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Effect of sleeping on memory and learning

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1. Abbreviations

AMPA-R - α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic aid receptor

CaMKII - calmodulin dependent protein kinase

cAMP - 3´-5´-cyclic adenosine monophosphate

CREB – cAMP response element binding protein

EEG – electroencephalogram

IEGs – immediate-early genes

LTM – Long-term memory

LTP – Long-term potentiation

NMDA-R - N-methyl-D-aspartate receptors

NREM – non rapid eye movement sleep

PER1 – Period 1

PGO - ponto-geniculo-occipital

PKA – Protein kinase A

REM – rapid eye movement sleep

SCN – Superchiasmatic nucleus

SWA – slow wave activity

SWS – slow wave sleep

2. Abstract

Sleep plays a key role in the cognitive function of all higher vertebrates and as of quite recently, invertebrates too. The definite reason for its function and different stages it not yet completely understood, but the newest research and research methods are discovering more and more than what we knew just a few years ago. The discovery of the electroencephalogram (EEG) in 1924 was revolutionary within the science of sleep physics because it made it possible to study the brain-wave changes of animals and humans during sleep, and how they change throughout the night. It has also been proved in several experiments on both animals and humans that there is a correlation between sleep, lack of sleep and learning and memory ability. Researchers are now trying to map out which of the sleep stages are important for the different types of memorization.

To understand this literature review, the basics of sleep must be understood, with all its regulations and steps. The regulation itself is very complex, especially since there are so many factors playing a part, sometimes down to molecular levels. Sometimes even slight disruption in the homeostasis of sleep can have severe consequences like psychotic disorders in humans, or in the worst case, even death. The process of memorization is also not a straight line, and as with sleep, several new terms and hypothesis are being made and discovered. One of these terms are reconsolidation, the hypothesis that a stable long-term memory trace being recalled can lead to transient destabilization, meaning it can be changed, discarded or reconsolidated and stored again.

The effect of the different stages and types of sleep on memory consolidation and reconsolidation depends on different factors. Some of these factors are e.g. whether or not the memory is declarative or procedural, how you measure gain of skill, or animal species. For memory consolidation, the context between REM sleep and NREM sleep is valid for mammals and avian, because, as of right now, these are the only species showing this kind of differentiated patterns in their sleeping cycle.

3. Introduction

What happens when we sleep, and how does this effect our everyday life? Why does cats sleep on average 15h a day, dogs 12-14h, while humans need on average 8h of sleep? In this literary review, I will write about how sleep affects your learning abilities, which phases of memorization is affected, and which phases of sleep are most important for the latter. This can be helpful in understanding how the mammalian mind and body work, and the best approach for conditioning and consecutive rest. To do this, how sleep affects the body on a physiological level will be described, what factors regulate sleep, even down to a cellular level. The importance of this is that some of the pathways found during sleep regulation is similar to those found during memorization processes (Müller, 2012).

It is well known that sleep is critical for an optimal cognitive function in humans, and mammalian species. Articles has also shown that certain invertebrates show states that can be categorized as sleeping, but not necessarily as detailed and complex as the humans' sleep, e.g. not prominent differentiation between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Miyazaki et al., 2017). Even for invertebrates has sleep and cognition been connected, as newer investigations show increased activity in brain-regions during sleep that is known to be important for learning (Miyazaki et al., 2017; Rattenborg et al., 2011; Müller, 2012). A study done by Müller in 2012 described how the molecular basis of learning and memory in some invertebrate species (*Aplysia, Drosophila,* honeybees) is based on the same concept as higher species; modulation of the strength of synaptic connections between neurons.

The newest information about how memories are stored and retrieved will also be summarized, as new theories about the "restorage" of memories are under development. This "restoring" is called reconsolidation and is now getting more acceptance as an important term when talking about the memory storage process. To understand how reconsolidation works, consolidation must first be understood, as they are subsequent events and can almost be considered synonyms. Before consolidation occurs, encoding on molecular level will be described, to get an understanding of what happens when a memory is stored in our neural pathways.

4. Sleep

On average 1/3 of our lifetime is spent asleep (Mandal, 2019). Descriptions of sleep have been found from all the ancient civilizations, in Indian sages, from the Egyptians, the Greeks and Romans, all describing sleep in a different way. Alcmaeon (450 BC) suggested sleep is a spell of unconsciousness brought on by lack of circulation to the brain, while Aristotle (350 BC) stated that its rather an arrest of consciousness deriving from the heart (Thomas, 2018). It wasn't until the 1900 after discovering the neuron, scientists really could start to try to describe the physiological processes of sleep (Mandal, 2019; Thomas, 2018). Especially the last half century, there has been a big focus on the study of sleep, as it shows correlation to a lot of psychiatric illnesses and physiological consequences (Brown et al. 2012; Cellini, 2016). It seems, that the more we discover about sleep, the more important its homeostasis seems to be for optimal life-quality.

Sleep is a state that is different from death, coma and hibernation, in the fact that its rapidly irreversible. It is an unconscious state that all animal species depends on, where the reaction to environmental stimuli is reduced (Carley and Farabi, 2016). It is also a state that changes throughout life. The pattern and physiology are not the same for a baby and an elderly person (Carskadon, 2011). Sleep is divided into two main sorts: rapid eye movement (REM) sleep, and non-rapid eye-movement (NREM) sleep, where the latter is divided into further 4 (3) different stages. These stages represent a continuum of relative depth. Every stage is unique, and has its own characteristics, e.g. amount of eye movements, variations in brain wave patterns, and muscle tone. But the sleep-wake cycle is not only regulated by the 4 stages of sleep, it also depends a lot on the circadian clock – our biological clock, that secretes hormones promoting the interplay between two major processes maintaining wakefulness, called Process C, or promoting sleep, called Process S, which advances throughout the day (Goel et al., 2013).

4.1 Sleep architecture in vertebrates and invertebrates

The basic structural organization of normal sleep divides it into two, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is further divided into 4, sometimes 3 phases; 1, 2, 3 (+4), which all differs in characteristics both physiologically, and in brain-wave activity, evaluated using an electroencephalogram (EEG). An EEG monitors the brains electrical impulses and brain activity during sleep and awake states. In 2007, the American Academy of Sleep Medicine (AASM) reclassified stage 3 and 4 of NREM sleep into one collective stage, Stage N3 (McNamara et al., 2007). There are still educational systems using the 4 different stages, like the VCAA of Victorian Australian educational practice, and for this reason the 4 stages will be described separately.

An article written by Miyazaki et al. (2017), stated that all the animal species, both vertebrates and invertebrates, investigated during their experiment exhibited sleep or sleep-like states, suggesting that sleep may benefit survival. Further, they found that mammalian and avian species shows both NREM sleep and REM sleep, but it is only hypothesized if the stages have unique roles in the different animals relating to learning and memorization. NREM and REM sleep alternate cyclically during a period of sleep. Why we have these two different types of sleep is not yet totally understood, but it is concluded that the lack of either stage is associated with several sleep and psychological disorders (Mandal, 2019). E.g. low levels of stage 4 sleep and abnormal REM sleep is associated with acute and chronic Schizophrenia (Hiatt et al., 1985).

A normal human sleep cycle starts with a period of NREM sleep. Stage 1 is the first, followed by stage 2, 3 and 4, and ending with REM sleep. This sequence is called one sleep cycle, and on an average night several cycles happens during one sleep period. The length of each cycle changes throughout the night, where the first cycle is on average 70-100 minutes, while the next once has an average of 90-100 minutes. NREM consists of 75-80% of the total time asleep, while REM sleep only consists of 20-25%. In human adults, the REM sleep increases as the night progresses, and is longest in the last third of the sleep episode. Stage 2 will account for the majority of NREM sleep, while stage 3 and 4 will sometimes disappear totally or mash together (Colten and Altevogt, 2006).

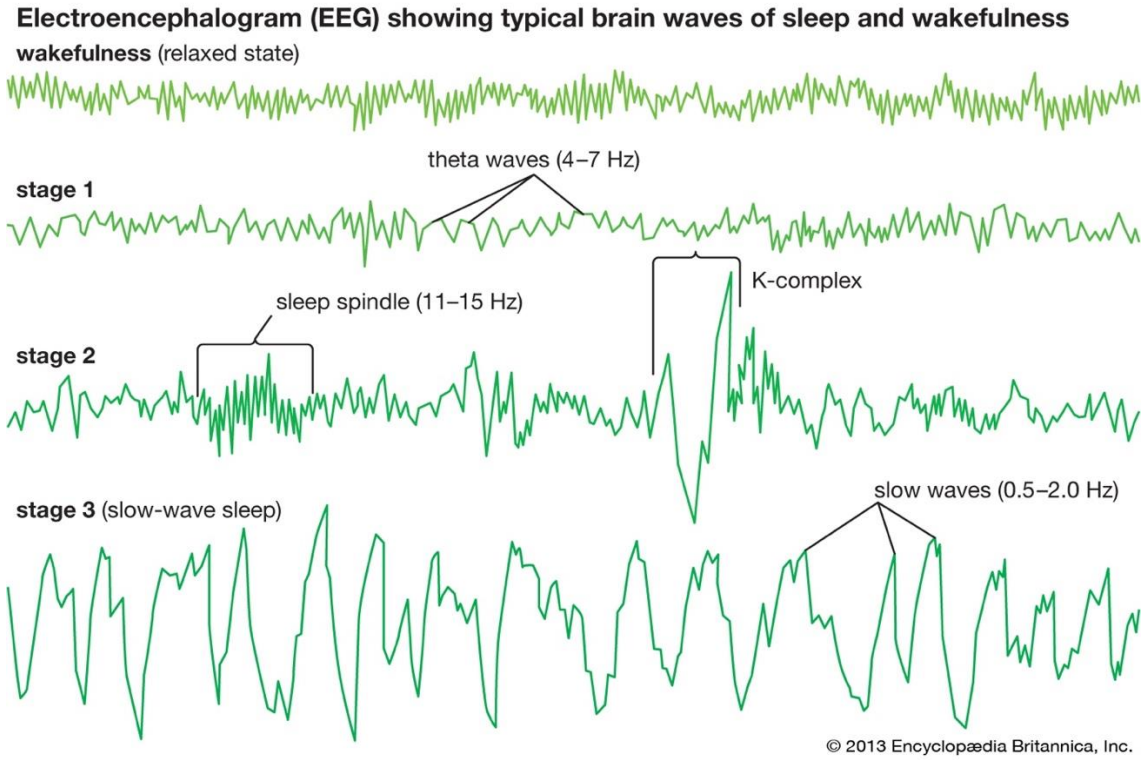

Figure 1: A demonstration of what a human EEG looks like during sleep and wake states. In relaxed wakefulness alpha-waves are prominent, characterized by a frequency between 8-12 Hz (Colten and Altevogt, 2006). During stage 1 the density of the waves decreases, and this stage is characterized by theta waves which are between 4-7 Hz. In stage 2, sleep spindles are characterized by a high density of spindle activity between 11-15 Hz. K-complexes are also characteristic for stage 2, and they are recognized as sudden burst of wave activity. In stage 3 SWS is characterized by slow waves with a frequency spectrum between 0.5-2.0 Hz (Encyclopædia Britannica, 2013).

Stage 1 of NREM sleep has more of a transitional role. It is sometimes referred to as relaxed wakefulness (Colten and Altevogt, 2006). A normal person's sleep starts in this phase. It lasts normally for 1-7 minutes in the initial cycle and will comprehend approx. 2-5% of total sleep during a sleep period. This phase is very superficial, and can be interrupted easily, especially with load noises. The EEG waves shows a transition from wakefulness to sleep, expressed as low-voltage brain waves to mixed-frequency brain waves. Alpha waves appear, and theta waves disappears (Brown et al., 2012).

Stage 2 lasts longer; 10-25 minutes in the initial cycle and getting longer each cycle. Of a total sleep episode, stage 2 will comprehend 45-55%. This phase is not as superficial as stage 1, so a more intense stimuli is needed to wake up (Colten and Altevogt, 2006). The

EEG are characterized by low-voltage mixed frequency activity with presence of sleep spindles and K-complexes. K-complexes have an important function in the physiological homeostasis during sleep, as it regulates respiratory rate and heart rate, while the sleep spindles are associated with memory consolidation (Albouy et al., 2013). Based on Albouys´ experiment, the individuals learning a new task have a significantly higher density of sleep spindles than those in the control group.

Depending on the literature you read, stage 3 and 4 can either be described as 2 different stages, or one stage together, since they both are categorized as slow-wave sleep (SWS) (Colten and Altevogt, 2006). It occurs mostly during the first third of the night. Stage 3 lasts for only a few minutes, constituting about 3-8% of sleep. In this stage the EEG shows increased high-voltage, slow delta waves (Brown et al., 2012). Stage 4 lasts longer, usually between 20-40 minutes during the first cycle, making up 10-15% of the total sleep episode. In this stage, our sleep is at its most profound, and requires more stimuli to be interrupted than the others (Colten and Altevogt, 2006).

When connecting sleep physiology with memory encoding, consolidation and retrieval, there are certain aspects of the sleep physiology in humans that should be explained in more detail. K-complexes seen during stage 2, together with spindles and other slow waves are considered to be isolated slow waves that are triggered by external or internal stimuli on a background of lighter sleep (Nir et al., 2011). SWS has shown to show to play a crucial role for memory consolidation. More specifically, the EEG slow wave activity (SWA) and spindle activity. The typical definition of SWA is EEG power during SWS in the 0.5-4.0 Hz frequency band (Nir et al., 2011). Slow oscillation is important for the up and down regulation of neural network activity. During slow oscillation, most of the neurons are in a down-state, meaning most of them are hyperpolarized, while during the subsequent depolarization, the firing activity increases (Vorster and Born, 2015). The slow oscillation is generated primarily within neocortical networks, partly as a function during wake periods. Spindle activity is the depolarized up-state of the neural networks, and in the sleep EEG spindle activity it refers to waxing and waning oscillatory activity between 12 and 15 Hz. This activity forms distinguished spindles during NREM sleep stage 2 but is also present during SWS (Vorster and Born, 2015).

REM sleep is characterized by the presence of low-voltage, mixed frequency brain wave activity, muscle atonia and bursts of rapid eye movements (Colten and Altevogt, 2006). In the first cycle, it only lasts for 1-5 minutes, but as the other stages, it gets longer and longer throughout the night. The EEG shows slow alpha activity, theta activity and "sawtooth" wave forms, similar brain patterns to when a person is awake (Brown et al., 2012). The muscle atonia plays an important role as this is the phase where dreaming is associated, and without it, the person dreaming would be able to react to the dream physically. 89% of vivid dream recalls results after arousal form this stage of sleep. REM sleep might be beneficial in both nondeclarative and procedural memories (Born et al., 2006). In animals, REM sleep is characterized by ponto-geniculo-occipital (PGO) waves, which are associated with intense bursts of synchronized activity from the pontine brain stem, and by hippocampal theta (4-8 Hz) activity. In humans PGO and theta activity are less readily identified. These waves have been proposed as a mechanism promoting plastic processes underlying memory formation during REM sleep in cats and rats (Rasch and Born, 2013).

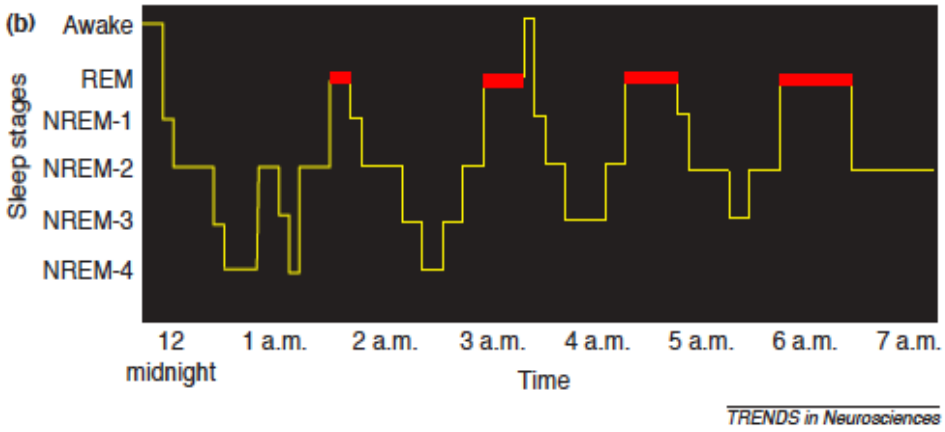

Figure 2: An example of a normal human sleep cycle throughout the night. REM sleep (colored in red) gets longer and longer throughout the night, while stage 1-4 have a more even dispersion. Source: Stickgold and Walker, 2005

The differences between NREM and REM sleep are numerous. This table summarize the most important physiological differences between the two during a normal night cycle.

Table 1: Physiological changes during REM and NREM sleep. Based on Colten and Altevogt, 2006

Physiological Process	**NREM**	**REM**
Brain activity	Decreases from wakefulness	Increases in motor and sensory areas, while other areas are similarly to NREM
Heart rate	Slows from wakefulness	Increases and varies compared to NREM
Blood pressure	Decreases from wakefulness	Increases up to 30 percent and varies from NREM
Sympathetic nerve activity	Decreases from wakefulness	Increases significantly from wakefulness
Muscle tone	Similar to wakefulness	Absent
Blood flow to brain	Decreases from wakefulness	Increases from NREM, depending on brain region
Respiration	Decreases from wakefulness	Increases and varies from NREM, but may show brief stoppage, coughing suppressed
Airway resistance	Increases from wakefulness	Increases and varies from wakefulness.
Body temperature	In regulated at lower set pint than wakefulness, shivering initiated than during wakefulness.	Is not regulated, no shivering or sweating, temperature drifts toward that of the local environment
Sexual arousal	Occurs infrequently	Greater than NREM

4.2 Physiology during sleep

How the body changes during sleep differs between species, and as mentioned in the table above, which phase of sleep you are in. These physiological changes are normally tolerated quite well by both humans and other mammalian and avian species. One of the many definitions of sleep, describes certain physiological states which all mammals, avian and invertebrates have in common (Goel et al., 2013. Miyazaki et al., 2017).

The cardiovascular system is controlled by the autonomic nervous system throughout the night. It causes changes in blood pressure and heart rate, with short increases with K-complexes, arousals, and large body movements (Lugaresi et al., 1978). During awakening, there is a sharp increase in heart rate and blood pressure. The deeper the NREM sleep is, the lower the sympathetic-nerve activity is, but certain bursts of activity happens following the K-complexes in stage 2. Its level of activity increases during the REM sleep (Somers et al., 1993).

Respiration flow during sleep becomes increasingly faster and more erratic, especially during REM sleep. During NREM sleep, the body hypoventilates, but still maintains a good oxygen saturation. Factors influencing the respiratory physiology during sleep are many, e.g. decreased pharyngeal muscle tone, reduced rib cage movement and increased upper airway resistance due to decreased intercostal muscle tone (Krieger et al., 2000).

The blood-flow to the brain and cerebral blood flow is significantly different in NREM and REM sleep, where during REM sleep certain parts of the brain (limbic system, and visual association areas) have increased activity and blood flow, while during NREM it is decreased. The renal blood flow decreases secretion of sodium, potassium, chloride and calcium during sleep, allowing the urine to be more concentrated and prevents the need to urinate in the middle of the night. Other changes in renal flow during sleep are quite complex, and they are found in both the renal blood flow, glomerular filtration rate, hormone secretion and sympathetic neural stimulation (Colten and Altevogt, 2006). Even certain hormones are secreted at a different rate during a sleep cycle. GH secretion starts within the first hours of sleep, while thyroid hormone secretion, on the other hand, takes place in late evening.

Melatonin is a hormone that induce sleepiness by reducing an alerting effect from a tiny region in the hypothalamus called the suprachiasmatic nucleus, and is influenced by the light-dark cycle, suppressed by light. Body temperature changes during sleep, due to the circadian system. During the night there will be a falling phase, where the body temperature decreases and heat loss increases, before it rises again close to awakening, sending a physiological signal that it’s time to disrupt sleep and promote waking (Troynikov et al., 2018).

4.3 Sleep-Wake Regulation

4.3 I. Two-process model

One of the first models that tried to describe the influence of sleepiness on prior sleep loss, time awake and circadian phase was developed by Borbély (1982) and was called the "Two-process model of sleep regulation". In this model, there are two processes regulating the onset and offset or the sleep and wake cycle; a sleep dependent process/ homeostatic process (Process S) and a sleep-independent circadian process (Process C). Process S is a function of prior sleeping time and shows an exponential decline during sleep and increase during waking. Process C is mostly reflected through REM sleep, as this phase is not dependent on prior waking time. The interplay between these two processes is only one of many ways to describe the regulation between a sleep state and awake state (Goel et al., 2013).

4.3 II. Circadian rhythm

The circadian rhythm is the near 24-hour oscillations in behaviors that are found in almost all organisms. This term is used as a collective term for several processes: 1) general states, such as daily alteration in sleep and wakefulness, 2) behavior, e.g. eating and walking, 3) physiology, such as body temperature, heart rate or muscle strength, 4) endocrine profiles, such as secretion of cortisol or growth hormone, and 5) tissue/ cellular oscillations (Gillette and Abbott, 2005). Both animals and plants possess endogenous clocks - organizing their daily and physiological rhythms with the external day-night cycle (Hiddinga et al., 1997). The circadian rhythm is also referred to as the biological clock, with its regulation-center located in the hypothalamus. The suprachiasmatic nuclei (SCN) neurons function as the master of circadian rhythms. The neurons located here, exhibiting more activity across the day, and less activity at night. Their input comes from a class of nerve cells in the retina, acting as brightness detectors. They also reset the clock genes on a daily basis. After receiving the signals, the SCN transmits them to the rest of the brain, before body signals brings all daily cycles in synchrony with the external day-night cycle (Buhr and Takahashi, 2013). The way it effects sleep is through a series of relays in the dorsomedial nucleus of the hypothalamus, which signals the wake-sleep systems to coordinate their activity with day-night cycles. This is only valid for organisms that experience light on a daily basis. For

animals and other organisms living in complete darkness most of their life, other physiological and genetic mechanisms help regulate their rhythm, but often longer than 24 h (Cavallari et al., 2011).

4.3 III. Molecular components of the mammalian circadian clock

The circadian clock mechanism also involves a cell autonomous transcription-translation feedback loop comprised of a core set of genes, that are highly conserved among animals, and expressed in a nearly 24-hour rhythm (Takahasi et al., 2008). For the regulation of the circadian molecular clock, the gene Period1 (Per1) plays a key component, because it is synchronized by the environmental light-dark cycle through the glutamatergic retino-hypothalmic tract. Clock genes like these (Bmal1, Period1/2, and Cryptochrome), are tied to circadian rhythms in all mammals and invertebrates. Clock and Bmal1, goes into the cell nucleus and bind to specific genes like Period1/Period2 and Cryptochrome to activate them (Daisuke and Yamanaka, 2016). They act like negative feedback on Clock and Bmal1, preventing them from binding to DNA again. Their products, as a result, will exhibit a rise and fall pattern of expression, with a periodicity close to 24 h. According to Goel et al., inconclusive investigations has been done on some of these clock genes to see if there is a link between them and behavioral circadian phase preference, suggesting that these traits are polygenic, influenced by several genes (Goel et al., 2013).

In addition to homeostatic mechanisms, circadian rhythms can also have an effect on memory processing and post-learning sleep through the regulation of transcription and translation within various brain regions, e.g. hippocampal gene expression and enzyme activity differs throughout the day (Takahashi et al., 2008). An example that supports this theory can be found in an experiment done by Eckel-Mahan et al. (2008), where they showed that certain molecular phosphorylation's (e.g. cAMP response element binding protein (CREB)) and increased cAMP (3´-5´-cyclic adenosine monophosphate) levels experienced circadian oscillations in the hippocampus, and by interfering with these (pharmacologically and physiologically) the maintenance of long-term memory was impaired. This can indicate that the reactivation of the cAMP-CREB pathway is influenced by circadian rhythms (see figure 3). Induction of sleep by stimulating sleep-regulating neurons, promotes the formation of long-term memories, and this effect is again canceled

by sleep deprivation (Wilckens et al., 2016). The clock genes may play a role in temporally restricted expression of the effects of learning in sleep (i.e. increased slow wave activity confined to the first few hours of sleep) or to explain why sleep still can be beneficial, even though it is delayed to later the same day (Korman et al., 2007). Genetic models focusing on clock genes and their role in sleep-memory interactions will maybe unlock more of the mysteries concerning sleep and memory interactions.

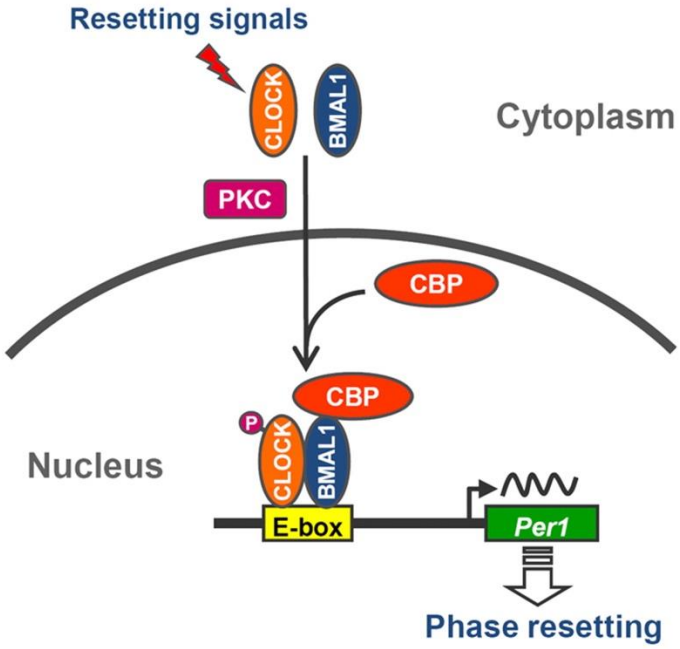

Figure 3: Proposed mechanism of Clock-Bmal1-mediated phase resetting of the circadian clock via CBP recruitment. Showing heterodimerization and nuclear translocation via Ca-dependent protein kinase C (PKA) pathway causing the CREB-binding protein to be recruited to BMAL1 in the nucleus. These genes are responsible for the expression of Per1 and Per2 genes, which are the genes that resets the circadian clock. E-box is the upstream regulatory region of target genes (Per1 and Per2) and the binding-site in the nucleus where Clock and Bmal1 attaches to their receptors. It is also a period 1 promotor, and an upstream regulatory region.
Source: Lee et al., 2004

4.3 IV. Homeostatic and circadian control of sleep-dependent memory processing

The regulation of sleep is not only regulated by changes in gene expressions and modification of proteins, but also by increased adenosine during sleep deprivation and increases in SWS when trying to pick up on lost sleep (Vassalli and Dijik, 2009). Another factor that plays a part is the amount of impressions and experiences a person processes during the day, as it has been shown to increase the length of NREM and REM sleep the subsequent night (Hellman and Abel, 2007). This should be taken into consideration when studying, as it can accompany learning-dependent alterations, giving more time for electrophysiological properties (e.g. power) of sleep-associated oscillatory events including sleep-spindles, expanding the time for memory consolidation. Learning-dependency increases the need for more sleep, consequently increasing the need for more SWA during NREM sleep. This is because of the higher number of sleep-spindles activated in the brain during the night enhances performance (Hanlon et al., 2009). On the other hand, Walker et al. showed that if you double the quantity of initial training during a finger tapping motor task, the amount of sleep-dependency didn't change, while in more difficult motor sequences sleep was more beneficial (Walker et al., 2003).

For associative learning paradigms (e.g. fear conditioning), the post-learning changes in sleep architecture and oscillatory patterns might depend on the difficulty of the task. In 2010, Steenland et al. did an experiment on rats with effects of trace fear conditioning with associative strength between a conditioned (a tone) stimulus (CS) and unconditioned (a foot-shock) stimulus (US) to see if there was changes in sleep architecture depending on the difficulty of the task. The difficulty of the task was regulated by prolonging the duration of trace time – the interval between termination of CS and start of US. The mice conditioned for a 15 sec trace, showed significant enhancement of delta power during NREM sleep relative to baseline the next night. For the other group of mice, the trace was 30 seconds (increased difficulty), but the enhancement in delta power was not significant. This advocate that learning and plasticity increases need for sleep and that memory enhancements can be modulated by the sleep's electrophysiological properties.

5. Memory

The term memory cannot be considered a single entity, due to its many categorizations and different meanings. Normally, it is divided into two systems, declarative and non-declarative memory, while its process is divided into three sub-categories: encoding, consolidation and retrieval (Vorster and Born, 2015). To better understand how we memorize things, it is important to keep in mind that the body´s physiological state is not constant throughout the day, going through several neural and metabolic activity changes. One of the most obvious changes during a 24h day is the difference between sleep and wake state. And like sleep, the memorization process goes through several steps, physiological and neurochemical changes (Lu et al., 2018; Stickgold and Walker, 2005). The two main systems mentioned above will be explained, together with different types of memories and learning-processes. To start with, the definition of learning and memory should be differentiated, where leaning is the acquisition of new knowledge/skill, while memorization is the retention of this learned information.

5.1 Declarative and Non-declarative memory

There are two different kinds of long-term memories, called declarative and non-declarative, or implicit and explicit memory. Declarative memory is used to describe facts and events that we can consciously recall and is often what is meant when the term memory and remembering is being used. This kind of memory was called declarative to signify that it can be consciously retrieved and "declared" (Squire, 1992). Other terms to describe this category is explicit or rational memory. The brain regions that are active during processing of an explicit memory is the hippocampus, amygdala and the neocortex (Lu and Woodruff, 2017).

This category is further divided into episodic and sematic memory. Episodic memory is the autobiographical life-experiences, e.g. first time going to a new country, first time visiting the beach (Curran and Morgan, 2014). It describes events that has happened in the past. Sematic memories are the memories of facts we recall when needed, e.g. capital of a country, name of previously owned dog. Declarative learning often involves sematic (rather than episodic) learning that requires acquisition of new explicit knowledge, such as word pairs associated during a learning phase (Carskadon, 2011).

Non-declarative memory, or implicit memory, is a collection of nonconscious, skill-based kinds of learning, often involving a motor component, such as typing a numerical sequence (Carskadon, 2011). First described in 1975 by Winograd as a procedural memory, used in contrast to declarative memory. They were memory phenomena that did not fit the category of declarative memory, but were not accommodated by the term procedural, which is why the term non-declarative was suggested by Squire (Squire, 1992). Non-declarative memory is further divided into 4 groups: procedural skill, priming, non-associated, and conditioning.

Procedural skills and habits are associated with the stratum in the brain. They include motor skill, perceptual skills and cognitive skills (Squire et al., 2015). Priming refers to the improved facility for detecting or processing a perceptual object based on recent experience and can involve acquisition of new information. It improves ability to identify stimuli but alters judgement and preferences that involve that stimuli. Habituation and sensitization are the two most known types of non-associated learning. Other example of non-associative learning is learning language, which is done by imitation of people who already speak (Mann, 1981). Conditioning or classical conditioning is when two stimuli are associated with each other.

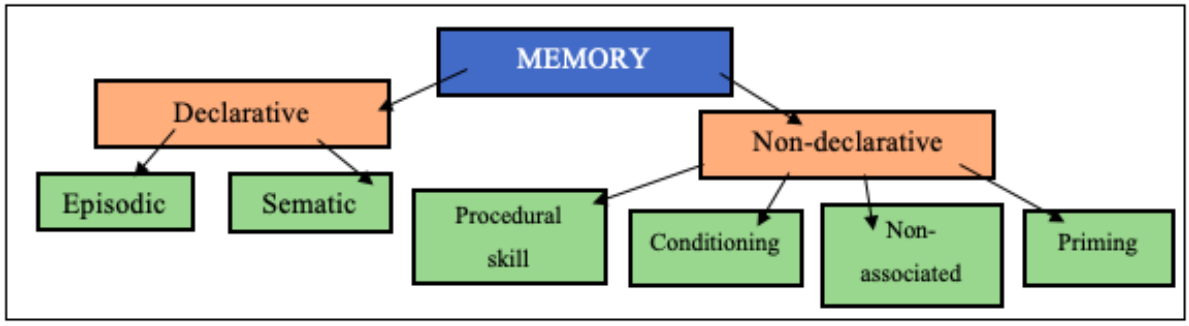

Figure 4: The two major classifications of long-term memory. Declarative allows us to recollect events and facts. It is generally indexed by our ability to explicitly recall or recognize those events or facts. Nondeclarative memory, in contrast, is accessed without consciousness or implicitly through performance rather than recollection (Curran and Morgan, 2014).

5.2 The process of memorization

The learning process itself can be divided into 3 categories; sensory memory, short-term and long-term memory. They all have different characteristics, but in the process of long-term memorization, there are three phases that must be completed. A model describing the connection between these three processes was made by Atkinson and Shiffrin in 1968 and is called by many names; Atkinson-Shiffrin model, 3-stage model, modal or multi-store model. It demonstrates the processes a sensation goes through before it is stored as a long-term memory (McLeod, 2017).

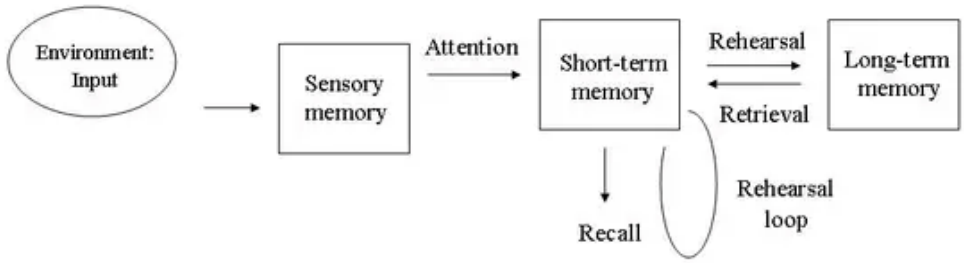

Figure 5: Atkinson-Shiffrin model showing how an environmental input transforms into a sensory memory and further into short-term memory, if attention is paid to the input. From the short-term memory, the input can either be recalled, rehearsed in a loop or rehearsed and stored in the long-term memory. From the long-term memory, it is possible to retrieve the memory, where it again might need a new rehearsal (McLeod, 2017).

This model demonstrates what happens to every environmental input a human receives, but these can be hard to connect with dependency to sleep. To understand why sleep is so important for memorization, a closer look on what happens to single entities going from an environmental input to a stabile memory, must be done. Between these two outer points, the entity goes through three fundamental processes called acquisition, consolidation, and retrieval. Furthermore, after retrieval, the memory can either be changed, discarded or reconsolidated into a stable form (Born et al., 2006).

For about a century, it was thought that the process of forming a long-term memory (LTM) was believed to be a singular linear process, but it has later been proved to be a lot more complicated than that (Alberini and LeDoux, 2013). The original concept of memory "consolidation" describes how a newly captured memory trace goes from being in an unstable form for a little while, to a more stable entity that is resistant to degradation over subsequent days to years (Hernandez and Abel, 2011; Boyce et al., 2017). This is no longer

completely true, as it shown that after retrieval of a memory from LTM storage, the entity can return to an unstable form, again open for changes and restorage (Born et al, 2006; Dieckelmann et al., 2011; Nader and Hardt, 2009).

Memory consolidation and reconsolidation is different levels of converting labile memory representations into more permanent ones that can be reactivated and recalled over a longer period of time. But even though this rather short process seems simple, it is actually very complex, consisting of several phases of stabilization, enhancement and integration, taking more time than originally thought. In addition, it is proven that these consolidation processes happen during specific time intervals and is influences by the specific wake-sleep states (Nader et al., 2003; Nader and Hardt, 2009; Boyce et al., 2017).

5.3 Acquisition/Encoding and storing Short-Term Memory

Long-term memories are evolved over a longer period of time and through several stages. The initial encoding of a memory happens within milliseconds or seconds, but after, it remains susceptible for change or loss. Encoding, or acquisition, is when perception is converted into a neural representation, which later can be recalled either from the short-term or the long-term memory storage in the brain (Rasch and Born, 2013). The different perceptions come from the different senses (smell, auditory, taste, visual). When these perceptions are payed attention to, the neurons in the brain starts to fire more frequently, intensifying the experience. By doing this, the likelihood increases that the impression is encoded as a memory. If emotions are also associated with this event, it further increases the possibility of the event to be encoded to the long-term memory. The increase in likelihood for LTM storage due to associated emotion is due to many things, including release of stress-hormones, arousal-related enhancement in noradrenergic activation and the release of glucocorticoids (Kensinger, 2009). The decoding of the different perceptions happens in the different sensory areas of the cortex in the brain. After decoding, they are combined to a single experience in the hippocampus. This is the part of the brain that is responsible for deciding and analyzing the memories coming from the amygdala, whether or not they are worth storing in the long-term memory by comparing and associating new perceptions with previously recorded once. If the hippocampus decides that the memory is worth storing, it goes through a process called consolidation (Colten and Altevogt, 2006).

The encoding and short-term retrieval of declarative memories rely on the hippocampus, but the retrieval of them is independent from it, which can be due to gradual transfer to neocortical networks. However, for declarative memories, hints of reorganization during consolidation have been provided for procedural, nondeclarative memories, which primarily rely on striatocortical circuitry (Born et al., 2006).

On a molecular level there are a lot of neurotransmitters involved in the encoding process. There is one process that has been stealing the spotlight in the study of learning and memory and its connection to long-term potentiation, and this is the glutamate-mediated transmission of information through α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic aid receptor (AMPA-R) and N-methyl-D-aspartate receptors (NMDA-R). In humans, the NMDA receptors are densely localized in the cerebral cortex and the hippocampus (Curran and Morgan, 2014). Transduction of environmental inputs through glutamate and other receptors, provokes transcription and translation of mechanisms that mediate gene expression, synaptic plasticity and ultimately behavior. Ca^{2+} influxes through these glutamate receptors and together with presynaptic changes, increases the contingency that the neurons will fire together in the future. Activity-dependent increases in intracellular Ca^{2+} levels can activate Ca^{2+} calmodulin which can then activate calmodulin dependent protein kinase (CaMKII), and protein kinase A (PKA). CaMKII and PKA can then phosphorylate AMPA and NMDA-R subunits, thereby altering synaptic transmission (Kandel et al., 2014). This increase in receptor function is temporary and allows information to be conveyed in the short term. Short-term memory can then be committed to long-term memory (LTM) or forgotten as the synaptic connections eventually weakens. How long-term potentiation (LTP) at a synaptic level relates to memory at behavioral level is not yet completely understood, but it is shown that drugs that block NMDA receptor (e.g. ketamine) inhibit the induction of LTP in the hippocampus (Curran and Morgan, 2014).

5.4 Consolidation

To stabilize the synaptic connections after the initial acquisition, consolidation must occur. The definition was first proposed in 1900 by Müller and Pilzecker, stating that consolidation is memorization resistant to interference from competing memories (Stickgold and Walker, 2005). Animal studies done in the middle of 20th century showed

that animals needed consolidation for resistance of electroconvulsive shocks and protein-synthesis inhibitors (Agranoff et al., 1965). In later years it was shown in human experiments that human motor-skill memories were disrupted if the object was put to another task within the first few hours after training on the original task (Wilckens et al., 2016). Whether consolidation is realized, depends on how interference is attempted or how learning is measured, e.g. one case where sleep-dependent consolidation interference was done, the consolidation was measured as improved performance accuracy, not measured as improved performance speed (Walker, 2005). What the term consolidation includes is also a point of discussion. Often processes that are automatic or occur with intent or awareness is included, but those requiring conscious or behavioral rehearsal are not (Stickgold and Walker, 2005). To explain how consolidation works, two theories have been proposed to explain the role of sleep in consolidation, homeostatic synaptic and active systemic consolidation model (Cellini, 2016).

The active system consolidation model proposes that during wakefulness, the environmental inputs are initially encoded parallelly in two different memory systems. These two encodings happen at different rates, where the hippocampal network is fast, while the cortical network is slower. These newly learned memory traces get reactivated the subsequent night, both in the hippocampus and the cortex. This reactivation happens especially during NREM sleep. Through a constant dialog between hippocampus and the neocortex, the reactivations resolve the redistribution of information in cortical areas. The new connections made are strengthened and stabilized through the other proposed theory, synaptic consolidation, making it less susceptible to change (Cellini, 2016). After consolidation, the memory becomes independent of the hippocampus, making the brain ready for new encodings. This model is good to use as a framework to describe consolidation of hippocampus-dependent information like declarative and explicit motor memories, but not for what is thought to be hippocampal independent like procedural memory for perceptual and motor skill (Vorster and Born, 2015).

Synaptic consolidation occurs within the first hours after learning or encoding, while systemic consolidation is hippocampal-dependent memories becoming independent, normally taking a few weeks or years (Born et al., 2006). Synaptic processing utilizes a phenomenon called long-term potentiation (LTP), which allows a synapse to increase in

strength by increasing number of signals transmitted between two neurons, making them more inclined to fire together in the future, and for them to be eventually permanently sensitized to each other. This happens both during wakefulness and sleep. After encoding during wakefulness, the strength between the synapses has increased. During the subsequent sleep, the external inputs are decreased, and the slow oscillations (especially during NREM sleep) renormalize the synapses by inducing synaptic depression. By suppression of certain synapses, unimportant information and less integrated information weakens, while the more important information (signal) relative to the phony (noise) information more salient. This process also makes it possible for the synapses to acquire new information (Cellini, 2016). More and more connections and pathways can be made by re-routing and re-arranging these organizations in the brain (Stickgold and Walker, 2005), offering an explanation of consolidation of both hippocampal (declarative) and non-hippocampal (non-declarative) information.

Consolidation can enhance memories, improving behavioral performance independent of further practice. A variety of experiments give reasons to believe that stabilization and enhancement of a memory trace reflect noticeable processes (Walker, 2005). To enhance motor skills in a motor sequence task, the consolidation processes continued up to ten times the primary period of stabilization during subsequent sleep, while for different visual tasks, the new consolidation processes could take several days (Walker et al., 2002; Stickgold et al., 2000). Interestingly, the enhancement for both the visual task and the motor sequence task happened during sleep, while the stabilization phase for the motor sequence happened during 6h wakefulness (Stickgold et al., 2000). Lastly, there was a change in the regional brain patterns during performance after sleep in the visual task, while for the motor sequence, the brain pattern after sleep and the equivalent time awake were different. This can point out that stabilization itself is not enough to cause ideal enhancement in performance. What is certain is that after initial stabilization, the memory can easily be retained for the next week or years and recalled easily if needed. The act of recalling a memory can make the memory go from a stable form to destabilized form, open for changes and possible erasing. Nader suggested in 2003 the term reconsolidation, the transformation of a “re-destabilized” memory into a stable memory again (Nader, 2003).

5.5 Reconsolidation

First described in the 1960s, the term memory reconsolidation has been brought up to light again for further investigations in the last decade (Nader, 2003). The traditional view of memory storage assumes that each time we remember some past experience, the original memory is retrieved. This view has been challenged by data showing that when memories are retrieved, they can be changed to such a degree that future retrievals calls upon the changed information and not the original memory itself. This “restoring” or “restabilizing” of a memory, is called reconsolidation (Alberini and LeDoux, 2013). Studies done on this term focuses mostly on the conditions under which reconsolidation can be observed, and how it differs from the original consolidation and encoding. A theory of why reconsolidation occurs, is that it could be a mechanism by which older memories are updated and crosslinked with newly formed memories (Hernandez and Abel, 2011). But a lot is still unknown about the reconsolidation process itself, e.g. the time-course, mechanisms and brain states producing them and its biological functions. What is known so far is that a consolidated memory can go through four different processes: reactivation (1), leading to destabilization (2), which can either turn into degradation (3) or reconsolidation (4) (Alberini and LeDoux, 2013).

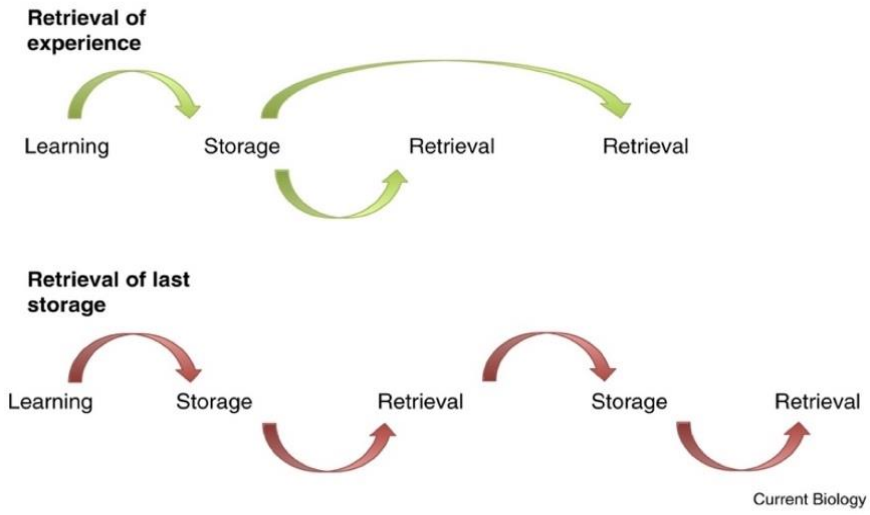

Figure 6: Comparing consolidation to reconsolidation. Two proposed theories about what happens to a memory after first time storage. The first picture shows that the memory gets retrieved as the same memory as originally encoded, and when retrieved it is always retrieved from the same storage. The second theory as seen on the most downward picture, is that the memory gets stored, retrieved and stored again through a new storage process, called reconsolidation (Alberini and LeDoux, 2013).

5.5. I. Time course of reconsolidation

Memory reactivation can presumably occur in a fraction of a second, but the destabilizing effects require a longer period of time. The extent of the destabilizing effect is correlated with the time spent in a previously learned environment. An experiment done by Nader and Hardt (2009) re-exposed rats to a fear-conditioned tone for just 30s and produced significant destabilization. On the other hand, Suzuki et al. (2004) did the same experiment, but saw destabilization only after 3 minutes, not after 1 minute. After more training and more foot shocks per trial, 10 min of re-exposure was required. What might be learned from this is that the intensity of training might also affect the susceptibility of initial consolidation to interference. No correlation between cellular-molecular or behavior have been made to the time-course of a destabilization, even though its duration has been studied intensively (Hernandez and Abel, 2011). By definition, destabilization ends when reconsolidation is complete. Degradation of a memory has only so far been defined as a behavioral trait as reduced performance of a learned task or response with little data on its time courses.

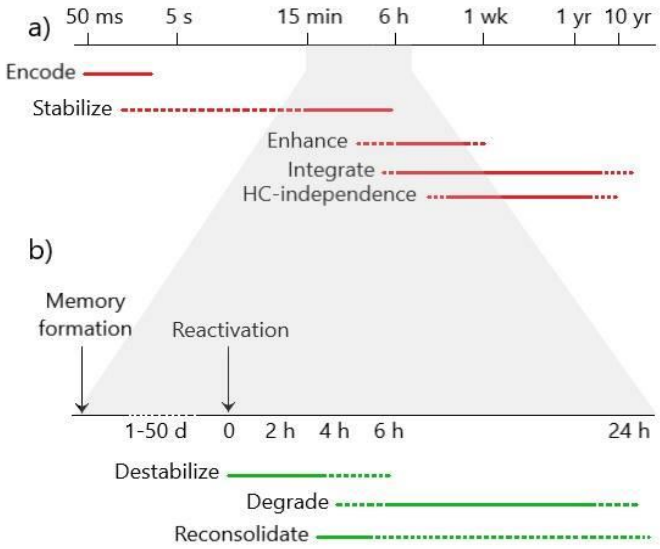

Figure 7.

Showing the time course of memory processes. (a) represent initial encoding and consolidation. The neural representation of the newly encoded memory goes through several processes, independent of rehearsal, intent or awareness. After stabilization and enhancement, the memory is resistant to interference and is more effective in guiding behavior. It can also integrate into the larger associative networks. Integration of episodic memories is thought to permit them to be recalled without hippocampal involvement (HC). (b) represents the reactivation and reconsolidation of a memory. The

grey shading is an enlargement of (a), showing the time period from a recalled memory to go from destabilized form to reconsolidated form. If reconsolidation is not permitted, the memory can be degraded. The dotted parts represent hypothesized or variable periods of processing, while the solid bars are periods of known processing.
Based on Stickgold and Walker, 2005.

But what is the reason for memory consolidation and reconsolidation? According to Stickgold and Walker (2005), they could serve three possible functions. The first of three is that the constraint on the brain needs to be decreased, and certain components or processes are necessary to deal with this. This could be due to the energy demand of rapid memory encoding in means of Ca^{2+}-influxes, or that the synapses are inadequate for long-term maintenance. On the other hand, the slower long-term processes that can maintain synaptic change (protein synthesis) cannot act rapidly enough to support rapid encoding. Another possible example could be network structures supporting episodic memories are incapable of supporting dense network storage of memories (Hernandez and Abel, 2011).

As mentioned under declarative and nondeclarative memory, processes of consolidation can also facilitate behavior through offline memory reorganization (Stickgold and Walker, 2005). Theories written by Stickgold and Walker (2005) suggested three possible ways of offline memory consolidation to facilitate behavior. One is through automate behaviors, shifting representation from declarative to procedural systems and by this reducing frontal demands. The second one is by extracting valuable details from complex episodic memories and consecutively, the third is to integrate this information into associative networks. Because of this, continued plasticity is crucial if old memories are to be integrated with the newly acquired information (Abraham and Robins, 2005). Since these processes are complicated and energy-demanding, sleep can have an important role in how well these processes function. This can be one of the reasons why people with sleep disorders like insomnia, obstructive sleep apnea, and narcolepsy often exhibit sleep-related impairment in the consolidation of declarative and procedural information (Cellini, 2016).

6. Memory and its sleep dependency

Today, it is widely known that sleep has an important role in the offline processing of memories. Several studies have been done on both humans and animals in order to try to map out which of the different stages of sleep is crucial for the different kinds of memory processes. It seems that various stages of sleep are important for certain forms of memory processes, while for others, being awake seems to be sufficient (Walker, 2005; Rasch and Born, 2013; Boyce et al. 2017). NREM sleep with its stage 2 and SWS has been associated with consolidation of motor skill tasks (Born et al., 2006). SWS and REM sleep have also been associated with the consolidation of visual skill memory (Stickgold et al., 2000). Thus, different forms of procedural memories require uniquely different sleep-stage-dependent brain states for consolidation enhancement. The theory that there is more than one sleep-dependent consolidation phase, can be enhanced by the evidence showing that deprivation of certain sleep phases causes disturbances in the memory consolidation (Stickgold et al., 2000).

6.1 NREM sleep and memory consolidation

6.1 I. NREM sleep and procedural memory consolidation

With regards to procedural memory, findings show that sleep after training of perceptual and motor skills can produce significant improvement (increased skill at later retest). This can indicate that an active reprocessing of skill representations occurs during sleep, sharpening the various representations (Rasch and Born, 2013; Stickgold and Walker, 2005). Enhancements are seen across a wide range of memory tasks, but they rely on different sleep stages or sleep characteristics (Walker et al., 2002). There are convincing behavioral indications for reorganization of skill representations during sleep, also coming from investigations of sequence-finger tapping skills. They showed that sleep favors the emergence of effector independent representation, benefiting both pressing sequence and target keys independent of hand, and also showed that sleep enhanced sequence-finger tapping performance when learning occurred by observation or motor imagery. An experiment done by Albouy et al. (2013), concluded that daytime sleep (90-minute nap) specifically enhances consolidation of the allocentric (spatial) representation of the sequence, but not the egocentric (motor) representation.

On the other hand, there are several examples of memory consolidation that are not dependent on sleep. When gain of skill is measured with reference to performance level at the end of training, improvement can occur within a few hours after training also in the absence of sleep (Walker et al., 2003), or when the homeostatic and circadian influences are controlled during the experiment (Rasch and Born, 2013). Another example is a gain in speed during finger tapping sequences. This gain in speed could be due to synaptic consolidation processes, strengthening the connections formed during training without recognizing memory representation (Rasch and Born, 2013; Born et al., 2006). A serial reaction time experiment executed by Robertson et al. (2004), where post-training improvement was measured, showed sleep-dependency when subjects were explicitly aware that there was a sequence to be learned, but when they didn't, the improvement occurred in both wake and sleep states. Also, an auditory task showed time dependent improvement even in the absence of sleep (Atienza et al., 2002). Questions to be raised from this is why only certain procedural tasks performance is enhanced after sleep.

6.1 II. NREM sleep and declarative memory consolidation

Regarding declarative memory formation, there are both evidence for and against sleep-dependent memory consolidation. Born and colleagues (2006), showed that daytime training can trigger changes in characteristics of early-night SWS, reporting changes in both number of sleep spindles and in the continuity of NREM low-frequency EEG oscillations. SWS sleep from phases of early night sleep turned out to be especially beneficial for this consolidation, suggesting that certain physiological processes are crucial, because the effect was only seen during SWS-rich periods early in the night, and not in REM-rich periods later the same night. Cellini (2016) wrote that human insomniacs had more problems learning declarative memories than the control group after a night-sleep, while the two groups performed equally after learning a procedural task. It was also shown that sleep has a stabilizing effect on both forms of declarative memory; the rate of deterioration during an interval of wake that follows sleep is significantly slower than when sleep does not precede the wake period (Payne et al., 2012).

What was interesting about Cellinis experiments in 2016, was that the patients experiencing parasomnias, e.g. sleepwalking, night terrors and REM behavior disorders didn't show any memory impairments. Her suggestion was that only sleep disorders characterized by increased post-learning arousal and disrupted sleep architecture seem to be associated with offline consolidation issues. It is further questioned if these sleep problems beginning at early age can potentially affect the development and maintenance of an individual's cognitive abilities, reducing their quality of life and increasing the risk of accidents. Another scientist who questioned sleeps effect on adolescence is Carskadon (2011), who wrote an article debating how important enough sleep is for learning in brains during pubertal development. Functional imaging, EEG assessments and other measures of brain activity all showed diminished alterations in poorly slept brains.

6.2 REM sleep and memory consolidation

There are plenty of hypothesis about whether or not REM sleep contributes to memory consolidation (Boyce et al., 2017; Stickgold and Walker, 2005; Rasch and Born, 2013). Some animal studies have shown consistent evidence of REM sleep for memory consolidation done using a variety of different tasks (classic, aversive and appetite conditioning) procedures, where a consistently increase in REM sleep was seen after learning. One of these experiments introduced rats to an enriched environment, where they showed a significant increase in both REM and NREM sleep compared to the rats introduced to a simpler environment (Gutwein and Fishbein, 1980). A lot of the newest literature agrees upon that REM sleep has a significant role in the memory consolidation of complex tasks in animal species, while the results in humans are not as consistent (Rasch and Born, 2013; Boyce et al. 2017).

Some human studies show increase in memory consolidation, but none of the experiments say the increases are consistent enough to call them significant. This could be due to the length of REM sleep in a cycle, which is different in humans and other animals, meaning that it could perhaps serve other purposes in humans. According to Smith (2001), studies using training tasks which were clearly for a declarative nature did not require REM sleep following acquisition for increased memory efficiency. On the other hand, those tasks that were clearly procedural or had a procedural component appeared to require REM sleep for maximum learning efficiency.

The inhibition of REM sleep seems to impair only memory formation of complex tasks, like a two-way shuttle box avoidance and complex mazes, which envelop a change in the animals' regular repertoire. For simpler tasks, the need for REM sleep was less consistently affected and mostly found in the first hours after learning. One of the more recent experiments done showed significant spatial and contextual memory consolidation in mice (Boyce et al., 2017). Combination of electrophysiological recording and up to date optogenic techniques, demonstrated neural activity occurring specifically during REM required for spatial and contextual memory consolidation

A lot of the experiments used to research the effect of REM sleep deprivation have been criticized for being too extreme and causing unnecessary stress for the animal. These experiments often involve a mouse or a rat sitting on a platform just big enough for them to sit on, surrounded by water. When they transition from NREM to REM sleep, the muscle atonia diminishes, and the mouse or rat loses its balance and a foot or other body part falls into the water (Boyce et al., 2017; Rasch and Born, 2013). Role of REM sleep has remained controversial also due to extreme difficulty in experimentally isolating neural activity during REMs. Identifying the underlying mechanisms behind these observations, precisely how they translate to humans, and clarifying the extent of REM´s role in other modalities of memory will be important for future sleep and memory studies.

6.3 Sleep-dependent plasticity

The evidence for sleep-dependent consolidation is not limited to behavioral data. Plasticity found at both local and systemic levels gives rise to the theory that sleep plays an important role in consolidation processes causing memory enhancements. At systemic level, neuroimaging studies have showed changes and reactivation in brain patterns during subsequent sleep after task training. Reorganization of sleep-dependent learning has also been shown during sleep (Walker and Stickgold, 2006; Cellini, 2016).

At a molecular level, both upregulations and downregulations of genes can be seen during sleep. After a sensorimotor rich environment, the plasticity-associated immediate-early genes (IEGs) *zif-268* is upregulated in granule cells of hippocampal dentate gyrus, piriform and frontal cortices during REM sleep. If the sensorimotor input is not there, *zif-268* is

downregulated. IEGs are expressed in neurons in response to activation, the first step in a cellular cascade involved in plasticity and is often used to identify brain regions activated during certain behaviors and cognitive tasks (Rattenborg et al., 2011). This is supported by an experiment performed on REM sleeps effect on the mouse brain, where the associated transcription factors CREB and cAMP were shown to be elevated in the mouse brain during REMs, while expression of *zif-268* was upregulated during REMs in rats following enriched environment exposure or LTP introduction. Kandel et al. (2014), wrote an article about the molecular and biology systems of memory. In the part about mammalian plasticity, they write that many parts of plasticity are subject to modulation by other transmitter systems and by the past stimulation history of the individual synapse itself, in what is referred to as metaplasticity (Abraham and Robins, 2005). If a synapse has recently undergone LTP, stimulation protocols that would previously have produced no synaptic change now produce LTD (Kandel et al., 2014).

Taken together, behavioral, brain, cellular, and molecular studies across species indicate that distinct components of memory consolidation take place across a range of memory systems, and a range of wake-sleep states (Walker and Stickgold, 2006). Until now, all different stages of sleep, except stage 1 NREM sleep is associated with different consolidation processes.

6.4 Sleep and reconsolidation

As of right now, it is not known if sleep acts differently on consolidation and reconsolidation (Rasch and Born, 2013). A theory called the “sequential hypothesis” stresses the importance of cyclic succession of SWS (or NREM sleep) and REM sleep for memory formations, with the sleep stages serving complementary functions in this process (Giuditta et al., 2000). This transient destabilization after reactivation during SWS could ease the neocortical knowledge networks to integrate the newly formed memories. In 2011, Dieckelmann et al. (2011) did experiments on humans to test this; whether a transient memory destabilization occurred during SWS as it does if reactivated during wake state. These reconsolidation studies showed that if a memory was reactivated during a wake state, the memory turned transiently susceptible to change, while the contrary occurred during SWS. The reactivation during SWS immediately stabilized the memories, increasing their resistance for interference. The experiment also showed that reactivated

memories during SWS does not necessarily need subsequent REM sleep as a stabilizing effect, as previously thought in the sequential hypothesis (Dieckelmann et al., 2011; Rasch and Born, 2013; Giuditta et al., 2000). Functional magnetic resonance imaging showed that reactivation during SWS was mainly located in hippocampal and posterior cortical regions, while reactivation during wake was primarily located in prefrontal cortical areas (Dieckelmann et al., 2011; Jagster and Born 2013).

Stickgold and Walker (2005) hypothesized if reconsolidation served no other practical purpose than preventing unintentional memory degradation. But their opinion was that both reconsolidation and consolidation are sophisticated modulating mechanisms. There are reasons to believe this can be shown in experiments done with inhibitors of ACh and noradrenaline, showing that neuromodulation of these receptors can prevent reconsolidation. ACh-reuptake and Beta-adrenoceptors are parts of the normal sleep regulation, and by blocking them, one can also block certain reconsolidation processes by classical interference training (Walker and Stickgold, 2006). Another experiment with NMDA-R antagonists showed that the antagonists can block destabilization (Nader and Hardt, 2009).

6.5. Sleep and learning in non-mammal species

6.5 I. Sleep and memory in birds

According to Vorster and Born (2015), birds are the only other taxonomical group that exhibits high amplitude slow oscillatory EEG activity during SWS and low amplitude mixed frequency EEG activity during REM sleep. Reptiles and amphibians do not show significant REM and SWS differences, suggesting that birds coevolved independently from mammals. The other noticeable difference is that in birds, the sleep cycles are more fragmented and in short bouts of 1-4 min duration. SWS lasts between 50s in the beginning, to 25s at the end of a sleep period, while REM sleep accounts for less than 10% of total sleep time. REM sleep seems to be in birds, like in mammals, driven by homeostatic mechanisms. Slow wave activity (SWA) consistent with notion that slow oscillations underlying SWA supports communication between widely distributed brain regions and integrative processing of information in these areas during SWS.

To understand the role of sleep in bird's memory and learning abilities, the differences and similarities between the mammalian and avian brain must be explained. Both groups show areas of highly interconnected neural regions, in mammals SWA originates from the neocortex, while the analogous in birds is the hyperpallium. Reptiles does not show any areas of the brain that can be called analogous to that of the previous mentioned, which could be one of the reasons why there are no significant SWA and REM differentiation during a sleep phase. The differences between memory storage in the avian and mammalian lies in the hippocampal (initial storage) and extra-hippocampal (long-term encoding) areas. In the avian brain, the hippocampus does not serve the same purpose as in the mammalian, but is responsible for olfactory and visual input from the hyperpallium. Its analogous to the mammalian brains prefrontal cortex is the nidopallium caudolaterale, which is not as close anatomically as the prefrontal cortex is to the hippocampus. This raises the question whether or not there is a unitary network existing analogous to mammalian hippocampus to store episodic like memory representations or not. Birds also lack EEG theta rhythm, where mammals experience prefrontal-hippocampal encoding during wake state and especially in rodents dominates hippocampal activity during REM sleep.

Juvenile birds have been under investigation to learn about the role of memory and sleep is during their song-learning. This is interesting because of its unique resemblance to human speech acquisition. Birds are also the only taxonomic group where neural reactivations of newly encoded representations have been identified during sleep (Vorster and Born, 2015; Rasch and Born, 2013). Song learning, like speech learning in humans, is a demanding task which might be accompanied by additional sleep need, as birds being first exposed to the singing of an adult tutor tend to fall asleep quickly after exposure (Rasch and Born, 2013). In zebra finches, quality of the learned song improved during intense practice, but structure and quality declined across nocturnal sleep. This did not only reflect a circadian rhythm, because the bird who was induced to sleep by melatonin during daytime, showed the same less precise song after awakening, but also, the decline was followed by practice-induced improvements in song structure during subsequent wake time. The birds that showed the highest degree of song deterioration after sleep turned out to be the best learners in the long run (Rasch and Born, 2013).

6.5 II. Sleep and memory in invertebrates

Interestingly, existence of a spinal cord does not seem to matter for the occurrence of sleep (Vorster and Born, 2015, Miyazaki et al. 2017; Albrecht and Born, 2014). Since invertebrates doesn't show the typical mammalian EEG signals, identification of sleep-like states relies primarily on behavioral signs like inactivity and presence of specific body postures, increased threshold to arousing stimulation, as well as demonstration of a rebound in sleep-like states occurring as a consequence of experimental sleep deprivation. An experiment done on bees done by Hussaini et al. in 2009 showed that sleep and sleep deprivation after learning period did not affect the retention of conditioned response at a later retest, but sleep promoted formation of extinction memory. In a study done about the evolution of sleep by Miyazaki et al. (2017), the *Drosophila* (fruit flies) sleep is associated with structural changes in multiple brain areas, including the mushroom body, which is important for learning and memory in this species. The *Drosophila* also showed an increase in sleep after using and enriched environment, or after learning a specific behavior, e.g. like suppression of courtship behavior.

What is important to remember when reading the differences and connections is that within both sleep and memory there is a lot of individual and species-specific differences. When talking about mammals, this mostly accounts for humans and rodents, as these are experimented on the most. Aquatic mammals like the dolphin have a unique way of sleeping, which is the unihemispheric sleep, where only one part of the brain is asleep at times (Colten and Altevogt, 2006). It is also shown that certain animals can go for a very long time without sleep, like certain long-range migrating birds (Rattenborg et al., 2011). This shows that it might be possible to sustain life without sleep during special circumstances, but the consequences of the prolonged sleep deprivation are not yet completely understood.

7. Conclusions

Conclusions are that there is a proven correlation between sleep and learning. Since more and more evidence supports this by showing that all stages except stage 1 has to do with one or more types of memory consolidation in humans or animals, there is close to zero doubt that memory is dependent on sleep. Sleep on the other hand is not equally dependent on learning but show changes in pattern and intensity after training or learning.

NREM sleep is important for declarative memory consolidation in both humans and other mammals, but why is only certain procedural memory consolidations in human dependent on consecutive sleep to show improvement?

There is not yet enough evidence to show a strong correlation between REM sleep and declarative learning improvement in humans. Most of the studies done, supports the theory that REM sleep can in many ways make memory processing more efficient. Cognitive procedural tasks are vulnerable to REM sleep loss, while declarative tasks are not. Questions to be answered is why REM sleep play a role in declarative tasks for some mammals, but the consistency in human is not enough to draw significant conclusions.

I have no doubt that within the next few years, a lot of these questions will be answered, as more advanced technology can be used as helping tools, and our understanding of sleep and sleep states throughout the animal world is explored. Maybe with this, the big question of why we actually sleep can be answered.

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