across all-night sleep in humans. They found that the beta-1 oscillation was also present during REM sleep. In contrast, gamma activity was present in all sleeping and awake states, although it decreased slightly during slow wave sleep. The researchers concluded that activity in the beta-1 band did exhibit characteristics similar to animal hippocampal theta, appearing during both wakefulness and REM sleep. They hypothesized that the human beta-1 may be a functional equivalent of the animal hippocampal theta rhythm.

According to Poe et al. (2000), a relationship exists between the theta rhythm phase and the human beta-1 in animals that appears during sleep with synaptic potentiation. During REM sleep release increases from hippocampal neurons that have been active during periods of previous alertness. The results described by these authors show that experience affects the release patterns of these neurons during REM sleep, which suggests a mechanism involving the hippocampus, by which cerebral circuits used in recent experiences are strengthened.

All of this leads to new questions: Is there a relationship between sleep and learning? Can we pinpoint the phase where it occurs?

A variety of experiments support an affirmative answer to the first question. Authors such as Henevin et al. (1995) focused on the effects of paradoxical sleep deprivation on learning and the changes learning has on REM. Such studies lead us to infer that the relevant information processing is possible during this sleep stage, that new association can be formed during REM sleep and that the information previously learned can be transferred to the awake state. All of this makes us suppose the dynamic processes taking place during post-learning REM can contribute to memory efficacy.

Experiments involving intensive language courses by De Koninck (1989, 1990) lead to the conclusion that learning demands induce a need for more REM sleep (rising from 19% to 21%, a significant increase). In fact, he proposed that REM activity reflects cognitive pressure and daytime learning. In 1996 Dotto (1996) stated that cognitive memory decreased with REM sleep deprivation, while declarative memory and motor task memory in stage 2 non-REM sleep were not affected. In 1997 Youngblood, showed in experiments with Wistar rats that selective deprivation of paradoxical sleep caused a decrease in spatial memory.

New imaging techniques are currently being used in the field. Maquet et al. (2000) used Tomography by positron emission and measurement of cerebral blood flow to demonstrate that experiences learned while awake influence cerebral activity in different areas during sleep. He showed that some areas activated when performing new tasks while awake were also significantly activated during later REM sleep.

Our second question was, "Can we pinpoint the sleep stage in which learning-related activity occurs?" In 2000 Stickgold et al. (2000) and Gais et al. (2000) both developed different studies to determine if REM sleep is singly related to learning, or whether short-wave sleep was also involved. They reached the conclusion that the sequence of slow waves followed by the REM stage in the first night after the new experience is needed to achieve optimum consolidation of learning, specifically in procedural learning. In the same line, Born et al. (1999) used a test of visual discrimination to find out which sleep stage is essential for memory consolidation. He reached the same conclusion that a period of initial short wave sleep followed by periods of REM sleep was needed.

If we accept the fact that sleep is associated with memory consolidation, and we have seen that hippocampal neurons are involved in this function, how do the different sleep stages influence synaptic plasticity, the natural phenomenon that underlies each learning process? Sei et al. (2000) has presently opened an exciting new focus that can begin to reveal the ultimate reasons for this crucial sleep function. Based on the well-known connection between the neural growth factor (NGF) and synaptic plasticity, he studied the relation between deprivation of different sleep stages in experimental animals. He has demonstrated that there is a decrease in NGF in the hippocampus after six hours of selective sleep deprivation. This indicates the relationship existing between sleep-neurotrophic factors-memory-learning.

Other authors (Sengpeiel 2001), following this line of research, have developed different laboratory experiments that show a relation between cortical plasticity and sleep.

Conclusions

1. Human beings present few or no physiological alterations after several days of sleep deprivation, but they do show a decrease in intellectual performance (Kandel et al. 2001).
2. It becomes continually clearer that one of the functions of sleep is information reprocessing and memory consolidation (Smith 1995, Picornell and Gil-Verona 1996, Gil-Verona and Gomez 2001).
3. The greatest learning is accompanied by an increase in the number and duration of REM episodes.
4. With new imaging techniques (PET), a similar pattern of neocortical activation has been shown to exist during tasks of new learning acquisition and REM sleep. This suggests that such reactivation during REM sleep reinforces what was learned.
5. Following studies of selective deprivation of different night sleep stages, it seems that the processes related with memory and learning that take place during sleep begin in the deep stages of slow sleep and are consolidated during REM sleep.
6. The synaptic plasticity needed to produce consolidation of what was learned during the day is due to the relationship between sleep-neurotrophic factors-memory-hippocamponeocortical circuit reactivation-learning.

As a final conclusion, we can say that current investigations suggest that sleep is increased following a learning session and that memory improves following a sleep session. This is a fascinating area of study that, although promising with respect to its results, needs further work. First of all, an adequate analysis of these aspects with respect to humans should be carried out. Secondly, there has to be additional investigation from all points of view, especially the neuropsychological, to specify exactly which of the two sleep stages are involved and to what degree they are needed to consolidate what has been leaned. Finally, the

effects each of these stages has on synaptic plasticity, the neuronal phenomenon that underlies the learning process, should be studied.

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