CHAPTER 7

General discussion
Chapter 7

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1. Sleep Deprivation and Different Memory Stages

This thesis represents a series of studies aimed at the consequences of sleep deprivation (SD) for memory processes. Disruption of sleep might affect different stages of memory processing, including acquisition, consolidation and adaptation. In our experiments we have studied the effects of SD at each of these stages.

Over the past decade, a variety of human and animal studies have shown that SD prior to learning affects behavioral performance during testing for memory (Drummond et al., 2000; Dametto et al., 2002; McDermott et al., 2003; Ruskin et al., 2004; Silva et al., 2004; Yoo et al., 2007; Ruskin and LaHoste, 2008; Tiba et al., 2008). However, most of these studies tested for memory after a delay of at least 24 hours after acquisition. As a consequence, these studies could not differentiate whether SD had an effect on memory encoding or on memory consolidation. In addition, these studies mostly focused on long periods of SD, which are not very common in everyday life. Therefore, in chapter 2 we assessed the consequences of SD prior to a novel arm recognition task on subsequent working memory performance. Our study has shown that a relatively short period (12 hours) of SD can, at least, have an immediate effect on working memory.

In addition to the effects of SD prior to learning, we also confirm that disrupting sleep immediately following learning affects memory consolidation. Importantly, we have shown this in different learning paradigms. In chapter 3 the effects of SD on maze learning in mice were studied. Mice subjected to 5 hours of SD following each daily training session changed the learning strategy used to solve the task. In Chapter 5 and 6 we used a fear conditioning paradigm in rats. Since this is a single-trial task, it has the advantage that one can examine the effects of one single SD period following training on selectively memory consolidation. We demonstrated that 6 hours of SD impaired memory consolidation for contextual fear conditioning. Whereas most human and animal studies focused on the effects of SD when training occurred close to or in the beginning of the resting phase (Karni et al., 1994; Smith and Rose, 1996, 1997; Stickgold et al., 2000a; Graves et al., 2003; Ferrara et al., 2006, 2008; Palchykova et al., 2006; Mograss et al., 2009), we have also demonstrated that SD affects memory consolidation when training occurs at the onset of the active phase, i.e. when training is not immediately followed by a substantial amount of sleep.

Furthermore, in chapter 3 we aimed to study the consequences of SD on the adaptation of a previously formed memory. This is an important aspect of successfully coping with changes that frequently occur in our surroundings, e.g., in case of moving to a new home, school or job. In our experiment, mice first had to learn to locate a food reward in one particular arm of a Y maze. When the animals mastered the task, they were confronted with the situation where the food reward was suddenly relocated in the previously non-rewarded arm. The results showed that SD for a brief period of 5 hours immediately after each training session reduced the flexibility and made it more difficult for mice to adapt their memory.

Altogether, our experiments clearly show that SD can affect different stages of memory processing. This is important from the point of view of understanding the precise role of sleep in learning and memory processes. However, for reasons of experimental control, the experiments in
this thesis, as well as in most other studies, applied a controlled and often single period of SD at specific experimental times to assess effects on specific aspects of memory. One may question therefore the validity of this approach for understanding the role of sleep shortage in the human society. In the western society, a large number of people are chronically sleep restricted and experience regular sleep loss due to our modern around-the-clock life style, work-related factors and psychosocial stress. In view of our current results, it seems likely that different memory stages may be affected simultaneously under conditions of more chronic sleep loss.

2. SLEEP DEPRIVATION AND THE HIPPOCAMPUS

The effects of SD on memory encoding, memory consolidation and memory adaptation may involve similar molecular mechanisms. At least at the level of brain regions, both SD prior to training in a learning task as well as SD following training often seem to affect similar crucial brain regions, especially the hippocampus (Smith and Rose, 1996, 1997; Graves et al., 2003; McDermott et al., 2003; Guan et al., 2004; Ruskin et al., 2004; Vecsey et al., 2009).

The hippocampus appears to be particularly sensitive to SD and, in fact, it has been shown that SD prior to as well as following training affects hippocampus-dependent memory, while leaving hippocampus-independent memory intact (Smith and Rose, 1996, 1997; Graves et al., 2003; McDermott et al., 2003; Guan et al., 2004; Ruskin et al., 2004; Vecsey et al., 2009). The data from chapter 3 of this thesis support this finding. In that study we showed that under conditions of SD there is a shift from hippocampus involvement to the striatum in a learning task. Animals subjected to SD avoided the use of a hippocampus-dependent spatial learning strategy and preferentially used a striatum-dependent response learning strategy to solve a maze task.

While there is evidence that the hippocampus is particularly sensitive to SD, it certainly can not be excluded that SD affects other brain regions as well, some of which are known to be involved in the learning tasks used in this thesis. Therefore, these brain regions might have contributed as well to the memory deficits we observed. For example, in case of the memory impairment in the novel arm recognition task in chapter 2 this might have been the perirhinal cortex (Liu and Bilkey, 2001). Similarly, the reduced memory flexibility seen in chapter 3 might have been due to impairments in the amygdala, medial prefrontal cortex and orbitofrontal cortex, three other regions critically involved in reversal learning (Elias et al., 1973; De Bruin et al., 1994; McDonald et al., 2004; Salazar et al., 2004; Ragozzino, 2007).

An intriguing question that remains to be answered is why the hippocampus is, perhaps not exclusively, but at least more sensitive to SD than various other brain regions. The literature suggests that the hippocampus is particularly sensitive to other manipulations as well, such as stress (Lupien et al., 1997; McEwen, 1999, Joëls, 2008), epilepsy, ischemia and neurodegeneration (Chang and Lowenstein, 2003; Nikonenko et al., 2009). This suggests that these various inputs and processes particularly affect a property that is specific for the hippocampus. Perhaps it has to do with the complexity of the hippocampal network or the amount of input the hippocampus receives. The
hippocampus is an important part of the brain for processing of information. It consists of several major subregions. Afferent input occurs at each of these regions and the output via the CA1 area is projected to several brain regions. One commonly suggested explanation for the high sensitivity of the hippocampus is its abundance in glucocorticoid receptors (De Kloet et al., 2005), but, as we will explain in section 4, this does not likely explain its sensitivity to SD. Another important feature of the hippocampus that may explain its sensitivity is the fact that it is one of the few brain regions showing substantial neurogenesis, even in adulthood (Abrous et al., 2005; Ming and Song, 2005). Newly generated neurons in the hippocampus may be involved in memory processes (Leuner et al., 2006) and neurogenesis is known to be sensitive to SD (Meerlo et al., 2009). We performed a number of experiments to test whether the SD-induced hippocampus-dependent memory impairments were associated with changes in neurogenesis, However, so far the results are inconclusive. In one of the experiments there was a tendency for reduced survival of new cells in mice subjected to SD following training sessions in a maze task. However, we did not find the expected learning-induced increase in cell survival in control animals. Therefore, we could not conclude that reduced neurogenesis and learning impairments in mice subjected to SD following training were actually linked (Hagewoud and Meerlo, unpublished results). Furthermore, it can also be suggested that a property within synaptic plasticity that is specific to the hippocampus is affected by SD.

3. SLEEP DEPRIVATION AND MOLECULAR PROCESSES INVOLVED IN HIPPOCAMPUS-DEPENDENT MEMORY

In several chapters of this thesis experiments were performed that may provide insight in the cellular and molecular mechanisms through which SD causes memory impairments. At the cellular level, changes in synaptic strength, the strength of the connectivity between two neurons, and membrane excitability are thought to be critical for the formation of memories (Bliss and Collingridge, 1993). Persistent changes in synaptic transmission are necessary for long term memory (LTM) and these changes require protein synthesis (Davis and Squire, 1984; Frey et al., 1993; Huang et al., 1994; Nguyen and Kandel, 1996).

In chapter 2 we assessed the consequences of acute SD on hippocampal AMPA receptors, particularly the GluR1 subunits, which are known to be important in synaptic plasticity underlying memory (Lamprecht and LeDoux, 2004; Malenka and Bear, 2004). While SD did not affect overall levels of the AMPA GluR1 protein, it did reduce phosphorylation at the serine 845 (S845) site. Since phosphorylation at this site is important for the incorporation of the receptors into the membrane, this may suggest that SD leads to reduced efficacy of AMPA receptor signaling. Such altered regulation of glutamate receptors may in part depend on SD-induced changes in the intracellular cAMP/PKA pathway. In our study we only found indirect evidence for this. Protein levels of PKA were not affected by SD, however, we did find a reduced expression of the scaffolding protein AKAP150, which binds and partly controls the actions of PKA. Another recent study in mice has indeed confirmed the idea that an acute brief SD period of 5 hours impairs cAMP/PKA signaling in the hippocampus (Vecsey et
That same study showed that SD impairs at least one major downstream target of the cAMP/PKA signaling pathway, namely CREB. SD caused a decrease in the phosphorylation and thereby activation of the transcription factor CREB.

In chapter 3 and 4 of this thesis we showed that SD immediately following training sessions in a Y-maze task also reduced the normal training-induced increase in phosphorylation of CREB. This transcription factor plays an essential role in regulating memory-related gene expression and protein synthesis which is necessary for LTM formation. Phosphorylation of S133 promotes transcription of downstream genes such as the immediate early genes \textit{c-fos} (Sheng et al., 1990) and \textit{zif268} (Bozon et al., 2003), whose products, in turn, induce the transcription of late downstream genes, and activate direct 'effector' proteins, such as structural proteins, signaling enzymes or growth factors, that are essential for LTM (Lanahan and Worley, 1998; Lonze and Ginty, 2002).

Thus, we have shown that SD following learning affects training-induced activation of proteins involved in memory formation. In our experiments, we studied the effects of SD on the molecular level in the hippocampus in combination with effects on behavioral performance. Therefore, we only assessed CREB phosphorylation at the end of the training phase (in chapter 4), after the probe trial in which the learning strategy was determined (chapter 3) and upon later testing for memory (in chapter 5). It would be important to also assess CREB phosphorylation in earlier phases of the training to confirm that SD indeed interferes with this cascade in the critical phases of ongoing memory formation. Available evidence suggests that the effect of SD earlier in the memory consolidation process itself indeed involves alterations in cAMP/PKA/CREB signaling. One recent study has shown that hippocampus-dependent memory deficits induced by SD following training were rescued by a treatment with an inhibitor of phosphodiesterase 4 (PDE4), an enzyme that degrades cAMP, immediately or 2.5 hours following training. This suggests that SD following learning disrupts hippocampus function by increasing PDE4 activity and protein levels, which then interferes with the cAMP/PKA/CREB signaling pathway (Vecsey et al., 2009).

Altogether, these data indicate that one way in which SD negatively affects hippocampus-dependent memory is through the inhibition of the cAMP/PKA/CREB signaling pathway, which in turn may affect protein synthesis and synaptic plasticity processes necessary for LTM. Furthermore, it can be suggested that sleep might act to enhance this signaling pathway and thereby promotes gene expression and protein synthesis required for memory consolidation. However, the question still remains what the primary element is that sleep directly acts on and that SD might directly affect in an opposite way.

An important feature of sleep is a decrease in serotonergic neurotransmission. The reduced levels of serotonin may contribute to memory consolidation, possibly through removal of the inhibition of activity of adenyl cyclase, an enzyme that increases levels of cAMP (Graves et al., 2001). Since it is known that SD increases serotonergic transmission in the hippocampus (Lopez-Rodriguez et al., 2003), it is possible that SD-induced impairments on memory consolidation are a result of SD directly acting on serotonergic transmission. Furthermore, during rapid eye movement (REM) sleep there are increased levels of acetylcholine in the hippocampus, which is also suggested to promote memory consolidation through activation of the cAMP/PKA signaling pathway (Graves et al., 2001). SD may
interfere with this through increased levels of acetylcholinesterase, an enzyme that degrades acetylcholine (Kalonia et al., 2008). The use of genetically modified mice will definitely contribute to the examination of the primary elements involved in memory consolidation on which sleep and SD directly act.

4. LACK OF SLEEP OR WAKING INTERFERENCE?

While studies discussed in previous sections clearly indicate that SD affects brain regions and molecular processes involved in memory processing, it remains a discussion whether sleep plays and active role in memory formation or merely a passive or permissive role by protecting memory against waking interference (Ellenbogen et al. 2006b). Indeed, it is often argued that memory impairments after SD may not be the result of sleep loss per se but, rather, the consequence of a disturbing influence of the extended wakefulness, which causes additional input of information during a time period when normally processes involved in memory consolidation would occur. Particularly in animal experiments, which often rely on forced wakefulness, the stimulation and stress involved in the SD method are often considered as potential interfering factors contributing to the SD-induced memory impairments. Therefore, we performed several experiments in this thesis to solve this critical issue.

In chapter 6 we investigated whether the number of sensory stimulations required to keep the animals awake was responsible for the memory impairments. Memory consolidation during the main resting phase was disrupted by a 6 hour SD period, whereas memory consolidation during the active phase with the exact same amount of stimulation remained undisturbed. Memory consolidation in the active phase was only significantly affected by a much longer period of 12 hours of SD by mild stimulation even though in that case the total amount of stimulations was still lower than the amount of stimulations used during 6 h SD in the resting phase. Importantly, since rats spend about 65 to 80% of the resting phase asleep and about 20 to 35% of the active phase (Borbély and Neuhaus, 1979; Lancel and Kerkhof, 1989; Franken et al., 1991; Tang et al., 2007), the 6 hours of SD in the resting phase and 12 hours of SD in the active phase are associated with comparable amounts of sleep loss. Altogether, these data do not support the notion that the memory impairments are due to the number of sensory stimulations during the SD period.

In addition to sensory stimulation as a form of waking interference, we also examined whether stress might be an SD-associated interfering factor that contributed to the memory impairments in our experiments. Yet, in several chapters we have demonstrated that 5, 6 and 12 hours of SD by mild sensory stimulation leads to very mild and most often non-significant increases in levels of the stress hormone corticosterone. While in all these experiments corticosterone (CORT) levels were only measured at the end of the SD period, we performed an additional experiment in which we took blood samples at different time points during a single 6 hour SD period. CORT levels were not significantly elevated after 30 minutes, 2 hours and 6 hours of SD (data not shown). These results demonstrate that SD did also not lead to an acute increase in plasma levels of CORT. In fact, the levels of CORT that we found in response to SD are in the same range or even lower than after spontaneous waking
activities such as feeding and grooming (Shiraishi et al., 1984). Arguing that such mild increases indicate a state of stress that might be responsible for memory impairment would effectively mean that any kind of spontaneous behavior following learning should interfere with memory processes.

Moreover, even when SD would cause small and acute increases in CORT levels during the consolidation phase, it is much more likely that it would contribute to memory consolidation in a positive way, and therefore opposite to the findings in this thesis. Contrary to the view that stress has adverse effects on memory consolidation, it is well known that glucocorticoids can contribute to memory in a positive way (Hui et al., 2004; Miranda et al., 2008; Abrari et al., 2009; Roozendaal et al., 2010).

One direct approach to experimentally test the role of stress and glucocorticoids in the SD-induced memory impairments would be to block the CORT release. To the best of our knowledge, such studies have not been performed with SD immediately following training, during the critical time period of memory consolidation. However, studies that examined the effects of SD prior to learning have shown by eliminating the adrenal stress response with adrenalectomy or by CORT inhibition with metyrapone that glucocorticoids do not mediate in the memory impairments seen after SD (Ruskin et al., 2006; Tiba et al., 2008).

Altogether, we did not find any support for the notion that waking interference by sensory stimulation or stress hormones mediates the negative effects of SD on memory processes. Although we cannot rule out some other form of interference, data from chapter 6 in particular suggest that the memory impairment after SD seems to be better explained by the amount of sleep that was lost following training. These latter data support the hypothesis that sleep might play an active role in learning and memory processes (Ellenbogen et al., 2000b).

Also human studies have contributed to the finding that sleep does not merely passively protect memories from waking interference, during which sleep only sustains memories by protecting them from waking interference but does not consolidate them. In one of the studies interference was controlled and experimentally manipulated (Ellenbogen et al., 2006a). Participants had to learn a list of word-pair associates, followed by a 12 hour offline retention period containing either sleep or normal wakefulness. Twelve hours of wakefulness resulted in a reduced performance during testing compared with 12 hours of sleep. However, when associative interference (a new list of word-pair associates) was introduced after the 12 hour SD period, this resulted in an even larger (58%) reduction in performance in the wake group compared with the sleep group. These results show that sleep protects against memory deterioration, as shown by a better recall after sleep than after wakefulness. In addition, it shows that sleep protected memory from future interference as shown by the resistance to interference after sleep but not after wakefulness. This study demonstrates that sleep strengthened the memory. Therefore it is suggested that sleep is somehow involved in memory consolidation, which makes memories resistant to interference instead of only passive memory protection.

To establish whether sleep is actively involved in memory consolidation, one has to show that memory consolidation crucially depends on neuronal or synaptic processes that are unique to sleep. There may be several ways to approach this question, but to separate sleep specific processes from
waking interference effects, one might try to manipulate relevant processes during sleep without inducing wakefulness. This will be discussed in the next section.

5. **Lack of NREM Sleep or REM Sleep?**

In the context of a possible role for sleep in memory consolidation, an important question is whether this role is fulfilled by Non-REM (NREM) sleep, REM sleep or both. Different approaches have been used to assess the role of different sleep stages in memory processes. One approach is to study sleep after the acquisition of a learning task and assess changes in the amount of certain sleep stages or changes in neuronal activity during these stages. A second approach is to selectively disrupt or deprive sleep stages or phenomena related to these phases and then assess the effects on subsequent memory.

The investigation of post-learning sleep modifications has shown changes in the amount of sleep stages as well as in electrophysiological phenomena occurring within these sleep stages. Studies in animals have shown that the amount of REM sleep is increased following training in a hippocampus-dependent learning task (Smith et al., 1998). Also, increases in hippocampal sharp-wave ripple activity, which are complexes of high-frequency oscillations, during slow wave sleep (SWS) have been observed following learning in hippocampus-mediated learning tasks (Eschenko et al., 2008; Ramadan et al., 2009). Human studies show increases in EEG activity during SWS following learning of a declarative task (Mölle et al., 2004) as well as following learning in a procedural task (Huber et al., 2004). Furthermore, it is suggested that changes in NREM stage 2 sleep are also relevant in memory consolidation processes since learning in a visuospatial task was associated with increased number of sleep spindles, the most synchronous oscillatory waveforms, during NREM stage 2 sleep (Clemens, 2006). However, other studies also show increases in the amount of REM sleep and in EEG activity during REM sleep following learning in declarative and procedural tasks (De Koninck et al., 1989; Fogel et al., 2007). Importantly, several human and animal studies have shown that post-sleep task improvement correlated with the increases in the amount of REM sleep and SWS (Stickgold et al., 2000b), in slow wave activity (SWA) (Huber et al., 2004) and in ripple density (Ramadan et al., 2009). Therefore, some of these electrophysiological phenomena in NREM and REM sleep may reflect crucial processes specifically involved in sleep-dependent memory consolidation.

The analysis of neuronal activity in animals has demonstrated that hippocampal activity observed during encoding was replayed during subsequent periods of SWS (Pavlices and Winson, 1989; Wilson and McNaughton, 1994; Kudrimoti et al., 1999) and was also observed in REM sleep (Louie and Wilson, 2001). Neuroimaging studies in humans find similar effects. Hippocampal activity was reactivated during SWS following learning in a spatial task and the amount of reactivation correlated with route recall performance the next day (Peigneux et al., 2004). Furthermore, a recent human study showed that cueing new memories during SWS by presenting an odor that had been presented as context during prior learning improved the retention of hippocampus-dependent memories (Peigneux et al., 2004).
memories (Rasch et al., 2007). This study therefore shows a causative role of neuronal reactivation during SWS for memory consolidation and indicates that sleep actively contributes to memory consolidation. The sleep-dependent neuronal replay may potentially allow the adaptation of synaptic strengths within specific networks. In addition to changes in electrophysiology and neuronal activity also changes in gene expression have been observed during sleep following training. For example, an upregulation of zif268, a gene known to be associated with synaptic plasticity, during REM sleep has been shown selectively following a rich sensory motor experience (Ribeiro et al., 1999).

These studies suggest that memory processes are associated with specific changes in the amount of certain sleep stages or with specific changes in neuronal activity during these stages. In themselves, these correlative phenomena do not provide evidence that a certain sleep stage is causally involved in the ongoing memory formation. For that, one needs to experimentally manipulate these stages and show that it results in disruption of memory.

In this thesis we used a mild sensory stimulation method that did not selectively deprive the animals of a certain sleep stage. Therefore, our findings cannot contribute to the importance of REM or NREM sleep in memory processing. While the idea of selective sleep stage deprivation sounds attractive, it is difficult to achieve in reality. The natural order is that sleep begins with NREM sleep, which at some point is followed by REM sleep. These two stages cycle through the sleep period. Selective NREM SD is not possible since it also prevents REM sleep. While selective REM SD appears feasible, the frequent awakenings upon REM sleep entry often lead to mild changes in the amount of NREM sleep as well. Nevertheless, this more or less selective REM SD has frequently been applied in animal studies.

It has been shown that memory in rodents is disrupted when REM SD is performed following training in several different hippocampus-mediated learning tasks (Smith and Butler, 1982; Smith and Rose 1996, 1997; Smith et al., 1998; Silva et al., 2004; Alvarenga et al., 2008). A different approach has been applied in humans, making use of the fact that deep NREM sleep mainly occurs in the first half of the night whereas REM sleep is more prominent in the second half of the night. According to some studies, SD during the first half of the night, which is rich in NREM sleep, disrupts consolidation of declarative memories, whereas SD during the second half of the night, which is rich in REM sleep, disrupts consolidation of procedural and emotional memories (Plihal and Born, 1997; Gais and Born 2004; Walker and Stickgold, 2006; Wagner and Born, 2008). However, it has also been shown that declarative memory was impaired following deprivation of late night REM-rich sleep (Rauchs et al., 2004). Importantly, also this method does not selectively disrupt one sleep stage and therefore cannot rule out the possibility that a shortage of a combination of both stages contributes to the memory impairments.

In addition to the attempts to more or less selectively deprive subjects from specific sleep stages, recent studies have applied more subtle approaches aimed to separate sleep specific processes from waking interference effects by disturbing sleep stages or specific aspects of these sleep stages without actual inducing wakefulness and changing the amount of sleep stages. One study showed that suppression of SWA during intact sleep was sufficient to disrupt subsequent successful encoding-related hippocampal activation and memory performance in a hippocampus-
mediated task in humans (Van der Werf et al., 2009). It would be worthwhile to apply this approach and assess whether SWA suppression after acquisition also specifically affects the consolidation of memory and underlying mechanisms. Importantly, it has already been indicated that deprivation of slow waves, without affecting sleep time and efficiency, following acquisition in a visuomotor task in humans prevents the behavioral improvement seen after normal sleep (Landsness et al., 2009). Along these lines, one could also try to interfere with other neurophysiological phenomena that specifically occur during the specific sleep stages following acquisition of a new task, without changing the actual amount of sleep, and then assess the contributions of these phenomena to specific types and stages of memory.

Altogether, findings from the above mentioned studies support an active role for sleep in memory formation but it remains unclear if there is one particular sleep stage that is crucially involved. It seems likely that both NREM and REM sleep are involved in the processing of memories. In fact, it has been suggested that it is the combined action of NREM and REM sleep that determines a gradual increase in the strength and consolidation level of memories (Ribeiro et al., 2004). Recently, a model has been proposed which states that sleep stage specificity exists for different stages involved in memory processing (Stickgold, 2009). According to that model, SWS is required for memory stabilization within the consolidation stage through a process of synaptic level consolidation that maintains and stabilizes synaptic modifications that are produced through memory encoding (Wang et al., 2006), whereas REM and NREM stage 2 sleep facilitate system level processes during consolidation that enhance the efficacy of the memories (Stickgold and Walker, 2007). Clearly the role of specific sleep stages in specific aspects of memory formation requires further study.

6. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The findings presented in this thesis demonstrate that acute SD prior to as well as following training impairs behavioral performance in hippocampus-dependent learning tasks and changes levels of proteins known to be involved in learning and memory processes.

The most important finding of the present work is that changes in behavioral performance are not always seen right away. While at the level of the brain clear changes in levels of proteins involved in memory processes are seen, the availability of alternative brain mechanisms and learning strategies that can compensate for a hippocampal deficit may determine whether or not SD has noticeable effects on cognitive performance. This may explain some of the discrepancies and discussions in the literature on whether or not deprivation of sleep really affects cognitive performance. However, effects of SD can still appear later on, because the alternative learning mechanisms and brain regions involved may result in reduced flexibility under changing conditions that require adaptation of the previously formed memory which is an important aspect of successfully coping with changes that frequently occur in our surroundings, e.g., in case of moving to a new home, school or job.
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The association between sleep and memory is a fascinating and dynamic area of research. The experiments presented in this thesis contribute to this knowledge and provide novel data on the effects of acute SD on memory processes and the possible underlying mechanisms. However, many important and challenging questions remain to be answered, which makes the future of the field truly exciting.

To me one of the most intriguing questions is why SD particularly affects the hippocampus. Furthermore, it is still largely unknown which molecular mechanisms in the hippocampus are affected by SD during the critical time period following training which is sensitive to sleep loss. In addition, it will be a great challenge to unravel the exact role of REM and NREM sleep in memory consolidation.

Also, the present thesis, as well as most other studies, has focused on effects of a single episode of SD at specific stages of memory processing. However, in our society humans are often chronically sleep restricted. Whereas people seem to recover easily from the effects of acute sleep loss, frequent or chronic loss of sleep may induce changes in the neurobiology of memory processing that accumulate over time and which might affect brain mechanisms underlying cognitive processes in as yet unexplored ways. Therefore, it is of great importance for future research to study the effects of chronic sleep loss on memory processes.

Since many people in the world regularly experience sleep loss, it is important to make people aware that sleep is extremely important for our functioning and well-being and that loss of sleep as little as a few hours can have serious consequences on behavioral performance and on molecular mechanisms in the brain that underlie memory processing.
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