Sleep-dependent memory consolidation

Bachelor thesis behavior and cognitive neurosciences

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Abstract

In 1924 Jenkins and Dallenbach presented the first experimental evidence for the existence of sleep dependent memory consolidation. In this thesis the role of sleep in memory consolidation is viewed. A separation is made between declarative and non-declarative memory systems. The aim of this thesis is to investigate the role of sleep on the different memory systems and also which molecular changes could be found in the brain during a period of sleep deprivation and the same period of sleep. The results showed convincing evidence for the role of sleep in declarative and non-declarative memory consolidation processes. Furthermore it is proved that during sleep there are molecular changes in the brain. These changes in molecules of plasticity support the brain to consolidate new memories. It seems that in humans generally the consolidation of declarative memory is slow wave sleep (SWS) dependent. The consolidation of non-declarative memory seems to rely mostly on REM sleep.

Introduction

Memory consolidation is defined as a couple of slow processes which stabilize a memory trace after the initial acquisition of the memory. Memory consolidation is distinguished into two different processes: synaptic consolidation and system consolidation. Synaptic consolidation is the process which occurs within the first hours after training, and system consolidation is the process where labile hippocampus dependent memories become more stable hippocampus independent memories. Consolidated memories thus remain accessible at a delayed retrieval.

In 1924 Jenkins and Dallenbach presented the first experimental evidence for the existence of sleep dependent memory consolidation. Jenkins and Dallenbach found that the retention of learned nonsense syllables over a period of time was significantly better after a night of sleep compared with retention after the same amount of time awake. [1]

Until the seminal paper of Karni and coworkers in 1994, the topic sleep dependent memory consolidation received relatively little attention. [2] After the paper of Karni et al. a large number of studies related sleep and all kinds of different memory consolidation tasks. These tasks could be divided into two different groups: declarative and non declarative memory. Declarative memories, which are memories that a person can recall to mind (what did I eat last night) and non declarative memories, which are the memories that are used without conscious recollection such as motor skills (learning to ride a bicycle). Declarative memories could be distinguished into episodic and semantic memories. Non declarative memories could be distinguished into procedural skills, conditioning, non associative and priming (see figure 1 for an overview). This thesis will be limited to a separation between declarative and non-declarative memories.

Nowadays is seems clear that sleep plays a significant role in memory consolidation, but still it is not completely clear which stage of sleep is involved in declarative and non-declarative memory consolidation. Therefore the aim of this thesis is to investigate the role of sleep on the different memory systems and also which molecular changes could be found in the brain during a period of sleep deprivation and the same period of sleep.

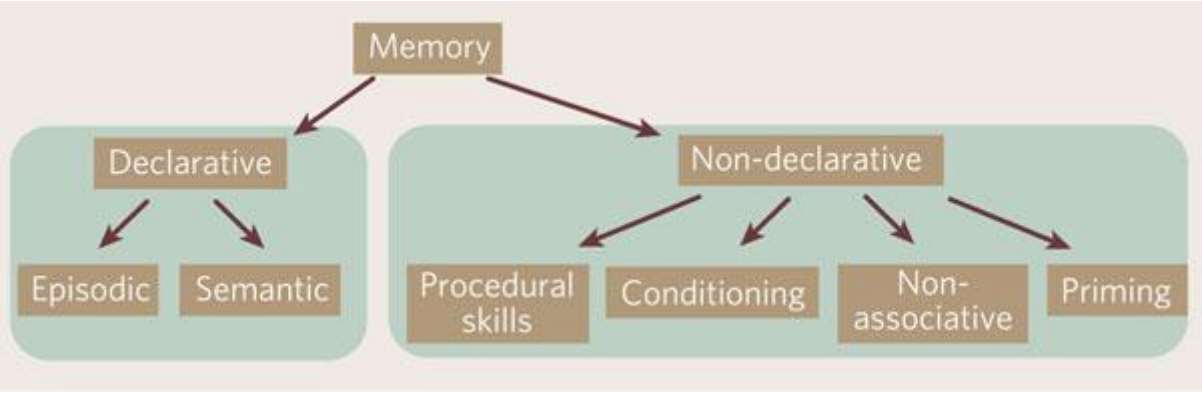

Figure 1. categorization of memory systems[3]

Different types of sleep and their characteristics

Sleep could be distinguished into two broad types: rapid eye movement (REM) sleep and non-rapid eye movement (NREM). These two sleep stages are distinguished from each other through the difference in electroencephalography (EEG). During REM sleep the EEG is characterized by a rapid low EEG, which is quite similar to an EEG during wakefulness. Furthermore there are rapid eye movements, increased heart rate, increased cortical blood flow, muscle paralysis and theta waves. The EEG of NREM sleep is characterized by slow waves in the EEG with a frequency around 4-13 Hertz. Furthermore NREM sleep could be divided into: stage 1, stage 2 and stage 3 and 4 whereby stage 3 and 4 are better known as SWS. For an overview see figure 2[3].

Sleep in humans occurs in four or five the same cycles: NREM stage 1, NREM stage 2, NREM stage 3, NREM stage 4 and REM sleep. Stage 3 and 4 are the deepest sleep stages with slow oscillations of 0.5–4-Hertz observed on the EEG. The first sleep cycle has an average length of 90 minutes and the last cycle will have a length around 120 minutes. Each of these sleep stages has its own characteristics and function.

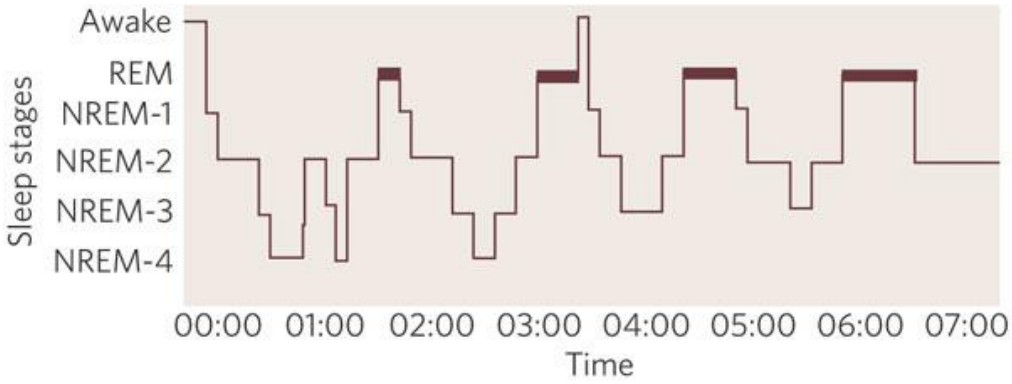

Figure 2. different sleep stages in humans

All these different sleep stages play their own role in sleep-dependent memory consolidation. The sleep spindles and slower K-complex signals which are characteristic for stage 2 NREM sleep, the slow wave oscillations in slow wave sleep and the theta rhythms seen in REM sleep are known to be involved in sleep-dependent memory processing[3]. Adults normally spend 60% of sleep in stage 2 and about 20% of sleeping time in REM sleep. The remaining 20% in the other sleep stages but mostly in slow wave sleep. During REM sleep there are 3 features which play a critical role in neuroplasticity. Hippocampal neurons exhibit temporally structured discharge patterns imitating those who are present during spatial learning tasks. These replays in the neurons help the stabilization of synaptic connections by some critical synaptic proteins. Furthermore there are theta bursts in neurons during REM sleep. These theta burst will help inducing long term potentiation (LTP) and will increase BDNF levels. The last feature is the brainstem phasic waves called P-waves, which are critical for retention of some different tasks[11].

A significant difference between SWS and REM sleep in memory consolidation is the involvement in LTP, which is important in memory consolidation. REM sleep has a normal synaptic plasticity, but in SWS LTP is more difficult to be induced through the reduced synaptic plasticity in this sleeping stage[4].

The role of CREB in sleep-dependent memory consolidation

cAMP response element binding protein, better known as CREB is a cellular transcription factor and is critical in many nervous systems including: synaptic plasticity, neurogenesis and memory consolidation[5].

Alberini et al. have shown that CREB-dependent gene expression is critical for long term facilitation, but not for short term facilitation[6]. Facilitation is a phenomenon in which postsynaptic potentials generated by an impulse are increased when that impulse closely follows the prior impulse. This facilitation process is an important phenomenon in memory consolidation. Together with Bartsch et al., Alberini et al. have shown the critical role of PKA-CREB in the molecular pathway underlying on long term facilitation[7]. Not only PKA is essential for the activation of the CREB pathway, also mitogen-activated protein kinase (MAPK or ERK) and CAMKII are essential in the activation of the pathway (see figure 3 for a schematic overview).

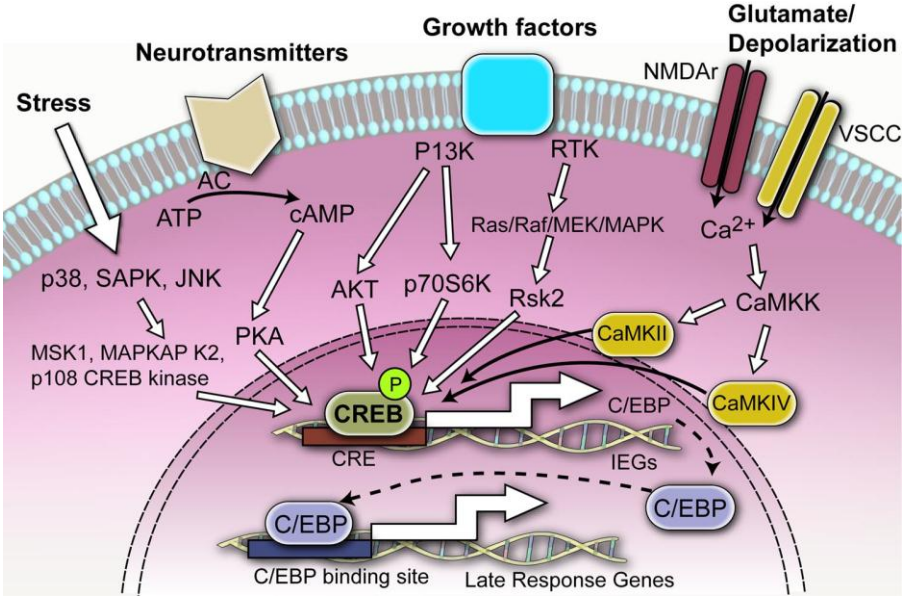

Figure 3 the CREB pathway[6]

The role of CREB in memory consolidation is further supported by a genetic study on Drosophila Melanogaster performed by Yin et al[8]. They have shown that mutants flies with defects in either long-term of short-term memory consolidation carried mutations in genes that are encoding for enzymes involved in the activation of the cAMP-PKA-dependent pathway. They also found that there are different isoforms of CREB, an activator and an inhibitor. The α- and Δ- isoforms of CREB are the onees that are most expressed in the brain. In a study with α- and Δ- CREB knock-out mice, there has been shown that these mice showed significant impaired memory on several types of memory tasks[9]. These knock-out mice revealed also impaired hippocampal long term plasticity (LTP), which plays an important role in learning and memory formation because of the increased synaptic plasticity.

It is not completely clear that the CREB pathway is the underlying mechanism of memory consolidation. There are some researchers who doubt the role of the CREB pathway in memory formation. This doubt is caused by the fact of the existence of a CREB-

independent form of LTP. Balschun et al. found that a complete CREB knocked-out mouse in the CA1 sub region of the hippocampus is not sufficient to impair LTP and contextual fear conditioning and a little impairment in the water-maze learning task[10].

Alberini et al. explained these contrasting findings by the fact that in some knock-out Lines or learning conditions protein compensation overcomes the requirement for CREB and that some forms of memories and LTP are CREB independent[6]. So there is an overwhelming amount of studies which indicate that CREB is critical for most types of memory formation.

So it is clear that CREB and some other molecules are involved in memory formation, but how does CREB react during sleep? Guzman Marin et al. had investigated the effect of sleep deprivation (8 and 48 hours) on the molecular markers of plasticity. They deprived rats using an intermittent treadmill system which equated total movement in the sleep deprived and control treadmill rats, but permitted sustained periods of rest in CT animals. They found a reduction in the amount of CREB and CAMKII (see figure 4). The other two molecules for plasticity, SynapsinI and BDNF were also significantly reduced. The changes in these molecules of plasticity are only found in the hippocampus and not in the neocortex. Furthermore they have shown a strong correlation between REM sleep and BDNF, SynapsinI and CREB and that NREM sleep is responsible for the levels of CAMKII in the hippocampus.

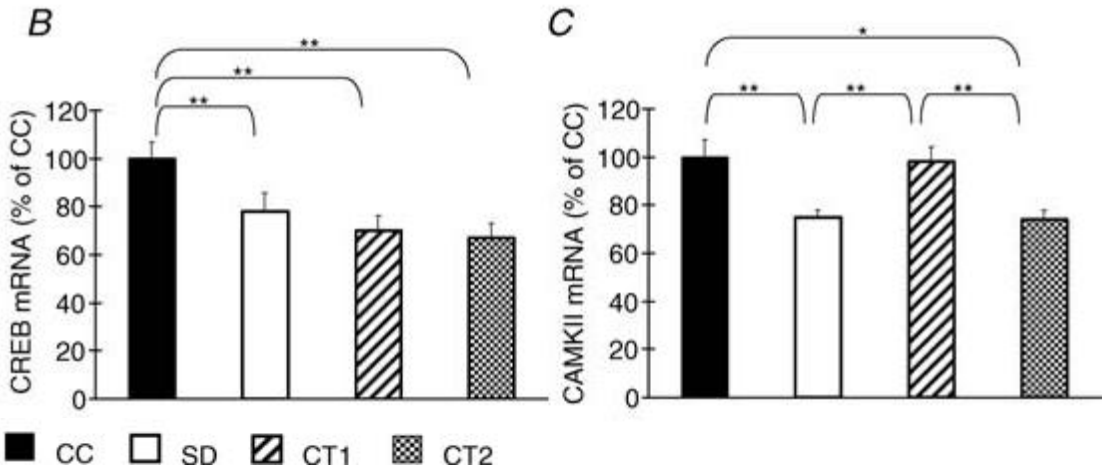

Figure 4. sleep deprivation leads to reduced levels of CREB and CAMKII. Data are presented as percent of the cage control (CC) group. SD, sleep deprivation; CT1, control treadmill 1 (15 min on/60 min off); CT2, control treadmill 2 (30 min on/120 min off).[11]

Sleep and declarative memory consolidation

Declarative memory, also known as explicit memory, is one of the two types of human long term memory. Declarative memories are the kind of memories which can recalled such as facts and knowledge. The ability to recall a declarative memory is highly dependent on the hippocampus.

It has been suggested that one the roles of sleep in declarative memories is the reactivation of hippocampal memories. This reactivation will lead to a transfer of the memory into neocortical systems and it will be stored in the long term memory[14]. The idea that the new learned information is reactivated during sleep is supported by the study of Louie et al. They have shown that the temporal patterns of activity across hippocampal neurons during a spatial task are repeated during SWS and REM sleep[20]. For this measurement they used a PET-scanner, which is able to show the exact place of activation of the brain. There are actually two different theories about the role of sleep in the consolidation of declarative memories. The first one is the active model, in which memory consolidation depends only on sleep. The second model is the permissive model in which time-dependency and the absence of interference-sensitivity processes play a major role.

The active model predicts that declarative memory consolidation depends on brain functions which are unique during the different sleep stages. This model suggests that one or more of the sleep stages has a positive effect on the consolidation of new learned memories.

The permissive hypothesis predicts that memories need a timeframe to consolidate in which they become resilient to interference of new memories. Sleep is the perfect timeframe for this consolidation because of the absence of interference of new learned memories. So sleep directly after a learning task should have more effect than sleep after the same period of wakefulness. During sleep there is no interference of a new formed LTP because of the period of LTP inhibition during SWS. So SWS sleep maybe produce an improved performance through the absence of LTP induced interference[16].

Aly et al. has investigated the differential role of sleep in the consolidation of memories in various aged adults. The first test they used was the Logical memory section of Wechsler Memory Scale III (WMS-III), which consists of two short-paragraph-length stories. The second test they performed was a list of 12 questions to assess personal episodic memories of a conversation and the news which has occurred on the day before. They showed that the adults memories were significant better following a period of sleep on the WMS-III task (P=0,001). The proportion recall was 0,96 following a period of sleep but only 0,68 following the same period of wakefulness. This is a significant difference in proportion recall of 0.28. The same results with a beneficial effect of sleep were found on the 12 questionnaire task[15].

Plihal et al. showed that the consolidation of a mental spatial rotation task is also sensitive for sleep. They had three different groups of which are two different sleep groups, the first had early retention sleep and the second group had late retention sleep. They showed that there is a significant increase in performance after a period of sleep compared with the same period of wakefulness. After the early retention sleep the recall of spatial memory was superior to the recall after late retention sleep ($p < 0.01$)[17].

It is known that the level of the hormone cortisol is the lowest in the early night during SWS sleep. Studies which did infusions of cortisol during this period of sleep found that this increased level of cortisol blocks the beneficial effects of sleep after learning associated word-pairs. The same phenomenon is found in the levels of acetylcholine in the early night. The reduction of acetylcholine levels may provide an ideal window for transferring memory traces that have been recently encoded in the hippocampus to the neocortex [28].

Schabus et al. have shown that the overnight improvement of verbal memory correlates with sleep spindles activity which is a signature of stage 2 NREM sleep. This finding is in line with the study done by Genzel et al. Participants of the study of Schabus performed a cued recall in the evening after they learned 160 word pairs. The same recall was done in the morning after 8 hours of undisturbed sleep with full polysomnography[18].

Datta et al. showed that rats which are trained on a two way avoidance task are sensitive for REM sleep deprivation. Furthermore they showed that a injection of P-wave activator can prevent the rats of a learning impairment and that there is a positive correlation between the level of P-waves and the performance of the rats[21].

Sleep and non-declarative memory consolidation

Non-declarative memories, also known as implicit memory, are the type of memories which are unconscious. Most of these memories are skills such as how to drive a car and how to tie a shoe. There are four types of implicit memory but in this thesis there won't be a separation between them. Implicit memories rely mostly on cerebella and striatal function apart from neocortical contributions, but the hippocampus is also activated during procedural tasks[23].

It has been suggested that during sleep there is a reactivation of the brain areas which are involved in skill learning. This is in line with the finding of Maquet et al. who showed in humans some brain areas are reactivated during REM sleep after an implicit learning task. To investigate this reactivation they used a positron emission tomography (PET) scanner. They found a reactivation in the left premotor area of the cortex and a reactivation in the bilateral cuneus, the areas which are activated during the learning task itselfs[22].

Maquet et al. showed in another study an overnight improvement of a pursuit procedural task. The participants had to do a pursuit task with the left hand in which the target trajectory was only predictable on the horizontal axis. Furthermore fMRI was used to show an increased brain activity in the superior temporal sulcus. There also was an increased connectivity showed between the superior temporal sulcus and the cerebellum. This result indicates a sleep related plastic change after a pursuit task[27].

Walker et al. showed a strongly improved procedural memory after sleep. They also showed a correlation between stage 2 NREM sleep and procedural memory in humans, the intersubject variance was explained for 52% by this sleep parameter alone (see figure 5 for the results). The participants were trained and retested on a computerized finger tapping task. The performance of the participants was defined as the number of repeated five key press sequences in a trail of 30 seconds. There were sleep and wake groups so the effect of sleep could be investigated[24].

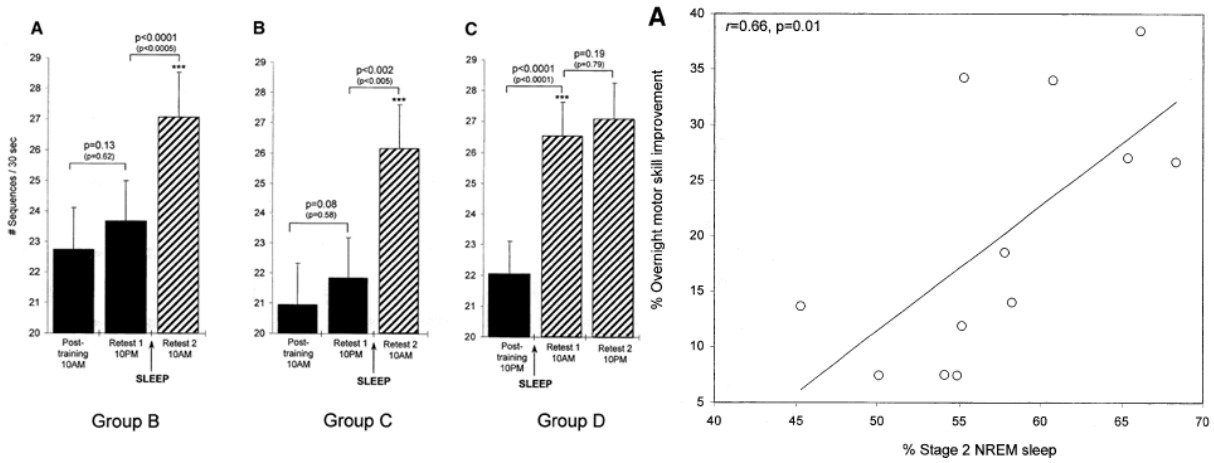

Figure 5. The effect of sleep on procedural memory and the correlation with Stage 2 NREM sleep.

The findings of Walker et al. that implicit memory is correlated with stage 2 NREM sleep are not in line with the correlation found by Stickgold et al. on a visual discrimination task[25]. Their results show no improvement of the task after a period of wakefulness. In contrast with these findings is the observation that after a night of sleep a significant improvement in the task was seen (p<.0001). The improvement was not time dependent but it was dependent on the amount of sleep, with a minimal amount of sleep for improvement of 6 hours. The improvement of the participants was strongly dependent on REM sleep in the last quarter of the night and SWS in the first quarter of the night. The other parts of the night seems to have none improvement on this task. The two step model (SWS and REM sleep) explained over 80% of the intersubject variance in this task.

These findings are in contrast with the findings of Genzel et al. who found that SWS deprivation and REM sleep deprivation had no effect on the performance of their participants, this will be discussed later on[26]. Overall there is enough evidence that procedural memory formation is supported by sleep.

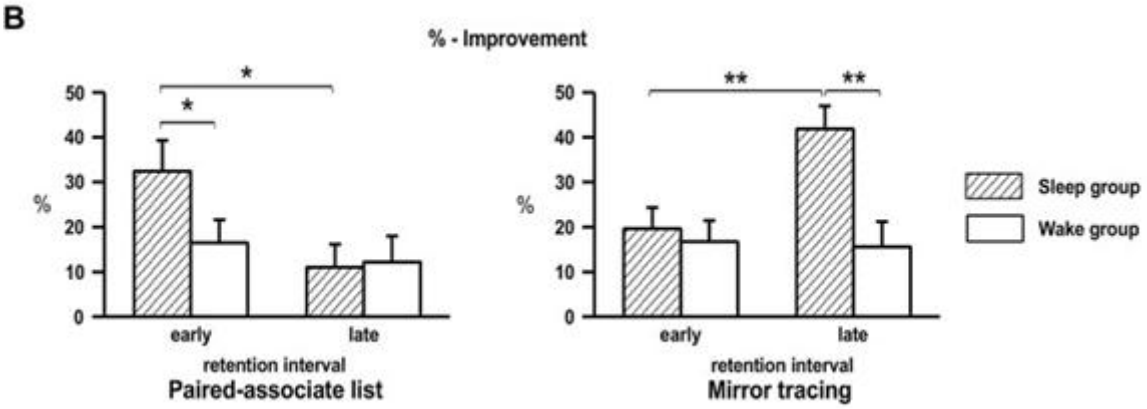

Figure 6. the differences in sleep-dependency in declarative and non-declarative tasks[23].

Discussion

It is clear that CREB and the other molecules of plasticity are involved in memory formation and that these molecules are reduced after a period of sleep deprivation[11]. This is supported by Ulloor et al. who have showed that BDNF and phosphorylated CREB levels and other synaptic-related molecules are up regulated in the hippocampus after a learning task. These reduced levels of plasticity molecules in sleep deprived groups are not the effect of stress because the corticosterone levels were not increased after sleep deprivation using the treadmill method[12]. The reduction in the gene expression of these molecules of plasticity after sleep deprivation could explain one of the roles of sleep in the formation of memory. This reduction in gene expressions leads to disturbances in learning in sleep deprived animals. It seems that REM has effect on the levels of BDNF, SynapsinI and CREB and that NREM sleep is responsible for the levels of CAMKII in the hippocampus[11]. So both sleep stages play a major role in the molecular changes during sleep.

As showed above there is enough convincing evidence which supports the role of sleep in declarative memory consolidation[15,16,17,18,20,21]. All of these studies showed a significant improvement of a declarative task after a period of sleep. There are some differences in the results of the involvement of REM and SWS in the consolidation of declarative memories. Further research is needed to make more clear which sleep stage plays the major role in the consolidation of declarative memories.

Borich et al. showed that both sleep and wakefulness could support consolidation of goal directed visuomotor skills. They suggest that sleep has beneficial effects on more complex tasks and that time provides benefits in less complex motor skills task. Furthermore they showed that explicit awareness of a complex motor task had more beneficial effect of sleep compared with an implicit learning task[29]. The finding of time dependency in the less complex motor skills task is partly in line with the previously discussed “permissive model”. This model contains that memories need a timeframe to consolidate in which they become resilient to interference of new memories. The findings did not support the active model which predicts that declarative memory consolidation depends on brain functions which are unique during the different sleep stages.

The findings of Plihal et al. are more in line with the active model. They showed that after the early retention sleep the recall of spatial memory was superior to the recall after late retention sleep ($p < 0.01$). It is known that early sleep is dominated by SWS sleep so it seems that the consolidation of a mental spatial rotation task is dependent on SWS sleep[17]. So not the time frame of sleep is important but a specific part of the night is important in a mental spatial rotation task. So with the observed studies in this thesis it is still not completely clear which of the two models is the best model in the consolidation of declarative memories. The active model seems more likely but further research needs to clarify this.

There is convincing evidence that implicit/ procedural memory consolidation is dependent on sleep. There are several studies who support this statement[22,24,25,27]. Most of these studies showed significant results or correlation which supports the sleep dependency of these types of memory consolidation. Genzel et al. found no effect of REM and SWS deprivation on memory performance on a motor task. This could be explained by the fact that the diminished REM and SWS groups were not enough diminished so there was still enough REM/ SWS sleep to consolidate for the motor task or the memory consolidation of this task was dependent on stage 2 NREM sleep. Recent nap studies support the first explanation by fact that short naps are very effective in some kinds of memory consolidation[26]. Furthermore results from sleep deprivation studies should be taken cautiously because the two groups are not treated exactly the same way. So it could be possible that not sleep but the deprivation is the explanation for the results that are found.

The results of Stickgold et al. provide evidence that learning of a visual discrimination task depends on neuronal changes that occur only during stage 2 NREM sleep. This result is in contrast with the finding of walker et al. who showed that the finger tapping task is dependent on the first quarter of SWS and the last quarter of REM sleep. The differences between these findings could be explained by the different tests they have done. It seems that not all implicit memory tasks rely on the same system of consolidation. As we know there are four different non-declarative memory systems. So motor skill learning is correlated with stage 2 NREM sleep and that perceptual learning is correlated with first quarter of SWS and the last quarter of REM sleep.

An explanation for the fact that minimal 6 hours of sleep is needed before a sleep dependent effect is seen, is the fact that REM sleep is the qualitatively different at the end of the night comparing to the first hours of sleep[25]. So it seems that the last quarter of REM sleep plays a prominent role in the consolidation of implicit memory. Another option is that some other events might be required during the first 6 hours of sleep before the REM sleep dependent process could be effective.

As shown in figure 6 there are some major differences between the sleep dependency of declarative and non-declarative memory consolidation. In the figure it is clear that in humans generally declarative memory is SWS sleep dependent and non-declarative memory is REM and stage 2 NREM sleep dependent. Figure 7 showed a more detailed report of the involvement of sleep in the different memory systems but overall is declarative memory SWS dependent and non-declarative memory mostly relies on REM sleep.

In my opinion there is a missing link between the different research fields. There are almost no studies which have investigated the molecular role of gene expression with a memory task. Most of the articles focus just on one of the two research fields. Furthermore

most articles don't pay any attention on the molecular changes in the brain during sleep after participants finished the learning task. A combined animal study could give us a lot of information about the molecular changes in the brain after a specific learning task. So it could be interesting to investigate what is happening in the brain after a sleep dependent memory task and compare the result with the results of skill improvement.

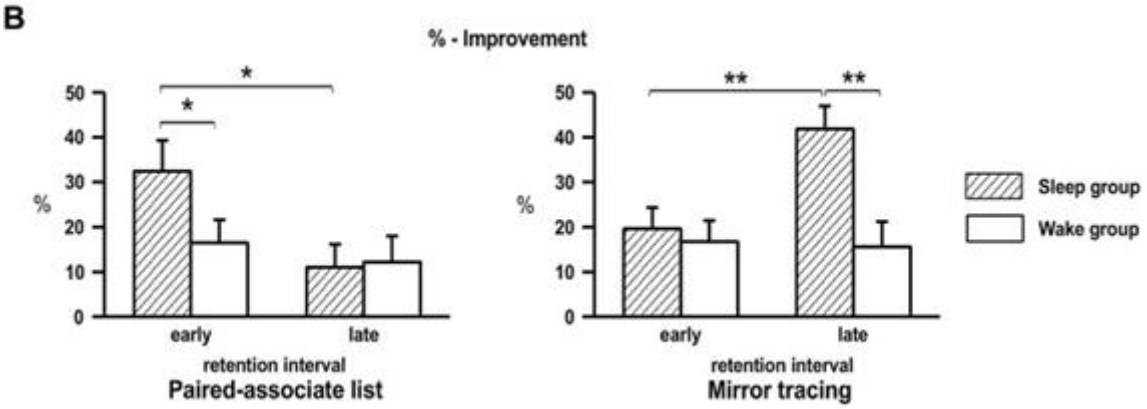

Figure 6. the differences in sleep-dependency in declarative and non-declarative tasks[23].

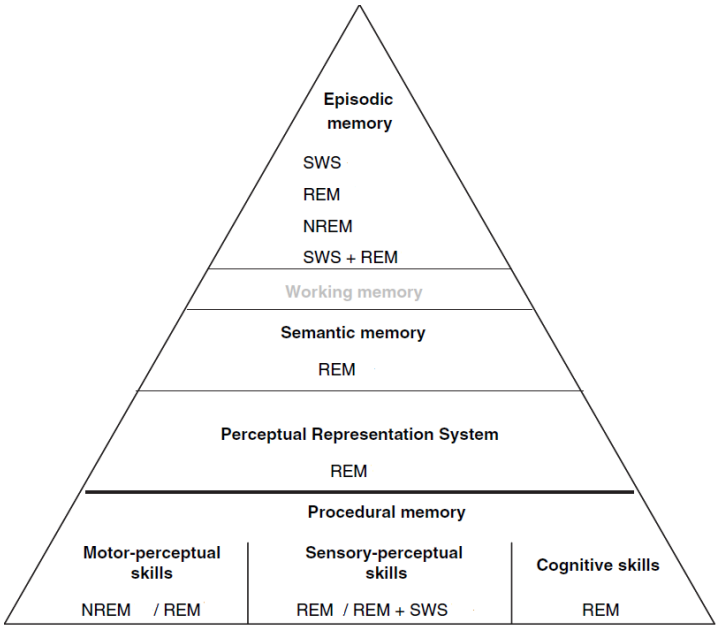

Figure 7. the detailed involvement of sleep in the different memory systems[28]

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