Aus dem Institut für Neuroendokrinologie

der Universität zu Lübeck

Direktor: Prof. Dr. Jan Born

Sleep-associated and neuroendocrine mechanisms of false memory formation

Inauguraldissertation

zur

Erlangung der Doktorwürde

der Universität zu Lübeck

– Aus der Medizinischen Fakultät –

vorgelegt von

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aus Dresden

Lübeck 2010

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Tag der mündlichen Prüfung: 07.02.2011

Zum Druck genehmigt. Lübeck, den 07.02.2011

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Abbreviations

ACTH:	Adrenocorticotropic hormone
ANOVA:	Analysis of variance
cAMP:	3'-5'-cyclic adenosine monophosphate
DRM:	Deese-Roediger-McDermott paradigm
EEG:	Electroencephalography
ERP:	Event-related potential
fMRI:	Functional magnetic resonance imaging
GC:	Glucocorticoid
HPA axis:	Hypothalamus-pituitary-adrenal axis
LTD:	Long-term depression
LTP:	Long-term potentiation
MC:	Mineralocorticoid
MTL:	Medial temporal lobe
NREM:	Non rapid eye movement
PET:	Positron emission tomography
PFC:	Prefrontal cortex
PKA:	Protein kinase A
REM:	Rapid eye movement
RKG:	Remember/Know/Guess
SEM:	Standard error of the mean
SRTT:	Serial reaction time task
SWS:	Slow wave sleep
TMS:	Transcranial magnetic stimulation

Introduction

Memory is a defining feature of human beings anchoring the individual in time, from the past through the present to the future. Research has provided substantial evidence that memory is not a literal record of the world, but instead what is retrieved from memory can be changed in a reconstructive process by new information as well as by pre-existing knowledge. Although memory is remarkably accurate in most instances, the reconstructive process of memory formation can sometimes go awry, leading to memory distortions and even "false memories". False memories are defined as memories of events that actually never happened. Although in the last decade research advanced in phenomenologically describing the generation of false memories, the neurobiological mechanisms underlying this phenomenon remain largely unknown. In recent years, substantial evidence accumulated that sleep plays a crucial role in the consolidation of newly acquired memories. Apart from a strengthening of memory traces for long-term storage, sleep has been shown to dynamically reorganize memory representations, which can lead to qualitative changes in these memories. Acute sleep deprivation, on the other hand, is known to distinctly impair cognitive functions including processes of memory formation. In addition, specific neuroendocrine factors have been identified to affect and alter the processing of memories. The studies conducted for the present thesis aimed at elucidating the role of sleep, sleep deprivation and specific neuroendocrine modulators for the generation of false memories.

Memory and processes of memory formation

Memory systems

Memory is not a unitary system. Different forms and subtypes of memory can be distinguished. According to the time frame in which memories are retained, memory can be subdivided in a sensory buffer, short-term memory and long-term memory (Squire, 1986; Squire et al., 1993). The sensory buffer maintains information for several seconds whereas short-term memory holds up information for several minutes or hours. Memories that last for days or even years are stored in long-term memory[*]. Long-term memory in humans can be divided at least into two types of memory, often referred to as declarative and non-declarative memory according to its content (Squire & Zola, 1996; Squire, 1998; Figure 1). Declarative

[*] In the present thesis, the term "memory" will basically refer to long-term memory in the following.

memory consists of memories accessible to conscious recollection that can be voluntarily controlled – this type of memory is therefore also called explicit memory. Declarative memory encompasses memories for events in a spatiotemporal and autobiographical context (episodic memory) as well as generalized knowledge without knowing where or when the content has been acquired (semantic memory; Squire et al., 1993; Squire & Zola, 1996). Specific tasks are typically used in experimental settings to assess declarative memory, e.g., word-list learning, learning of paired associates, or learning of pictures. On the other hand, non-declarative memory consists of heterogeneous memory processes, e.g., procedural memory, priming, and classical conditioning (Squire et al., 1993). Procedural memory, or skill learning, respectively, describes a process in which a specific skill is acquired unconsciously through repeated practice. Procedural memory is typically investigated by tasks of motor learning, like finger sequence tapping tasks, mirror-tracing, or rotary adaptation. Priming refers to a change in the processing of a stimulus as the result of prior exposure to the same or a related stimulus, e.g., a word or an abstract object. Conditioning is a kind of associative learning in which the relation between two or more events is learned, e.g., between a stimulus and a response (e.g., air puff and eye blink). All types of non-declarative memory are mostly acquired without voluntary control and without conscious knowledge. Therefore, non-declarative memory is also referred to as implicit memory.

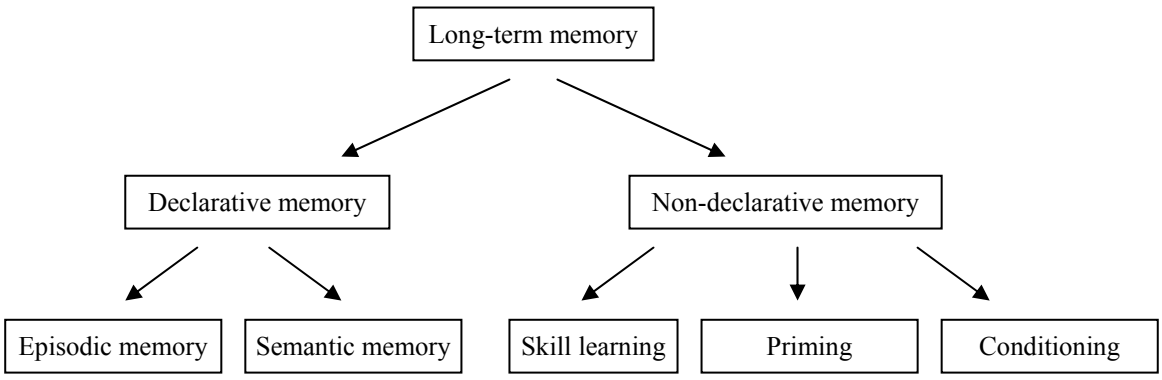

Figure 1. Multiple systems of long-term memory (Squire & Zola, 1996)

Declarative memory critically depends on the medial temporal lobe (MTL), including the hippocampus and adjacent regions (Squire & Zola-Morgan, 1991). The importance of the MTL system for declarative memory processes has been studied in patients with damage to this brain region, revealing that they suffer from a severe impairment of memory called amnesia (Milner, 2005; Cipolotti & Bird, 2006). Such patients are unable to form new

memories for the long-term after the onset of MTL damage (anterograde amnesia) and also have difficulties retrieving memories that had been stored before the lesion (retrograde amnesia; Squire & Zola, 1996; Spiers et al., 2001). Most often retrograde amnesia is temporally graded, such that the longer the events lay back in the past, the more likely they are to be still remembered (Squire & Alvarez, 1995; Squire et al., 2001), suggesting a temporary role of the hippocampus in memory storage. Non-declarative memory, on the other hand, appears to be independent from the MTL system. It rather recruits different brain regions depending on the type of non-declarative memory (Squire & Zola, 1996). Procedural memory is primarily supported by motor regions, such as basal ganglia, cerebellum, and the motor cortex. Priming, on the contrary, depends on modality-specific neocortical areas (perceptual priming) and amodal language-specific regions (conceptual priming). Conditioning mainly relies on cerebellar, amygdalar, and medial temporal circuits (for an overview see Gabrieli, 1998).

Stages of memory formation

Memory encompasses three successive stages: encoding, consolidation, and retrieval. In the encoding phase, new information is acquired and transformed into a neural representation that is initially labile and vulnerable to disrupting and interfering influences. During the consolidation phase, these fresh and labile memory representations are strengthened and transformed into a more robust and stable form that is relatively resistant to interfering influences. Finally, memories can be recalled during the phase of retrieval. Successful remembering thereby depends on the effective accomplishment of all three stages of memory formation. The stages of consolidation and retrieval will be discussed more detailed in the following.

Consolidation describes all post-experience processes of memory stabilization, strengthening, and reorganization. At least two kinds of consolidation can be distinguished: synaptic consolidation and system consolidation (Dudai, 2004; Frankland & Bontempi, 2005). Synaptic consolidation involves changes in synaptic connectivity in localized neural circuits and is completed within the first few hours following learning. These changes include the growth of new synaptic connections as well as the restructuring of existing synaptic connections. Long-term potentiation (LTP) is considered a key mechanism of synaptic consolidation, providing enduring synaptic plastic changes (Bliss & Lomo, 1973; Bliss & Collingridge, 1993; Malenka & Nicoll, 1999). Through the repeated co-activation of pre- and

postsynaptic neurons, the synaptic connections between these neurons become strengthened (potentiated), such that subsequent presynaptic signals lead to an enhanced postsynaptic response (Hebb, 1949). Conversely, synaptic connections can also become weakened through a similar mechanism of long-term depression (LTD). LTP and LTD have been observed in different brain regions including the hippocampus (Bliss & Collingridge, 1993; Nicoll & Malenka, 1995) and neocortical regions (Bear & Kirkwood, 1993).

Apart from local synaptic changes, consolidation also comprises a more prolonged process that involves the gradual reorganization of brain regions on the system level, which is therefore termed "system consolidation" (Marr, 1971; Dudai, 2004). System consolidation refers to a time-dependent process that promotes the gradual redistribution of memory traces from a temporary store to sites for long-term storage (Figure 2). For declarative memories, the temporary and long-term stores are represented by the MTL, especially the hippocampus, and the neocortex, respectively. The hippocampus serves as an intermediate buffer that allows learning at a fast rate, holding the information only temporarily, whereas neocortical regions serve as long-term store that learns at a slow rate but has also a slow rate of forgetting (Buzsaki, 1989; McClelland et al., 1995). Initially, new events are encoded in parallel in the hippocampus and in distributed regions of the neocortex whereby the hippocampus binds together the single aspects of an encountered event in different cortical modules to form a coherent episode (Eichenbaum, 2004; Morris, 2006). In subsequent periods of system consolidation, the newly encoded memory traces are repeatedly reactivated in the hippocampus which drives concurrent reactivation in the slow learning neocortical long-term store. Thereby new memories become gradually transferred and redistributed to neocortical regions (Frankland & Bontempi, 2005; Rasch & Born, 2007). Through the repeated reactivation of new memories, in conjunction with related and similar older memories, the hippocampus acts like an internal "trainer" of the neocortex to gradually integrate the new memories into the pre-existing network of long-term memories. Such reactivations lead to a strengthening of the connections in the neocortical long-term store, so that after some time memories in the long-term store become independent from the hippocampus (McClelland et al., 1995; Squire & Alvarez, 1995). It has been suggested that the prefrontal cortex (PFC) might subsequently take the integrative role of binding single elements of remote memories via reciprocal connections with different cortical modules (Buckner & Koutstaal, 1998; Buckner & Wheeler, 2001; Frankland & Bontempi, 2005). As both the temporary hippocampal store and the neocortical long-term store are also associated with the encoding of information, the reactivation and redistribution of memories primarily take place offline

(i.e., during sleep) when no encoding occurs, in order to prevent interference (see below; Buzsaki, 1998; Maquet, 2001; Diekelmann & Born, 2010).

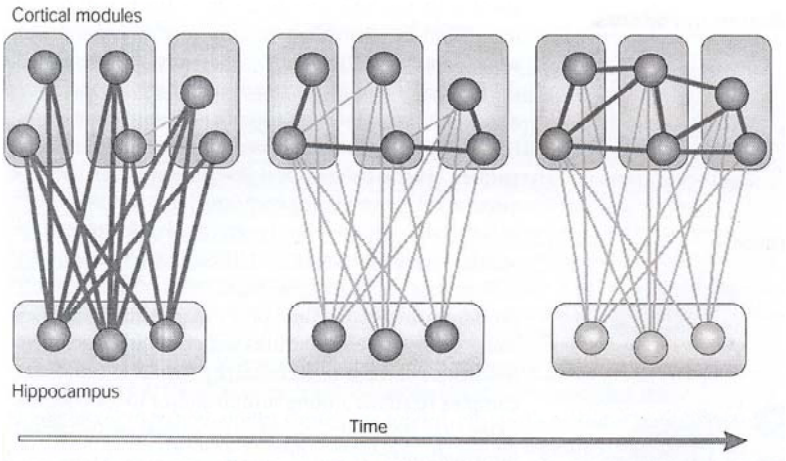

Figure 2. A model of the system consolidation process. The hippocampus has a time-limited role in temporary storage and binding of information that is stored in distributed cortical networks for the long-term (Frankland & Bontempi, 2005).

Memory retrieval, similar to consolidation, is a complex process that depends on different modulating factors. For example, retrieval performance is better if the same processes are required at retrieval testing as during encoding (transfer appropriate processing; Morris et al., 1977), if adequate retrieval cues are available (Tulving & Osler, 1968), or if retrieval takes place in the same context or the same state as learning (context- or state-dependent memory; Godden & Baddeley, 1975; Eich et al., 1975). Importantly, there are different declarative memory tasks that considerably vary in their strategic memory demands, i.e., in the amount retrieved memories must be evaluated, manipulated, and transformed. Recall and recognition procedures are the most commonly used experimental retrieval tests (Nobel & Shiffrin, 2001; Kahana et al., 2005). Recall is the ability to remember a previously encountered stimulus in the absence of that stimulus, i.e., the to-be-remembered stimulus has to be *generated* by the subject himself/herself, either without any specific cues given (free recall) or in response to a cue previously paired with that stimulus (cued recall). Recognition is the ability to decide in the presence of a stimulus whether this stimulus was previously presented or not, i.e., the learned stimulus has to be *recognized* by the subject. Recognition can be expressed as "recollection" (or “remembering” in a more specific sense) which refers to a re-identification of a stimulus with a sense of “re-living” including detailed spatiotemporal context information of its presentation, or as a feeling of "familiarity" (or “knowing”) referring to simply knowing

that the stimulus was previously encountered without the retrieval of specific context information (Gardiner et al., 2002; Squire et al., 2007; Paller et al., 2007). Different theories have been postulated on the relation between recall and recognition. Strength theory assumes that the study of to-be-learned items strengthens the associations between these items and the performance in recognition and recall tests depend on the strength of these associations. Accordingly, recognition is usually easier than recall because recognition can be successfully performed with weaker associations, whereas associations need to be sufficiently strong for successful recall performance (Kahana et al., 2005). However, several experimental variables have been shown to exert opposing effects on recognition and recall, speaking against the simplistic strength theory (Gardiner, 1988; MacLeod & Kampe, 1996). The "generate-recognize" theory provides an alternative view, suggesting that recall involves two stages: the generation of possible responses and a recognition test to decide whether each of these generated responses was actually learned or not, whereas recognition is characterized by the absence of the first generation stage (Bahrick, 1970). Thus, recall compared to recognition is assumed to specifically depend on strategic memory search processes that allow identification and generation of the to-be-recalled items (Rohrer & Wixted, 1994; Nobel & Shiffrin, 2001). Recall and recognition have further been suggested to depend, at least partly, on distinct neuroanatomical structures. Recall involves hippocampal function whereas hippocampal contributions to recognition, and especially to familiarity judgments, appear to be less well established (Baddeley et al., 2001; Mayes et al., 2002; Bastin et al., 2004; Holdstock et al., 2005; for an overview see Squire et al., 2007).

Memory distortions and false memories

As described above, memories are stored in different distributed neocortical brain regions with the single elements of an episode being initially bound by the hippocampus and later on by the PFC. Retrieving an event or object from memory requires bringing together the different kinds of information that are distributed across cortical sites and reassembling the information into a coherent whole (Schacter, 1996; Schacter et al., 1998). Remembering an event does not simply reflect the "re-instantiation" of the activation that this event induced during encoding but only some fragments of the memory or even other non-corresponding parts may be activated, depending on different conditions. Thus, what is retrieved from memory can differ from what was originally stored. In this respect, memory can be viewed as a constructive and reconstructive process, an idea first introduced by Bartlett in 1932. In his

classical experiment, Bartlett had subjects read a story which they were required to retell repeatedly after 15 minutes, several days, weeks, and even years. Bartlett demonstrated that the greater the interval between reading the story and retelling it, the more altered the original story. Subjects tended to abstract more and more from individual features of the original story and adapted it to their own general knowledge, previous experiences, and cultural backgrounds. Bartlett concluded that memory is reconstructive in the way that features of an experienced event are altered so that they fit in pre-existing schemas. Aspects of the remembered event itself are combined with background information of related material and general knowledge. Thus, memories can be altered and can seriously deviate from the actual event (a phenomenon called "memory distortions"), and sometimes people even claim to remember entire events that actually never happened (a phenomenon called "false memories").

A vast amount of evidence on memory distortions and false memories has been accumulated in the last decades (Loftus et al., 1995; Schacter et al., 1998; Schacter, 1999; Schacter et al., 2003; Loftus, 2003). Elizabeth Loftus and her colleagues (1995) have shown that stored memories can be modified by the acquisition of new, interfering information. In typical studies, participants observe a specific event via slides or videotape, e.g., a car accident, and are then asked questions about that episode, with some questions containing suggestions of incidents that never occurred. Frequently, subjects falsely recognize such suggested events at a later retrieval test and incorporate this new information into their memory representations, an effect referred to as the "post-learning misinformation effect" (Lindsay & Johnson, 1989; Loftus & Hoffman, 1989; Weingardt et al., 1995; Loftus, 2005). Apart from suggestive information, the mere imagination of an event can increase the likelihood of falsely remembering this event (Loftus, 1997; Schacter et al., 1998; Seamon et al., 2006). Subjects, who were asked to imagine events that they had not previously experienced, subsequently were more likely to claim that they actually did experience these imagined events. Because increasing the number of imaginations enhances the probability that subjects will falsely remember to have experienced those imagined events, this effect has been termed "imagination inflation" (Goff & Roediger, III, 1998; Thomas et al., 2003). Loftus and her colleagues even succeeded in implanting their subjects with entire memories for events that never happened (Loftus, 1997; Libby, 2003; Laney & Loftus, 2008). In a classical study, subjects were given brief descriptions of four events that supposedly occurred in their childhood and were asked by relatives to try to remember these events. Three were actually true events and one was a false event of having been lost in a mall at the age of five. Being

asked again after one week, 25 % of the subjects “remembered” having experienced this event and sometimes even described vivid details of the situation and their feelings. This effect was replicated several times with different implanted events (Loftus et al., 1995).

Another line of evidence indicates that an intriguing feature of human memory is the ability to extract the general meaning or the “gist” of single encountered events in an adaptive process (Roediger, III & McDermott, 1995; Schacter et al., 1998; Schacter, 1999; Schacter et al., 2003). Several studies investigated the abstraction of a prototype or schema from single deviations of that prototype using different materials. Subjects who were presented with dot patterns, which were all different but deviants from one prototype that was not presented during the study phase, subsequently falsely recognized the prototype with high confidence, even more than actually presented patterns (Posner & Keele, 1968; Strange et al., 1970). Similar results were obtained using sentences that contained different semantic information, with each single sentence including only some aspects of a whole episode (Bransford & Franks, 1971). The sentence that contained all the information about the episode was not presented during learning but was most frequently recognized during the recognition test. Likewise, extraction of abstract forms out of single deviant exemplars (Bransford & Franks, 1971) as well as abstraction of the theme out of different melodic variations has been reported (Welker, 1982). The most commonly used experimental procedure that follows the idea of schema abstraction from single learned exemplars is the Deese-Roediger-McDermott (DRM) paradigm (Deese, 1959; Roediger, III & McDermott, 1995). In the DRM paradigm, subjects learn lists of semantically highly associated words like “white”, “night”, “cat”, “dark”, and so forth, while the common theme or gist word of the list, in this example “black”, is not presented during learning. On a later retrieval test, subjects frequently and with high confidence falsely remember having encountered the gist word. This paradigm has been extensively used to study false memories because it yields unusually and consistently high levels of false recall and false recognition (McDermott, 1996; Payne et al., 1996; Toglia et al., 1999; Thapar & McDermott, 2001; Seamon et al., 2002; Roediger, III et al., 2004; Senese et al., 2009). This technique was first described by Deese (1959), who conducted a series of experiments in which he was interested in the influence of associative factors on memory recall. He presented subjects with lists, each of which contained 15 words that varied in their inter-item associative strength. He found that the stronger the associative bonds between list items the more likely were subjects to produce the same common associate as an intrusion. Roediger and McDermott (Roediger, III & McDermott, 1995) extended and modified this procedure and showed that subjects falsely recognize the gist words as often as they correctly

recognize actual list items. Moreover, participants were extremely confident that the gist words had been presented and even claimed that they actually "remembered" their presentation, recollecting specific contextual details, rather than simply "knowing" that it had been presented (Seamon et al., 2002; Marsh & Bower, 2004).

Several studies examined the characteristics of false memories in the DRM paradigm. By varying the delay between learning and retrieval testing, researchers analyzed the processing of true and false memories over time. Both true and false memories decreased when retrieval was tested after a long delay of 24 hrs, 48 hrs, one week, two weeks, or two months. However, false memories of the gist words decreased to a much lower extent (Toglia et al., 1999; Thapar & McDermott, 2001; Seamon et al., 2002), suggesting that the schema representation underlying such false memories might be retained over longer time intervals whereas specific details of the single learned exemplars are forgotten. Thus, false memories and true memories appear to be differentially processed during the post-learning consolidation phase. Further, false recognition of gist words even occurred if subjects were instructed to forget the learned word lists (Toglia et al., 1999; Thapar & McDermott, 2001; Seamon et al., 2002) and if subjects were explicitly educated about the false memory effect and warned not to be fooled by gist words (Neuschatz et al., 2001). Such warnings to reduce false recognition seem to be more effective in young adults than older adults (McCabe & Smith, 2002; Watson et al., 2004). Further, warnings are more effective when given before study instead of before the recognition test (McCabe & Smith, 2002) and if subjects can pay full attention to the study of word lists compared to divided attention conditions (Peters et al., 2008). In other experiments, word lists were presented by different speakers during learning, and at recognition testing subjects were asked to indicate which speaker spoke the actually "unspoken" word. Subjects attributed about 90 % of the falsely recognized gist words to one of two speakers (Payne et al., 1996) and even attributed the specific gist word to that speaker who read out the associated list items of this gist word (Roediger, III et al., 2004; Hicks & Starns, 2006).

Theoretical frameworks of false memory formation

Although the DRM false memory effect has been extensively studied under different conditions, the mechanisms underlying this robust phenomenon remain largely obscure. Basically, two main theoretical frameworks have been proposed to explain this strong memory illusion: gist- (or schema-) based theories, and monitoring theories. Gist-based

theories propose that subjects remember the gist (i.e., the concept or schema) of single events rather than the specific details of the individually learned exemplars. One prominent example of gist-based theories is the so-called "fuzzy trace theory" that postulates that there are separate memory systems for verbatim (item-specific) and gist memory (Brainerd & Reyna, 1998; Reyna & Brainerd, 1998; Brainerd & Wright, 2005). According to this theory, the single list items in the DRM paradigm are stored in verbatim memory whereas, in parallel, the gist word of each list, which all list items have in common, is encoded in gist memory (Reyna & Brainerd, 1998; Brainerd & Reyna, 2001). The critical non-presented item is subsequently falsely remembered because it is consistent with the gist representation (Brainerd & Reyna, 1998). In this view, the critical item does not need to be activated prior to retrieval, but instead it is falsely remembered because it is consistent (i.e., similar in meaning) with those items that were studied, thus being highly familiar (Brainerd & Reyna, 1998; Reyna & Brainerd, 1998). Another gist-based theory is the "semantic features theory", postulating that semantic features that are encoded from the single list items ("exemplars") overlap with those of the gist item ("prototype"), and this overlap leads to a strong activation of common features and hence false remembering (Posner & Keele, 1968; Ainsfeld & Knapp, 1968; Bransford & Franks, 1971). In this view, only individual exemplars need to be stored whereby the prototype or the schema is generated spontaneously through overlapping features from these exemplars (Hintzman, 1986). Each of the single exemplars reveals a specific pattern of activation in the associative network during encoding. Since all of the exemplars are derived from one prototype, they share common features resulting in the activation of overlapping representations which, most importantly, also overlap regarding to networks that represent the prototype (Bransford & Franks, 1971; Nelson et al., 1998). During encoding, the networks representing the prototype thus become automatically activated due to spreading activation from the individual exemplars and, paradoxically, the prototype even receives the greatest activation (because it has the most features in common with all single exemplars), although it was never encountered by the subject as individual pattern (Alba & Hasher, 1983; Hintzman, 1986). Gist-based theories are supported by findings of a different decay rate for specific details and the gist memory. Memory for the non-presented gist or prototype is more stable over time than memory for the individual studied exemplars (Posner & Keele, 1970; Thapar & McDermott, 2001; Seamon et al., 2002).

Monitoring theories, on the other hand, assume that subjects during learning consciously or unconsciously generate the prototype of the single exemplars, e.g., the gist word in the DRM paradigm, and this internal generation produces a sense of familiarity at

subsequent retrieval testing (Johnson et al., 1993; Gallo & Roediger, III, 2002). The cause for the occurrence of a false memory is assumed to be a failure of retrieval monitoring, i.e., the subject mistakes this sense of familiarity for having actually encountered the gist word or prototype during encoding (Johnson et al., 1993; Marsh & Bower, 2004; Mitchell & Johnson, 2009). Thus, subjects confuse their mere thinking of the word or schema with actually hearing it. Effective retrieval monitoring, i.e., the ability to discriminate between familiarity due to external presentation or internal generation, has been shown to be essential for avoiding false memories (Curran et al., 2001). One prominent example of monitoring theories is the "activation-monitoring theory", postulating that the single associated items during encoding activate the gist in the associative memory network which in turn increases the probability that subjects will make errors to the highly associated gist word at subsequent retrieval testing (Roediger, III et al., 2001; Gallo & Roediger, III, 2002). Although all of these gist-based and monitoring theories have been proposed independent of each other, it is likely that false memory generation can be best accounted for by a combination of the different postulated processes, with specific situations and conditions possibly favoring one process over the other.

Neuronal correlates of false memories

Mainly two different approaches have been used in the last two decades to identify specific brain regions that are implicated in true as opposed to false memory creation. Several studies used functional neuroimaging techniques – functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) – whereas other studies investigated the formation of true and false memories in neuropsychological patients with lesions in specific brain areas (for an overview see Schacter et al., 1996d; Schacter et al., 1998; Schacter & Slotnick, 2004). Neuroimaging studies suggest that a variety of brain regions is involved in the occurrence of memory distortions and false memories. Specifically, the MTL region including hippocampus, early sensory processing areas and the PFC have been implicated in the ability to distinguish true from false memories. According to the "sensory reactivation hypothesis" (Fabiani et al., 2000; Slotnick & Schacter, 2004), true memories as compared to false memories should be accompanied by a greater activation in sensory/perceptual brain areas because only true memories engage perceptual encoding processes that are presumably not involved in the generation of false memories. Support for this hypothesis comes from studies revealing that true memories compared to false memories show greater activation in sensory

and contextual brain areas like temporoparietal regions for auditory material (Schacter, 1996; Kim & Cabeza, 2007a), occipital regions for visual material (Okado & Stark, 2003; Schacter & Slotnick, 2004), and parahippocampal regions for contextual information (Cabeza et al., 2001). Further, activation of the MTL has been shown to be greater for true than false memories, suggesting that true memories might be mediated primarily by a recollection-based mechanism supported by the MTL (Kim & Cabeza, 2007b). Other studies, however, found similar activation of MTL regions for both accurate and false memories which might indicate that they both depend on the recovery of semantic information (Schacter et al., 1996b; Schacter et al., 1997b; Cabeza et al., 2001). Notably, temporarily inhibiting the left anterior temporal lobe, a region known to be involved in semantic memory and schema representation, by transcranial magnetic stimulation (TMS), reduced the generation of false memories but left memory for true events unchanged (Gallate et al., 2009). A consistent finding with neuroimaging techniques is that false memories reveal greater activations in PFC regions than true memories (Garoff-Eaton et al., 2007; Marchewka et al., 2008), especially in the dorsolateral/anterior PFC (Schacter et al., 1996c; Schacter et al., 1997a). These PFC regions have been previously found to be implicated in strategic retrieval processes, such as specifying retrieval cues, monitoring and verifying the source of memories (Henson et al., 1999; Rugg et al., 1999; Dobbins et al., 2002; Dobbins et al., 2004). Such prefrontal activations might reflect the need for evaluation or monitoring of the strong sense of familiarity produced by false gist items (Schacter et al., 1996a; Schacter et al., 1997a; Kubota et al., 2006).

Studies in patients with damage to specific brain areas basically support the findings from neuroimaging studies. Case studies as well as group studies of patients with localized brain damage in frontal regions show pathologically high rates of false recognition, suggesting that these patients have deficits in strategic retrieval monitoring or rely too much on global similarities between studied items and gist items and the resulting sense of familiarity accompanying gist items (Rapcsak et al., 1996; Parkin et al., 1996; Schacter et al., 1996a; Swick & Knight, 1999). Increased false memory rates were likewise observed in elderly people (Rankin & Kausler, 1979; Koutstaal & Schacter, 1997; Norman & Schacter, 1997; Schacter et al., 1997b), who show a reduced functioning of PFC regions in effortful retrieval (Schacter et al., 1996c; McCabe et al., 2009), supporting the notion that these regions are essential for retrieval monitoring processes to reduce false memory occurrence (Duarte et al., 2008). In contrast, amnesic patients with damage to the MTL are less likely to produce false memories of gist or schema items (Schacter et al., 1996d; Koutstaal et al., 1999;

Verfaellie et al., 2002). Also patients suffering from Alzheimer's disease and Korsakoff's syndrome, both characterized by neuropathology of MTL regions, exhibit distinctly reduced susceptibility to false memories of semantically or perceptually related items (Balota et al., 1999; Budson et al., 2000; Van Damme & d'Ydewalle, 2009). These findings indicate that MTL structures are implicated in the storage of gist information that underlies false memories as observed in the DRM paradigm and that MTL damaged patients might suffer from a degraded gist representation.

In sum, there is now considerable evidence that memory is not a literal record of the world but rather is a reconstructive process that is prone to changes and distortions. Specific characteristics of memory distortions and false memories as well as some neuropsychological processes and brain circuitry underlying this phenomenon have been identified in recent years. Notably, if memory is constructive and changeable in such a way, this has profound implications for the question of the veridicality of memory and the extent to which it may be influenced not only by psychological variables like suggestion, misinformation or schema abstraction, but also by specific physiological conditions and neuromodulatory factors.

Sleep and memory

Sleep and memory consolidation

Sleep is a system process that is most prominently characterized by physical quiescence, reduced responsiveness to external stimuli, an increased arousal threshold, as well as the regulation by homeostatic processes (with sleep deprivation leading to a sleep rebound) and by the circadian rhythm. Sleep is not a unitary process but is composed of different sleep stages (Rechtschaffen & Kales, 1968). Rapid eye movement (REM) sleep, which is characterized by wake-like high-frequency patterns in the electroencephalographic (EEG) recording as well as by REM despite global muscular tonus abolition, is opposed by non-REM (NREM) sleep, which is further divided into four stages corresponding to increasing sleep depth (sleep stages 1, 2, 3, and 4). Sleep stage 1 represents a very shallow kind of sleep that typically occurs only for short time periods at the transition from and towards the wake state. Sleep stage 2 corresponds to light sleep and is characterized by sleep spindles (12-15 Hz) and so-called "K-complexes" in the EEG. Sleep stages 3 and 4 represent deep sleep, i.e., slow wave sleep (SWS), which is characterized by delta activity (1-4 Hz) and slow oscillations (0.5-1 Hz). The different sleep stages presumably serve different physiological functions (see below). Amongst the different functions proclaimed for sleep, like energy

conservation, body restoration, or predator avoidance, the importance of sleep for the consolidation of memories has received an upsurge of attention in recent research. Indeed, memory consolidation might be the only function that eventually can explain the loss of consciousness experienced during sleep, based on the fact that the brain uses basically the same limited neuronal network capacities for the acute conscious processing of information and its long-term storage. Acute processing and storing information might be mutually exclusive processes that cannot take place in the same networks at the same time (McClelland et al., 1995; Born et al., 2006).

In 1924, Jenkins and Dallenbach were amongst the first to provide experimental evidence that sleep favors memory consolidation (Jenkins & Dallenbach, 1924). They systematically tested the retention of learned nonsense syllables over time and found that memory performance was better following a night of sleep than after an equivalent amount of time awake. Since then, numerous studies examined the role of sleep for memory processing focusing on different memory tasks, different types of learning and retrieval, and on the characteristics of post-learning sleep (Diekelmann et al., 2009). Overall, these studies provide not only compelling evidence that sleep indeed serves memory consolidation, but also important insights into some of the underlying mechanisms (Peigneux et al., 2001; Smith, 2001; Maquet, 2001; Stickgold, 2005; Born et al., 2006; Walker & Stickgold, 2006; Rasch & Born, 2007; Diekelmann & Born, 2010).

Factors modulating memory consolidation during sleep

The consolidating effect of sleep is not revealed under all circumstances but is linked to specific conditions (Diekelmann et al., 2009). Numerous studies have confirmed the beneficial effect of sleep on both declarative and procedural memory in a wide variety of tasks (Smith, 2001; Robertson et al., 2004; Marshall & Born, 2007). Compared with a wake interval of equal length, a period of post-learning sleep enhances the retention of declarative memories in paired associate learning (Jenkins & Dallenbach, 1924; Barrett & Ekstrand, 1972; Plihal & Born, 1997; Tucker et al., 2006; Rasch et al., 2007; Lahl et al., 2008), as well as of nonsense syllables (Jenkins & Dallenbach, 1924; Benson & Feinberg, 1975; Idzikowski, 1984), object locations (Rasch et al., 2007), short stories (Tilley & Empson, 1978), and word lists (Empson & Clarke, 1970; Lahl et al., 2008). Sleep likewise improves performance in procedural skills like in finger sequence tapping tasks (Fischer et al., 2002; Walker et al., 2003a; Walker et al., 2003b; Korman et al., 2007), visual texture discrimination (Stickgold et

al., 2000a; Stickgold et al., 2000b; Gais et al., 2002; Mednick et al., 2003), or mirror tracing (Plihal & Born, 1997). Apart from declarative and procedural memory, sleep likewise supports the consolidation of emotional information (Wagner et al., 2001; Payne et al., 2008; Nishida et al., 2009). Effects of a 3-hour period of sleep on emotional memory were even detectable after a delay of four years (Wagner et al., 2006).

Consolidation of memories in the different memory systems has been suggested to differentially depend on specific sleep stages. Two main hypotheses have been proposed regarding the role of sleep stages in memory consolidation. The dual process theory assumes that the specific sleep stages support consolidation of different types of memory, specifically that SWS supports declarative memory consolidation whereas REM sleep does so for procedural memories (Plihal & Born, 1997; Plihal & Born, 1999a; Maquet, 2001; Gais & Born, 2004a). The sequential hypothesis, on the other hand, proposes that sleep benefits memory optimally through the cyclic succession of both SWS and REM sleep. The original version of this hypothesis assumed that SWS functions to weaken non-adaptive memory traces whereas REM sleep re-stores the remaining traces (Giuditta et al., 1995; Ficca & Salzarulo, 2004). The dual process hypothesis received support mainly based on the early vs. late sleep comparison, i.e., an approach comparing effects of retention intervals covering the first (SWS-rich) and the second (REM sleep-rich) half of nocturnal sleep. SWS-rich early sleep was consistently found to support consolidation of hippocampus-dependent declarative memories, i.e., for word-pairs (Yaroush et al., 1971; Barrett & Ekstrand, 1972; Fowler et al., 1973; Plihal & Born, 1997) and spatial relations (Plihal & Born, 1999a), as well as for memories explicitly recollected in recognition tasks (Drosopoulos et al., 2005; Daurat et al., 2007), whereas REM sleep benefited non-declarative types of memory like priming (Plihal & Born, 1999a; Wagner et al., 2003) and mirror-tracing skills (Plihal & Born, 1997). However, this dichotomy does not fit all results. Several non-declarative tasks, like visual texture discrimination (Gais et al., 2000) and rotation adaptation (Huber et al., 2004), are also supported by SWS whereas REM sleep in some instances seems to benefit aspects of declarative memory (Fogel et al., 2007), especially if emotional materials are used (Wagner et al., 2001; Rauchs et al., 2004; Payne et al., 2008; Nishida et al., 2009). Although these divergent findings could reflect that stimuli used in memory tasks are often not of one type of memory system, they rather agree with the sequential hypothesis, which argues that sleep benefits the consolidation of both declarative and non-declarative memory optimally when SWS and REM sleep occur in succession (Giuditta et al., 1995). Support for the sequential hypothesis comes mainly from studies introducing disruptions of the natural cyclic sequence

of SWS and REM sleep by awakenings from REM sleep (Ficca et al., 2000; Ficca & Salzarulo, 2004). Although this approach can be criticized because awakenings from REM sleep can induce stress and thus confound the results (Born & Gais, 2000), several studies of undisturbed sleep, using correlation analyses, have suggested that the overnight gain in performance on a procedural visual discrimination task is in fact greatest when SWS *plus* REM sleep occur in succession during post-learning sleep (Gais et al., 2000; Stickgold et al., 2000b; Mednick et al., 2003). Thus, both SWS and REM sleep might be implicated in declarative and procedural memory consolidation. Both approaches, i.e., the dual process hypothesis and the sequential hypothesis could be reconciled by assuming that both declarative and procedural memory benefit optimally from the succession of SWS and REM sleep, but declarative memory, due to its integrative nature (binding features from different memories in different memory systems), might benefit more from SWS-associated system consolidation, whereas procedural memories, due to their specificity and discrete nature, might benefit to a greater extent from REM sleep-associated synaptic consolidation in localized brain circuits (see below).

Memory representations can differ greatly in the strength of the underlying associations (Tilley & Empson, 1978; Cipolli, 1995). Sleep-associated memory consolidation has been suggested to depend on the strength of the acquired associations with the benefit from sleep being greater for weaker than for stronger traces (Diekelmann et al., 2009). Examining declarative memories for word-pairs, Drosopoulos et al. (Drosopoulos et al., 2007) showed that post-learning sleep produced a distinctly greater memory benefit for word-pairs learned to a criterion of 60 % correct responses than for lists learned to a criterion of 90 % correct responses. Also word-pair associations that had been weakened by post-learning interference benefited distinctly more from sleep compared to wakefulness than word pairs that were not weakened through interference (Ekstrand, 1967; Drosopoulos et al., 2007). Focusing on procedural memory, Kuriyama et al. (2004) varied the difficulty of a finger sequence tapping task and found that post-learning sleep induced the greatest performance gain for the most difficult task. However, two recent studies reported divergent results, i.e., greater sleep benefits for strong memories. Using a repetition priming task, Hauptmann et al. (2005) found delayed gains after 24 hours only in subjects whose performance had reached an asymptotic plateau during training. In a study by Tucker and Fishbein (2008), only subjects who performed well in declarative learning tasks showed a benefit in retention after a nap, in comparison with a wake control condition, whereas no difference was observed for low-performers. However, both lines of evidence might be reconciled by assuming an inverted u-

shaped function for the sleep benefit of memories with different strengths of the underlying associations. Both very weak and very strong memories might fail to benefit from sleep, while those with intermediate levels of initial encoding performance might show the greatest benefit (Stickgold, 2009).

Whether or not specific memories benefit from sleep-dependent consolidation likewise depends on whether or not these memories are behaviorally relevant to the individual and in any way associated with future reward. In a recent study, monetary reward was associated with one of two previously trained finger tapping sequences before 12-hr retention intervals of nocturnal sleep and daytime wakefulness (Fischer & Born, 2009). The sleep-dependent gain was significantly greater for the sequence that had been associated with monetary reward, regardless of whether this sequence was trained firstly or secondly. Sleep also preferentially supports memories that are needed to execute a future plan at an appropriate time (Diekelmann, Wilhelm, Wagner & Born, submitted). Successful implementation of the plan specifically depended on SWS rather than REM sleep, and the enhancing effect of sleep on the memory for the plan was nullified by executing the planned behavior already before sleep. In another study, subjects were or were not informed after learning that they will need to recall the learned materials after a night of sleep or respective wake intervals (Wilhelm et al., in press). Only those subjects expecting retrieval testing showed enhanced recall after sleep compared to wakefulness, whereas subjects not expecting retrieval did not benefit from sleep. Taken together, these findings indicate that there is a selection mechanism determining whether or not a memory is strengthened by sleep. Sleep does not non-selectively strengthen previously acquired memories, but preferentially benefits those memories that are motivated by future plans and expectancies. At the neuronal level, the intentional or motivating component of a memory might translate into a tagging of respective neuronal ensembles for preferred reactivation of these representations during ensuing sleep (Marshall & Born, 2007; Diekelmann & Born, 2010).

Apart from factors inherent to the memory itself, also characteristics of the experimental test situation can determine whether or not a benefit of sleep can be expressed. Especially for declarative memories, the type of retrieval test might be critical. Experimentally, retrieval of declarative materials is tested using either "recall" or "recognition" procedures (see above). Most studies that report beneficial effects of sleep on declarative memory consolidation used cued recall procedures (Yaroush et al., 1971; Barrett & Ekstrand, 1972; Fowler et al., 1973; Benson & Feinberg, 1977; Grosvenor & Lack, 1984). Cued recall performance was consistently enhanced after post-learning periods of sleep,

especially after SWS during the first half of the night, compared to respective wake intervals (Plihal & Born, 1997; Gais et al., 2002; Gais et al., 2006; Ellenbogen et al., 2006; Gais et al., 2007; Drosopoulos et al., 2007). Free recall procedures likewise revealed a pronounced superiority of retention intervals filled with sleep as compared to wakefulness (Benson & Feinberg, 1975; Idzikowski, 1984; Lahl et al., 2008). Recognition memory has only scarcely been examined, and these studies report only small effects (Koulack, 1997; Wagner et al., 2007) or even no beneficial effect of sleep on overall recognition performance (Rauchs et al., 2004; Drosopoulos et al., 2005; Hu et al., 2006). Two studies found sleep effects only for recollection after SWS-rich sleep, but not for familiarity judgments (Drosopoulos et al., 2005; Daurat et al., 2007). These studies indicate that cued and free recall procedures are better suited to identify the effects of sleep on declarative memory consolidation than recognition tests. For correct recall, as compared to recognition, the subject himself/herself reinstates the item to be remembered. This process is thought to reflect basically the accessibility of a memory (Gillund & Shiffrin, 1984). With enhanced recall, the target item is embedded in a richer network of neighboring associations providing possible access. This could be the consequence of sleep promoting the integration of newly acquired memories into the network of pre-existing long-term memories (Diekelmann & Born, 2007; Diekelmann & Born, 2010). In recognition, on the other hand, the target stimulus needs not to be generated by the subject but is already sufficiently activated through its presentation. Whether it is recognized or not mainly depends on the strength of that particular memory to exceed a certain threshold. Additionally, recall and recognition differ in their underlying neuroanatomical structures. Recall is known to involve hippocampal function whereas hippocampal contributions to recognition, and especially to familiarity judgments, appear to be negligible (Baddeley et al., 2001; Mayes et al., 2002; Bastin et al., 2004; Holdstock et al., 2005). On this background, findings of greater and more consistent sleep-dependent improvements in recall than recognition procedures indicate that consolidation during sleep supports processes that can be better detected in recall than in recognition.

Mechanisms of sleep-dependent memory consolidation

Since the publication of Hebb's seminal book (Hebb, 1949), memory formation has been conceptualized as a process in which neuronal activity reverberating in specific circuits promotes enduring synaptic changes. Building on this, it is widely held that the consolidation process that takes place off-line after encoding relies on the reactivation of neuronal circuits

that were implicated in information encoding. This would promote both the gradual redistribution and reorganization of memory representations to sites for long-term storage (i.e., system consolidation) and the enduring synaptic changes that are necessary to stabilize memories (i.e., synaptic consolidation). The conditions enabling these two processes during sleep differ strongly between SWS and REM sleep. During SWS, active system consolidation integrates newly encoded memories with pre-existing long-term memories, thereby inducing conformational changes in respective representations. Ensuing REM sleep seems to stabilize the transformed memories by enabling undisturbed processes of synaptic consolidation. Although REM sleep has been suspected for a long time to play the key role in memory consolidation, research paid little attention to the fact that REM sleep naturally follows SWS, pointing towards sequentially complementing contributions of SWS and REM sleep to memory consolidation (Giuditta et al., 1995; Figure 3).

The concept of active system consolidation during SWS originated from the standard two-stage model of consolidation proposed for declarative memory (Marr, 1971; Buzsaki, 1989; McClelland et al., 1995; Frankland & Bontempi, 2005; Rasch & Born, 2007), but might also account for consolidation in other memory systems (Marshall & Born, 2007). It is assumed that in the waking brain events are initially encoded in parallel in neocortical networks and in the hippocampus. During subsequent periods of SWS the newly acquired memories are repeatedly reactivated and thereby become gradually redistributed such that connections within the neocortex are strengthened, thus forming more persistent memory representations. Reactivations of the new representations gradually adapt them to pre-existing neocortical “knowledge networks”, thereby promoting the extraction of invariant repeating features and qualitative changes in the memory representations (McClelland et al., 1995; Rasch & Born, 2007). Several studies found that this reactivation and reorganization can lead to the extraction of new explicit knowledge, e.g., sequence knowledge in an implicit serial reaction time task (SRTT; Fischer et al., 2006), and explicit insight into the hidden structure of a problem solving task (Wagner et al., 2004). The finding that in rats the spatiotemporal patterns of neuronal firing, which were present during exploration of a novel environment and simple spatial tasks, are reactivated in the same sequential order in the hippocampus during subsequent sleep provided a major breakthrough in memory research (Pavlides & Winson, 1989; Wilson & McNaughton, 1994; Nadasdy et al., 1999; Ji & Wilson, 2007; Euston et al., 2007; Lansink et al., 2008). Signs of such neuronal reactivation of ensemble activity were rarely observed during REM sleep (Poe et al., 2000; Louie & Wilson, 2001), but mostly during SWS, and often during the first hours after learning (but see Ribeiro et al., 2004). They

are also observed in the thalamus, in the striatum, and in the neocortex (Ribeiro et al., 2004; Ji & Wilson, 2007; Euston et al., 2007; Lansink et al., 2008). Sleep-dependent reactivations of brain regions implicated in prior learning were also revealed in human neuroimaging studies (Maquet et al., 2000; Peigneux et al., 2004). The first evidence for a causal role of reactivation during SWS in memory consolidation came from a study in humans who learned spatial locations in the presence of an odor (Rasch et al., 2007). Re-exposure of the odor during SWS, but not REM sleep, enhanced the spatial memories and induced hippocampal activation even greater than during wakefulness, indicating that during SWS hippocampal networks are particularly sensitive to inputs that are capable of reactivating memories. Likewise, the presentation of specific sounds during sleep that were previously associated with individual words induced an improvement in word retention after sleep. These findings suggest that reactivation during sleep is selective by strengthening individual memories (Rudoy et al., 2009).

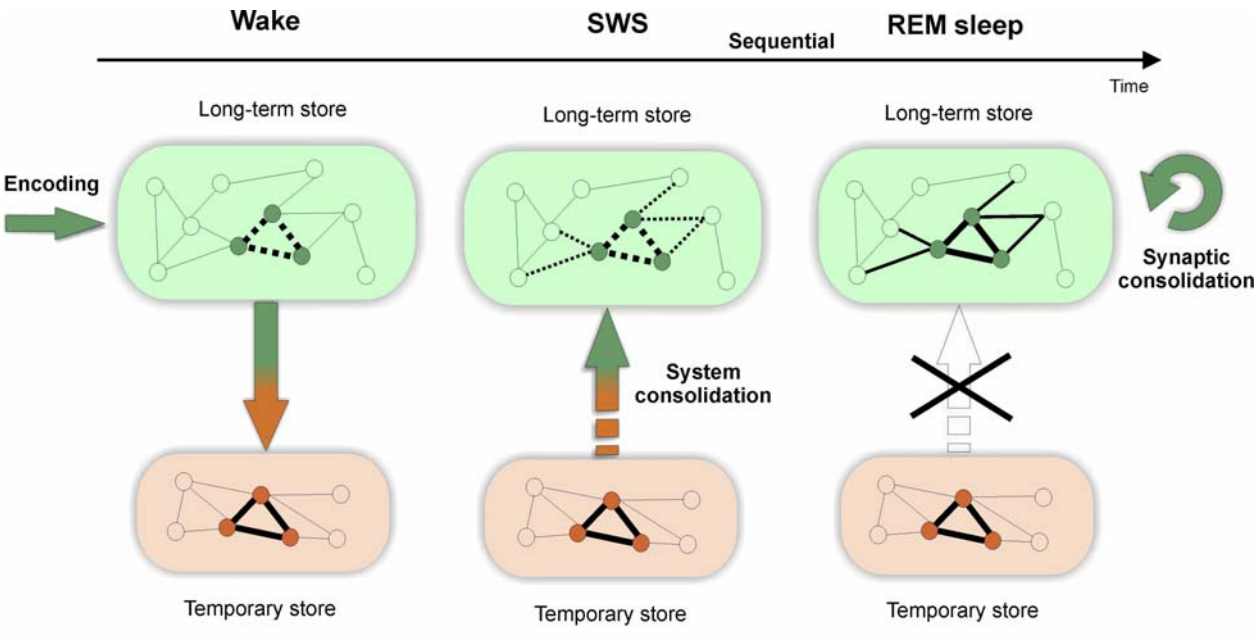

Figure 3. Sequential contributions of SWS and REM sleep to memory consolidation in a two-stage memory system. Following encoding in the wake state, memories become reactivated and gradually integrated into the long-term store in a process of SWS-dependent system consolidation. During ensuing REM sleep, reorganized memories become strengthened through processes of synaptic consolidation. Modified after (Frankland & Bontempi, 2005).

Reactivations in hippocampal networks seem to be particularly enabled by the low cholinergic tone characterizing SWS (Hasselmo, 1999; Hasselmo & McGaughy, 2004; Gais & Born, 2004b). Moreover, there is evidence that the reactivation and redistribution of memories

during SWS is regulated by a dialogue between neocortex and hippocampus that is essentially under feed-forward control of the slow oscillations (< 1Hz): by globally inducing up- and down-states of neuronal activity, they provide a global temporal frame whereby the depolarizing up-states repetitively drive the reactivation of memories in hippocampal circuits (represented by sharp wave-ripples) in parallel with thalamo-cortical spindles and activity from other regions (e.g., noradrenergic locus coeruleus bursts). This enables synchronous feedback from these structures to the neocortex during the slow oscillation up-state, which is likely a prerequisite for the formation of more persisting traces in neocortical networks. Consistent with this concept, neuronal reactivations in the timeframe of slow oscillations have been demonstrated, whereby hippocampal replay seems to lead reactivation in neocortex (Ji & Wilson, 2007; Peyrache et al., 2009). Moreover, slow oscillations drive ripples that accompany hippocampal reactivation, thus allowing the formation of spindle-ripple events as a mechanism of effective hippocampus-to-neocortex information transfer (Siapas & Wilson, 1998; Molle & Born, 2009; Wierzynski et al., 2009). The concept of a redistribution of memories during sleep has been corroborated by human brain imaging studies (Fischer et al., 2005; Orban et al., 2006; Takashima et al., 2006; Gais et al., 2007; Sterpenich et al., 2009). Interestingly, in these studies, the redistribution of hippocampus-dependent memories was revealed to target particularly PFC regions (Takashima et al., 2006; Gais et al., 2007; Peyrache et al., 2009), regions that also substantially contribute to the generation of slow oscillations (Massimini et al., 2004; Murphy et al., 2009). These processes of local reactivation and redistribution of selective neuronal representations during SWS might act in concert with a global synaptic downscaling that serves mainly to preclude saturation of synaptic networks (Tononi & Cirelli, 2003; Tononi & Cirelli, 2006; Vyazovskiy et al., 2008; Dash et al., 2009).

The assumption of system consolidation leaves one challenging issue open: reactivation and redistribution of memories during SWS alone cannot sufficiently explain that post-learning sleep improves the retention of memories. Hence, sleep presumably supports, in addition, a synaptic form of consolidation for stabilizing memories. This indeed could be the function of REM sleep. The view of synaptic consolidation being favored by REM sleep is supported by molecular and electrophysiological events characterizing this stage. REM sleep, unlike SWS, is associated with an up-regulation of immediate early gene activity like *arc* and *zif-268*, which are known mediators of synaptic remodeling (Ribeiro et al., 2002; Ulloor & Datta, 2005; Ribeiro et al., 2007). The up-regulation depends on learning experience during prior wakefulness and is localized to brain regions involved in prior learning. Interestingly,

immediate early gene activity during REM sleep is positively correlated with EEG spindle activity during prior SWS (Ribeiro et al., 2007). Activity of plasticity-related early genes depends on cholinergic tone (von der Kammer et al., 1998; Teber et al., 2004), which is enhanced to wake-like levels during REM sleep. Cholinergic activation strengthens the maintenance of long-term potentiation (LTP) in the hippocampal-medial PFC pathway (Lopes Aguiar et al., 2008), which is probably a main road of memory transfer during preceding SWS-dependent system consolidation (Takashima et al., 2006; Gais et al., 2007; Wierzynski et al., 2009; Peyrache et al., 2009). Electrophysiological signatures of REM sleep, such as ponto-geniculo-occipital (PGO) waves, are also increased during post-learning sleep, and might causally contribute to immediate early gene activity as well as memory consolidation (Datta et al., 2008). The EEG indicates that brain activation during REM sleep is enhanced to wake-like levels, which could act non-specifically to amplify local synaptic plasticity in an environment unbiased by external stimulus inputs (Cantero et al., 2003; Axmacher et al., 2008; Montgomery et al., 2008). In combination, investigations of these core mechanisms of consolidation tempt to hypothesize that SWS supports the reactivation and redistribution of new memories (system consolidation) and thereby could prime respective networks for synaptic consolidation processes and LTP that are supported by subsequent REM sleep.

Effects of sleep deprivation on memory functions

As compared to the number of studies on the role of sleep for memory consolidation, the effects of *sleep deprivation* on memory processes are less well investigated. On the one hand, sleep deprivation prevents the beneficial effect of sleep on consolidation of previously acquired memories. On the other hand, sleep deprivation, i.e., prolonged wakefulness of more than 24 hrs, is characterized by specific alterations in numerous electrophysiological, neurochemical, and cognitive processes. Since sleep is regulated homeostatically, the organism responds to acute or prolonged sleep loss with a specific pattern, which includes changes, mostly deficits, in various neurophysiological functions. With prolonged wakefulness, the organism has an increasing tendency to access the “sleep mode” of central-nervous processing which, among others, is expressed in higher sleep propensity, e.g., reduced sleep latency and SWS latency (Carskadon & Dement, 1987; Bonnet & Arand, 1998). Additionally, extreme sleep deprivation is a stressor on which the organism responds with an enhanced secretion of stress hormones, e.g., cortisol and noradrenaline (McEwen, 2006).

Sleep deprivation has consistently been found to substantially impair performance in almost all neuropsychological functions. According to a meta-analysis performed by Pilcher and Huffcutt (Pilcher & Huffcutt, 1996), the performance of sleep-deprived subjects lies on average 1.37 standard deviations below that of non-deprived subjects. Thus, performance after sleep deprivation corresponds to the lowest percentile of performance in non-deprived controls. Although cognitive performance is generally impaired after sleep deprivation, different cognitive functions are differentially affected. Impairing effects of sleep loss are most pronounced in functions that are particularly dependent on the PFC, e.g., working memory, executive functions, vigilance, attention, and complex cognitive functions (Harrison & Horne, 2000b; Durmer & Dinges, 2005; Boonstra et al., 2007; Lim & Dinges, 2008), all being particularly important for effective memory processing (Sarter et al., 2001; Chun & Turk-Browne, 2007). Sleep-deprived subjects show significantly worse performance in working memory tasks compared to non-deprived controls (Chee & Choo, 2004; Mu et al., 2005), slower reaction times, and more lapses in vigilance tasks (Lim & Dinges, 2008), impaired response inhibition in a "go/no-go" task (Drummond et al., 2006) and in the "Haylings-test" (Harrison & Horne, 1998) as well as redundancy and perseveration, e.g., in the "random number generation task" (Retey et al., 2006). These impairments of frontal functions can be explained by results from brain imaging studies investigating the effects of sleep deprivation on regional brain activity. Such studies found that sleep deprivation-related changes in brain activity are most pronounced in prefrontal areas and particularly during performance on tasks recruiting the PFC (Thomas et al., 2000; Chee & Choo, 2004; Mu et al., 2005; Chee et al., 2008). However, while most studies observed a reduction in task-related brain activity following sleep deprivation (Drummond et al., 1999; Thomas et al., 2000; Chee & Choo, 2004), others found an increase in regional PFC activation (Drummond et al., 2000; Choo et al., 2005). Such apparently paradoxical increases in prefrontal activation have been interpreted as a mechanism to compensate deficits in performance following sleep deprivation. Interestingly, the PFC is strongly deactivated during normal sleep, especially during SWS (Maquet, 2000). Slow oscillations during SWS are also most pronounced in prefrontal regions (Massimini et al., 2004) and recovery sleep after sleep deprivation is characterized by increased slow wave activity primarily in frontal cortical areas (Cajochen et al., 1999; Finelli et al., 2000). These findings suggest that the PFC displays "deeper" sleep compared to other cortical regions, probably because of its particularly strong work load during wakefulness (Horne, 1993; Jones & Harrison, 2001), which would likewise explain the

high susceptibility to the negative effects of sleep deprivation of cognitive functions strongly relying on the PFC.

Thus, basic cognitive functions that are critical for effective long-term memory processing, like working memory, attention, and executive functions, are substantially impaired following sleep deprivation (Sarter et al., 2001; Chun & Turk-Browne, 2007). However, there are only few studies directly testing the impact of sleep loss on long-term memory. A recent study found that learning of new memories (words) is impaired after one night of sleep deprivation in healthy young subjects (Chuah et al., 2009). Also, free recall (but not recognition) in a verbal learning task was impaired after 24 hrs of sleep deprivation, which was associated with decreased activation in temporal lobe regions and increased activity in prefrontal areas compared with rested controls (Drummond et al., 2000). Harrison and Horne (2000a) reported that sleep-deprived subjects successfully recognized the previously presented stimuli (faces), but had difficulties in remembering in which of two lists the faces had appeared, reflecting context or source memory. Consistent with these findings, a study using event-related potentials (ERP) known to reflect the memory effect in an old/new recognition paradigm (Friedman & Johnson, Jr., 2000) found that after sleep deprivation subjects displayed reduced ability to discriminate new items from those that had been studied. Sleep-deprived subjects compared to non-deprived controls showed impaired stimulus discrimination and impaired automatic categorization, as indicated by an increased negativity in the N200, as well as reduced elaboration of the information retrieved from episodic memory, as indicated by a reduced difference in the amplitude of old and new items in a late positive component (LPC/P600; Mograss et al., 2009). However, all of these studies tested memory shortly after encoding and, thus, cannot dissociate the effects of sleep deprivation on encoding from that on retrieval. In another study, subjects who were sleep-deprived before encoding of a set of pictures showed distinctly diminished recognition memory performance two days later, i.e., after two nights of recovery sleep (Yoo et al., 2007). Interestingly, sleep-deprived subjects again exhibited significantly reduced activation of hippocampal regions during encoding which was related to impaired recognition performance in the subsequent memory test. Findings of reduced hippocampal activation following sleep deprivation are consistent with studies in rats and mice showing that sleep deprivation impairs 3'-5'-cyclic AMP (cAMP)- and protein kinase A (PKA)-dependent synaptic plasticity in the hippocampus (Vecsey et al., 2009) and reduces spontaneous as well as learning-induced hippocampal neurogenesis, which is thought to underlie hippocampus-dependent learning (Roman et al., 2005; Hairston et al., 2005; Mueller et al., 2008; Meerlo et al., 2009).

While there is considerable evidence that encoding and consolidation are distinctly disturbed by sleep deprivation, there are only few data on the impact of sleep deprivation specifically on memory *retrieval*. Blagrove (1996) tested whether sleep deprivation at retrieval testing would lead to a disruption of the ability to discriminate and detect discrepancies between original and misleading information. Subjects learned a short story about a street robbery and were tested in a free recall test to ensure that all subjects correctly encoded the information. They were further asked several leading questions on the story and were given negative feedback on their answers. When asked these questions again after 43 hrs of sleep deprivation, subjects more frequently changed their answers to leading questions and thus were more susceptible to misleading remarks compared to subjects who were allowed to sleep normally. Although sleep deprived subjects were more suggestible to misinformation, they maintained highest confidence on their answers even though these answers were inaccurate (Blagrove & Akehurst, 2000). Thus, during retrieval in the state of acute sleep deprivation, subjects were not able to discriminate actually learned information from subsequently presented misleading information. Effective retrieval processes, and specifically strategic retrieval monitoring and source discrimination, are well-known to essentially depend on the PFC (Rugg et al., 1996; Schacter et al., 1996b; Henson et al., 1999; Dobbins et al., 2002), i.e., the brain structure most profoundly affected by sleep deprivation.

Neuroendocrine modulators of memory formation

Apart from global states of sleep and sleep deprivation, memory formation is modulated by various neuroendocrine factors, most of which are also differentially regulated during sleep, sleep deprivation, and rested wakefulness. Sleep, especially SWS, is characterized by a marked decrease of the stress hormone cortisol and a distinct increase of growth hormone concentrations, as well as in decreases of adrenaline and noradrenaline compared with wakefulness (Born & Fehm, 2000). Sleep deprivation, on the other hand, is associated with an increase in cortisol, pro-inflammatory cytokines and a most pronounced increase in adenosine concentrations (Porkka-Heiskanen, 1999; McEwen, 2006). Although all of these and also other neuromodulators can affect processes of memory formation, only cortisol and adenosine will be described in more detail here, because they will be directly targeted in the experiments of this thesis.

Cortisol

The stress hormone cortisol is the most important human glucocorticoid that is secreted from the adrenal cortex in response to an increased activation of the hypothalamus-pituitary adrenal (HPA) axis. Upon activation, the hypothalamus secretes corticotropin-releasing hormone (CRH) which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland which acts on the adrenal cortices that eventually produce cortisol. Cortisol in turn acts back on the hypothalamus and the pituitary gland (to suppress CRH and ACTH production) in a negative feedback cycle. Release of cortisol relies on a pronounced circadian rhythm: it decreases to a minimum during early sleep dominated by SWS, increases during the late night with predominance of REM sleep, reaches its maximum shortly after awakening, and then continuously declines across the day (Born & Fehm, 2000; Wilhelm et al., 2007). Cortisol binds to two different receptor subtypes, the glucocorticoid (GC) and mineralocorticoid (MC) receptors (Reul & de Kloet, 1985; de Kloet et al., 2005). MC receptors bind cortisol with a higher affinity than GC receptors, resulting in high occupation of MC receptors (> 90%) but low occupation of GC receptors (~ 10%) during the circadian trough. During stress and/or the circadian peak, MC receptors are completely saturated and ~ 70 % of GC receptors are occupied. The two receptor types are also differentially distributed across the brain. MC receptors are preferentially located in the hippocampus, parahippocampal gyrus, and insular cortex, whereas GC receptors are present in both subcortical (e.g., hippocampus and parahippocampal regions) as well as cortical areas, specifically in the PFC. Cortisol is an important mediator of the organism's response to stress, including effects on the immunologic, metabolic, and cognitive level (de Kloet et al., 2005; Ulrich-Lai & Herman, 2009). For example, cortisol up-regulates the expression of anti-inflammatory proteins and down-regulates the expression of pro-inflammatory proteins, stimulates gluconeogenesis and fat breakdown in adipose tissue, and affects various cognitive functions like vigilance, attention, emotional processing, and memory (McEwen, 1998; Lupien et al., 2007). Particularly, cortisol is well-known to distinctly alter processes of memory formation during sleep as well as during wakefulness (Born & Wagner, 2004; Het et al., 2005; Lupien et al., 2005; Wagner & Born, 2008). In this context, it is important to dissociate the effects of cortisol from those of stress on memory functions. Although the increase in cortisol is one of the main features of the physiological stress response, stress is also characterized by several other factors that can affect processes of memory formation like activation of the sympatho-adrenal axis, release of catecholamines and mood changes (Lupien et al., 2007; Ulrich-Lai & Herman, 2009). For this reason, effects of selective cortisol

manipulation by acute oral or intravenous cortisol administration on memory functions will be primarily considered in the following.

There is increasing evidence that cortisol administration differentially affects memory depending on the stage of memory formation (Het et al., 2005; Wolf, 2009). Several studies in animals and humans suggest that the encoding of new information is facilitated by increased cortisol. However, this effect might depend on the time of day (morning vs. afternoon) of cortisol administration (Het et al., 2005). While in humans encoding is impaired following cortisol treatment in the morning (Kirschbaum et al., 1996; Tops et al., 2003), increased cortisol levels in the afternoon slightly improved encoding of new materials (Buchanan & Lovallo, 2001; Abercrombie et al., 2003; Rimmele et al., 2003). This dependency of cortisol effects on the time of day is probably related to the different receptor occupation across the day together with the idea that a moderate occupation of GC receptors (as observed in the afternoon) is beneficial for memory encoding whereas high GC occupation (like in the morning) impairs encoding processes (Lupien & McEwen, 1997; Lupien et al., 2007). While the only study investigating the effect of cortisol treatment on memory consolidation during wakefulness in humans observed no effect (de Quervain et al., 2000), studies enhancing cortisol pharmacologically during sleep found an impairment of sleep-dependent consolidation and subsequent memory performance (Plihal & Born, 1999b; Wagner & Born, 2008). Apart from its effects on encoding and consolidation, cortisol has been consistently shown to impair memory retrieval. Subjects treated with cortisol before retrieval testing displayed a distinct decrease in recall performance, e.g., in cued recall or free recall of words or word pairs (de Quervain et al., 2000; Wolf et al., 2001; de Quervain et al., 2003). When subjects were administered cortisol before retrieval, they performed on average half a standard deviation below subjects who received placebo (Het et al., 2005). Interestingly, not only retrieval of newly acquired memories in a laboratory setting is influenced by cortisol, but acute cortisol administration likewise impairs recall of older autobiographical memories (Buss et al., 2004). The findings of impaired recall in humans are consistent with retrieval impairments following cortisol treatment previously described in rats (Roozendaal, 2002). Although effects of cortisol on memory seem to be most pronounced, executive functions that are known to critically depend on the PFC, like working memory and response inhibition, have likewise been shown to be distinctly impaired by cortisol treatment (Young et al., 1999; Lupien et al., 1999; Hsu et al., 2003). Such cognitive effects of cortisol are suggested to rely on the impact of cortisol on brain areas implicated in memory formation and executive functions, respectively, like the MTL including the hippocampus, the amygdala (for

emotional memory), and the PFC. Using PET scanning, elevated cortisol during rest and memory retrieval was found to induce a large decrease in regional cerebral blood flow in the MTL (de Leon et al., 1997; de Quervain et al., 2003). Reduced activation of the hippocampus and PFC during memory retrieval following cortisol treatment were also observed in a recent fMRI study (Oei et al., 2007). Chronically enhanced levels of cortisol, e.g., in depression and Alzheimer's disease, have even been found to reduce hippocampal volume associated with an atrophy of hippocampal neurons (Brown et al., 2004; Elgh et al., 2006).

Adenosine

Adenosine is a potent inhibitory neuromodulator in the central nervous system primarily inhibiting excitatory neurons (e.g., cholinergic and glutamatergic; Porkka-Heiskanen et al., 1997; Dunwiddie & Masino, 2001). The expression of adenosine is regulated by neuronal activity, i.e., adenosine levels constantly increase with activation of neurons and with associated increase of energy demands (Mitchell et al., 1993). Adenosine, in turn, decreases neuronal activity and thus decreases energy need, presumably as a self-controlling mechanism to prevent cell damage (Porkka-Heiskanen et al., 2002). During prolonged wakefulness, extracellular adenosine concentrations start to rise as response to prolonged neuronal activity. Increased adenosine levels accordingly decrease neuronal activity which hampers effective cognitive processing and eventually induces sleep. During recovery sleep, mainly during SWS, adenosine levels gradually decline back to their baseline levels (Porkka-Heiskanen et al., 1997). This pattern of activity-dependent increase and decrease of extracellular adenosine concentrations has been specifically observed in the basal forebrain (BF) and cortex but not, or to a much lesser extent, in other brain regions (Basheer et al., 2000; Porkka-Heiskanen et al., 2000). Interestingly, however, sleep-wake related variations in adenosine have likewise been observed in the hippocampus as well as in the frontal cortex, i.e., brain regions critically implicated in memory functions (de Sanchez et al., 1993; Huston et al., 1996). Of the four subtypes of adenosine receptors presently known (i.e., A_1, A_{2a}, A_{2b}, and A_3), the effects of adenosine on vigilance state are mediated primarily through A_1 receptors apart from some mediation of the A_{2a} receptor (Porkka-Heiskanen et al., 2002). The A_1 receptor is the most abundant adenosine receptor, is widely distributed across the brain and, together with the A_{2a} receptor, appears to be responsible for the stimulant effects of adenosine receptor antagonists (Dunwiddie & Masino, 2001).

Caffeine is the most widely used psychoactive drug in the world and primarily antagonizes adenosine A_1 receptors which reduces adenosine transmission in the brain and thereby blocks adenosine-induced neuronal inhibition (Fredholm et al., 1999; Fisone et al., 2004). By curtailing central nervous adenosine action, caffeine increases wakefulness and restores, or at least improves, cognitive functioning following sleep deprivation (Fisone et al., 2004; Bonnet et al., 2005). Caffeine at several dose levels has been found to improve performance on various cognitive and psychomotor tasks in different aspects of performance. In a choice reaction time task, sleep-deprived subjects who were administered caffeine before testing performed significantly better in reaction time, accuracy, and response failures compared to controls who received placebo (Wright, Jr. et al., 1997; Beaumont et al., 2001; Wesensten et al., 2002; Wesensten et al., 2005). Also executive functions, vigilance performance, grammatical reasoning as well as performance in simulated driving were substantially facilitated by caffeine administration following sleep deprivation (Bonnet et al., 1995; Horne & Reyner, 1996; Lagarde et al., 2000; De et al., 2003; Killgore et al., 2009). For short-term memory, caffeine has likewise been shown to improve performance during sleep loss, e.g., in the digit symbol substitution task (Bonnet et al., 1995; Durlach, 1998; Beaumont et al., 2001). Caffeine administration further alleviates memory impairment in a variety of brain disorders, e.g., in animal models of Alzheimer's disease (Arendash et al., 2006), Parkinson's disease (Gevaerd et al., 2001), in age-related cognitive decline (Riedel & Jolles, 1996) as well as in scopolamine-induced amnesia in humans (Riedel et al., 1995). The beneficial effects of caffeine on memory functions following sleep loss could at least partly rely on its beneficial effect on LTP in the hippocampus. Caffeine prevents the sleep deprivation-induced impairment of LTP in area CA1 of the hippocampus as well as associated impairments in hippocampus-dependent learning in rats (Alhaider et al., 2010a; Alhaider et al., 2010b). High doses of caffeine increased neurogenesis in the hippocampus (Wentz & Magavi, 2009). Apart from the hippocampus, caffeine also facilitates functioning of the PFC by increasing prefrontal dopamine and acetylcholine transmission (Acquas et al., 2002). Generally, the effects of caffeine during sleep loss have been examined over a dose range from 32 to 600 mg in single doses and up to 1200 mg in divided doses over 24 hrs in humans. Most studies found beneficial effects of caffeine on performance mainly in the medium dose range from 200-300 mg, with lower and higher doses being less effective and higher doses additionally provoking undesirable side effects (Bonnet et al., 2005). In parallel with performance improvements, caffeine likewise positively affects subjective alertness and mood. Caffeine typically ameliorates the decreases in subjective alertness as well as the

increases in fatigue and sleepiness during sleep deprivation, with a time course mostly similar to that seen for performance variables (Penetar et al., 1993; Bonnet et al., 1995). Thus, caffeine is a potent stimulant that effectively facilitates cognitive functioning following sleep deprivation, including processes of memory formation.

Objectives and hypotheses

The literature on memory distortions and false memories shows that, despite a detailed phenomenological description of these phenomena, the neurobiological mechanisms underlying the formation of false memories are largely unknown. Sleep as well as sleep deprivation and specific neuroendocrine factors are well-known to distinctly affect the formation of accurate memories at different stages, i.e., encoding, consolidation, and retrieval. The three studies reported in the present thesis were designed to enlighten the role of specific sleep-associated mechanisms and neuroendocrine modulators in the generation of false memories.

Sleep is well known to benefit the consolidation of memories through the active reactivation and reorganization of previously acquired memory traces (Maquet, 2001; Stickgold, 2005; Diekelmann & Born, 2010). Importantly, processes of memory reactivation and reorganization during sleep do not only quantitatively strengthen memory traces for long-term storage. Rather memory representations become actively manipulated and restructured within the consolidation process which can eventually lead to qualitative changes in the encoded representations, e.g., in the extraction of explicit knowledge from implicitly learned skills or in the generation of insight into hidden rules (Wagner et al., 2004; Fischer et al., 2005). It has been proposed that new memories become dynamically adapted to previously existing knowledge networks during sleep and thereby general concepts or schemas can become extracted from singular learned events (Diekelmann & Born, 2010). The first objective of the present thesis therefore is to test whether *sleep-dependent consolidation* by reorganizing memory representations leads to the generation of false memories. The DRM paradigm has been extensively used to study false memories and appears to be particularly well suited for the present purpose since false memories in this paradigm reflect a kind of schema or concept, i.e., the gist word extracted from lists of single associated words. It is *(i)* hypothesized that sleep after learning increases the generation of false memories in the DRM paradigm compared to a retention interval of wakefulness. Because it has further been suggested that the consolidating influence of sleep depends on the kind of retrieval test used,

it *(ii)* can be assumed that false memory generation after sleep might depend on whether recall or recognition procedures are applied to test memory retrieval.

Sleep deprivation has consistently been found to impair cognitive processes, particularly those functions that critically depend on the integrity of the PFC (Harrison & Horne, 2000b; Jones & Harrison, 2001; Durmer & Dinges, 2005). Amongst these are fundamental functions that are essential for effective memory retrieval, specifically the ability to discriminate actually learned information from new or misinformation (i.e., retrieval monitoring). Impaired retrieval monitoring can lead to an increased generation of false memories (Johnson et al., 1993). The second objective of the present thesis is therefore to examine the effects of acute *sleep deprivation at retrieval* on the occurrence of false memories in the DRM paradigm. It is *(iii)* hypothesized that sleep deprivation at retrieval enhances the amount of false memories. There is further evidence that the adenosine antagonist caffeine can counteract the impairments in cognitive functioning following sleep deprivation. Thus, it is *(iv)* hypothesized that the administration of caffeine before retrieval testing abolishes the sleep deprivation-induced enhancement of false memories.

The stress hormone cortisol is a known modulator of memory formation (Het et al., 2005; Lupien et al., 2005; Wolf, 2009). Specifically, elevated cortisol levels at retrieval disrupt accurate memory retrieval. There are two main theoretical frameworks on false memory formation, both of which would predict different effects of cortisol at retrieval on the generation of false memories. According to monitoring theories, false memories are generated at retrieval due to a failure in the ability to discriminate actually learned items from internally generated items (retrieval monitoring; Johnson et al., 1993). Gist-based theories, on the other hand, postulate that false memories are generated in the normal process of memory formation and consequently rely on the same basic mechanisms as accurate memory (Posner & Keele, 1968; Brainerd & Reyna, 2001). Elevated cortisol by impairing accurate memory retrieval and retrieval monitoring should increase false memories according to monitoring theories, but would be expected to decrease false memories to the same extent as accurate memories according to gist-based theories. The third objective of this thesis is therefore to test *(v)* whether cortisol administration at retrieval increases or decreases false memories what would shed light on a basic mechanism underlying false memory formation.

These three objectives will be addressed in Studies 1, 2, and 3, respectively, which will be presented in detail in the following.

Study 1 – The role of sleep and sleep deprivation for false memory formation in a recognition paradigm

Published as: Diekelmann, S., Landolt, H.-P., Lahl, O., Born, J. & Wagner, U. (2008). Sleep loss produces false memories. *PLoS ONE, 3(10)*, e3512.

Introduction

As mentioned above, human memory is not a literal record of the world, but is influenced by knowledge representations that already exist in the brain (Bartlett, 1932). Consequently, what is retrieved from memory can substantially differ from what was originally encoded (Loftus et al., 1995; Schacter et al., 1998). One particularly interesting example are false memories, i.e., when people claim to remember events that in fact never happened. Typically, false memories are semantically strongly associated to actually encoded events, and subjects are highly confident about the correctness of these memories (Roediger, III & McDermott, 1995; Schacter, 1996; Toglia et al., 1999; Seamon et al., 2002). It can be assumed that the development of false memories follows the same basic principles of memory formation as the development of correct memories, comprising the three different sub-processes encoding (learning), consolidation (off-line processing and strengthening of memory traces after encoding), and retrieval of the learned material (Schacter et al., 1998).

Sleep represents a neurobiological condition that is critically involved in memory formation. Specifically, sleep plays an active role in memory consolidation (Buzsaki, 1998; Smith, 2001; Stickgold, 2005; Born et al., 2006). During sleep, newly acquired memory traces are not only strengthened in distinct neural circuits (synaptic consolidation), but fresh memory traces are also redistributed to other brain regions for long-term storage and integrated within pre-existing long-term memories, a process termed system consolidation (Dudai, 2004; Fischer et al., 2005; Diekelmann & Born, 2007). This active restructuring may also lead to the formation of false memories, because after active reorganization and integration within pre-existing representations, the memory representation can qualitatively differ from what was originally encoded (Fenn et al., 2003; Wagner et al., 2004). In this case, false memories would be created during consolidation as new and enduring knowledge representations, which are “false” in the sense that they abstract from the actually encoded

material by generalizing to semantically associated knowledge. By this way, sleep itself may promote false memories during memory consolidation.

On the other hand, the occurrence of false memories could result from acute disturbances in the retrieval process that do not rely on false representations per se. In this case, prolonged *loss* of sleep would be expected to enhance false memories. Ample evidence indicates that sleep deprivation markedly impairs cognitive functions like vigilance, attention, working memory, divergent thinking and other executive functions (Harrison & Horne, 2000b; Durmer & Dinges, 2005). Importantly, memory retrieval is likewise acutely impaired under sleep deprivation, which has been attributed to reduced source and reality monitoring (Horne, 1993; Drummond et al., 2000; Harrison & Horne, 2000b; Chee & Choo, 2004), and the same mechanisms may also acutely support the generation of false memories.

A series of four experiments was performed to test these hypotheses, applying the well-established Deese-Roediger-McDermott (DRM) false memory paradigm (Deese, 1959; Roediger, III & McDermott, 1995), which uses word lists reliably yielding unusually high amounts of false memories (Schacter et al., 1996b; Toglia et al., 1999; Seamon et al., 2002). Subjects learned lists of semantically associated words (e.g., “night”, “dark”, “coal”, etc.). The strongest associate, however, the “theme” of the list - “black” in this example - was not presented during learning. At retrieval testing, 9, 33 or 44 hours after learning, list words were presented again together with the “theme” (i.e., gist) word and unrelated distractor words, and subjects had to indicate for each word whether it was presented during learning or not (recognition test). Subjects either slept or stayed awake in the consolidation phase immediately following learning, and they were or were not acutely sleep deprived at retrieval. Sleep deprivation at retrieval, but not sleep after learning, substantially enhanced the proportion of false memories. This effect was neutralized when caffeine was administered before retrieval testing, indicating that adenosinergic mechanisms can contribute to false memory generation following sleep loss.

Methods

Participants

A total of 145 healthy adults [age 23.7 ± 3.2 (mean ± SD), range 18-35 yr, 59 females] with regular sleep-wake cycles (≥ 6 hours sleep per night) and no shift work for at least six weeks prior to the experiments participated in the study. Subjects were not allowed to ingest any

caffeine or alcohol from the day before until the end of the experiments. Prior to experimental nights all subjects spent an adaptation night in the sleep laboratory. Subjects in Experiment IV were moderate caffeine consumers (< 250 mg per day). They had to rate themselves as being caffeine-sensitive, and to abstain from caffeine for two weeks prior to the experiment to exclude withdrawal effects. All subjects gave written informed consent and were paid for participation in the study, which was approved by the local ethics committee of the University of Lübeck.

Design and procedure

A series of four experiments was performed to disentangle factors related to consolidation and retrieval in sleep-associated false memory generation, carefully controlling for possible circadian influences on memory formation (Schmidt et al., 2007; Exp. I to III) and exploring possible underlying neurophysiological mechanisms in a pharmacological study (Exp. IV). An overview of the experimental designs used in these experiments is given in Figure 4.

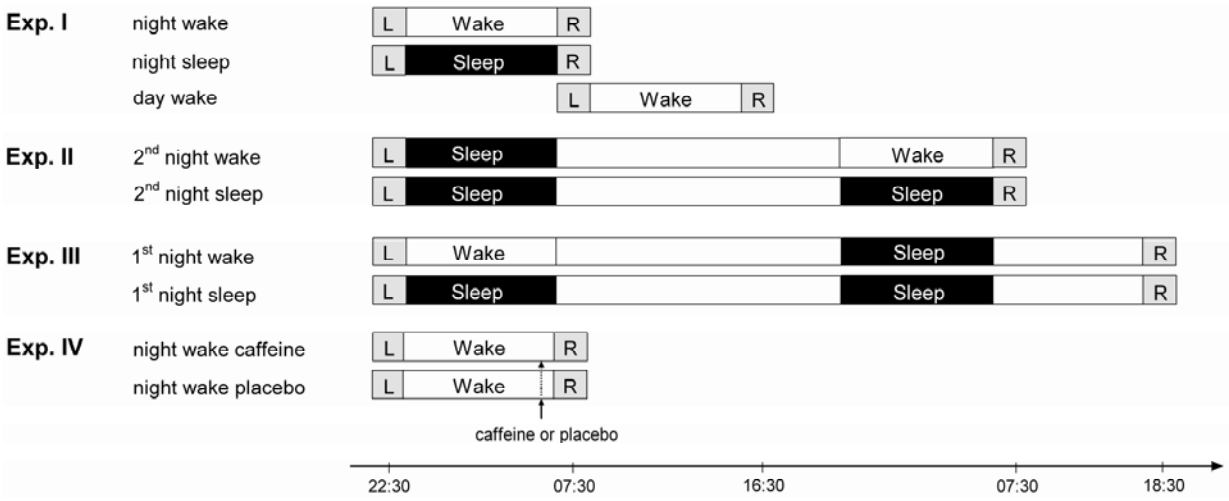

Figure 4. Experimental design. Subjects either slept or stayed awake in the consolidation phase following learning, and either were or were not sleep deprived at retrieval. Black fields refer to sleep periods; blank fields represent times of wakefulness. Times of learning (L) and retrieval (R) are indicated for Experiments I to IV.

Experiment I

This initial experiment compared false memory rates in three groups of subjects with a delay of 9 hours between learning and retrieval testing, where the effect of regular sleep in the consolidation phase following learning ("night sleep") was compared with two wake conditions, one with ("night wake") and one without ("day wake") acute sleep deprivation at retrieval testing. In the "night sleep" and "night wake" group subjects learned at 22:30 h. Thereafter, subjects in the "night sleep" group were allowed to sleep from 23:00 to 07:00 h in the sleep laboratory with standard polysomnographic recordings. Subjects in the "night wake" condition stayed awake in the laboratory and were allowed to read, watch TV and play simple games. Retrieval testing in both groups was performed at 07:30 h. For the "day wake" group learning and retrieval occurred at 08:00 h and 17:00 h. During the retention interval they engaged in everyday activities, which they reported in a questionnaire afterwards.

Experiment II

By comparing a "2nd night wake" and a "2nd night sleep" group, with normal sleep in the night following learning for all subjects, only the factor "sleep-deprived vs. non-deprived state at retrieval" was manipulated, while the factor "sleep vs. wakefulness after learning" was held constant. Subjects in the "2nd night wake" group learned at 22:30 h and retrieval testing was performed 33 hours later at 08:00 h. They slept at home during the first night after learning and stayed awake the second night prior to the retrieval session in the sleep laboratory. Subjects in the "2nd night sleep" group slept both nights between learning and retrieval. All subjects were instructed to go to bed at home between 22:00 and 00:00 h, to get rise between 06:00 and 08:00 h, and to sleep at least 7 hours. They wore Actiwatches® (Cambridge Neurotechnology Ltd) and filled in questionnaires to control for bedtimes and estimate total sleep time.

Experiment III

By comparing a "1st night wake" and a "1st night sleep" group, with retrieval testing performed after subjects had slept normally in the second night, only the factor "sleep vs. wakefulness after learning" was manipulated, while all subjects were not sleep-deprived at retrieval. Subjects in both groups learned at 22:30 h and recognition testing occurred 44 hours later at 18:30 h in order to match the time of day for learning and retrieval. During the first

night, subjects in the "1st night sleep" group slept in the sleep laboratory with polysomnographic recording. Subjects in the "1st night wake" group were kept awake in the laboratory (as described for Experiment I). They went home at 07:00 h and were asked to stay awake until 20:00 h the next evening. Adherence to this instruction was confirmed by actigraphy. During the second night, subjects in both groups slept at home (see above) and filled in sleep questionnaires for bedtimes and total sleep time.

Experiment IV

This experiment investigated the influence of the adenosinergic antagonist caffeine on false memory generation at retrieval in subjects who were acutely sleep deprived. Subjects learned at 22:30 h and recognition performance was tested at 07:30 h the next morning. Between learning and retrieval all subjects stayed awake in the laboratory as described for Experiment I. One hour before the start of the recognition test, subjects were either administered a capsule containing 200 mg caffeine ("night wake caffeine") or placebo ("night wake placebo") according to a randomized, double-blind design.

Materials

The standard Deese-Roediger-McDermott (DRM) procedure (Deese, 1959; Roediger, III & McDermott, 1995) was used to induce false memories. All subjects learned 18 DRM lists, selected from Stadler et al. (Stadler et al., 1999) and translated into German. Each list consisted of 15 semantically associated words (e.g., "night", "dark", "coal", etc.). The strongest associate, however, i.e. the "theme" of the list ("black" in this example) was not presented during learning. For each list, words were presented in the order from the strongest to the weakest associative strength with respect to the theme word. The list words were recorded electronically in a female voice and presented once sequentially with a delay of ten seconds between lists and 750 ms between words. Subjects learned individually in a sound-attenuated room where the words were presented via loudspeakers. They were instructed to pay attention to the words and to memorize them as accurately as possible because memory would be tested later.

At retrieval testing, recognition memory was tested by a computerized programme. Three types of words were presented: list words (actually presented during learning, specifically the words of serial position 1, 5 and 10 of each list), unrelated distractors (which

were not presented during learning and not associated to the list words; specifically, these words were list words from other DRM lists, e.g. “highway” and “tall” for the theme word “black”) and the theme words of the lists (that had not been presented during learning, but were semantically strongly associated to the list words). Words were presented visually in white letters on a black background in the middle of a 17’’ computer screen. Altogether, 108 words (54 list words, 36 distractors and 18 theme words) were presented to the subjects. For each word they had to give an old/new judgment (i.e., to indicate whether the word had been presented during learning or not) and a confidence rating for their answer on a 4-point scale ranging from 1 (“I had to guess”) to 4 (“absolutely sure”) by clicking with the mouse on the corresponding buttons. After all 108 words were presented, those words that were previously judged as “old” were presented again, and the participants gave a Remember/Know/Guess (RKG) judgment according to established procedures (Seamon et al., 2002; Gardiner et al., 2002). There was no time limit for any judgments.

Control variables: subjective ratings, sleep data, and salivary cortisol

Prior to learning and recognition testing, subjects in all experiments rated their subjective sleepiness, activation, motivation and concentration on 5-point Likert-scales with 1 indicating “not at all” and 5 indicating “very much”. In Experiment IV subjects additionally filled in a caffeine symptom questionnaire after recognition testing (Retey et al., 2007; 20 items, each ranging from 0 = "not at all" to 3 = "very much"). “Caffeine effect scores” differed significantly between the “night wake caffeine” and “night wake placebo” groups [14.27 ± 3.07 vs. 5.39 ± 1.35, $t(31) = 2.80$, $P = 0.016$]. Sleep quality in Experiments I to III was controlled by standard polysomnographic recordings and sleep questionnaires, as detailed above. Polysomnographic recordings were visually scored as wake or stages 1, 2, 3, 4 and REM sleep according to standard criteria (Rechtschaffen & Kales, 1968).

In Experiment I, salivary cortisol concentrations were additionally measured immediately before, during and after recognition testing to control for possible influences of circadian and awakening-related variations in glucocorticoid release known to influence memory function (Wilhelm et al., 2007; Wagner et al., 2007).

Statistical analysis

Data from subjects whose false memory performance differed from the group mean by more than two standard deviations were identified as outliers and excluded from analysis. This criterion applied to four subjects whose false memory rate was drastically below the group mean [one subject was removed from each of the following groups: night wake (Exp. I), 2nd night wake (Exp. II), 1st night sleep (Exp. III), night wake caffeine (Exp. IV)]. Data from two subjects had to be rejected because one performed completely at chance level (~ 50 % hits, false memories and false alarms), and the other had almost 100 % hits, false memories and false alarms, making an adequate evaluation of memory performance impossible.

Memory data were analyzed by standard procedures of recognition memory analysis (Snodgrass & Corwin, 1988). Basically, this analysis uses false memory rates, hit rates and false alarm rates as the primary dependent variables, which were corrected prior to analysis as recommended by Snodgrass and Corwin (Snodgrass & Corwin, 1988) to account for deviations from the normal distribution due to positive skewness. Additionally, to correct for baseline propensity to accept items the discrimination indices P_r and bias indices B_r were computed for hits and false memories according to the Two-High-Threshold model, i.e., correct recognition: P_r = hit rate – false alarm rate, false recognition: P_r = false memory rate – false alarm rate; B_r = false alarm rate / (1 - P_r), for correct and false recognition, respectively (Snodgrass & Corwin, 1988). Measures were compared between groups using one-way analyses of variance (ANOVA) in Experiment I, and pairwise t-tests for independent samples in Experiments II to IV. Confidence ratings and Remember/Know/Guess judgments were analyzed using a 3 (group) x 3 (word type) ANOVA in Experiment I, and 2 (group) x 3 (word type) ANOVAs in the Experiments II to IV. “Group” served as between-subjects factor and “word type” (list words, distractors, theme words) as within-subjects factor. For analyses of subjective ratings a 3 (group) x 2 (session) ANOVA in Experiment I, and 2 (group) x 2 (session) ANOVAs in Experiments II to IV were conducted, with “group” as between-subjects factor and “session” (learning vs. retrieval) as within-subjects factor. In case of significant effects, post-hoc pair-wise t-tests were computed. When appropriate, Greenhouse-Geisser correction of degrees of freedom was applied. The significance level was set to P = 0.05, two-tailed (except for false memories in Experiment II which were tested one-tailed due to a directional hypothesis).

Results

Memory performance

Experiment I

We first compared false memory rates in three groups of subjects with a delay of 9 hours between learning and retrieval testing (Figure 4). Two groups learned in the evening and were tested the next morning, after they had slept ("night sleep", n = 15) or stayed awake during the intervening night ("night wake", n = 14). The third group ("day wake", n = 14) learned in the morning and was tested in the same evening after normal daytime wakefulness.

Subjects of the "night wake" group who were acutely sleep deprived at retrieval testing exhibited significantly more false memories than subjects in the two other groups [$F(2, 40) = 6.90$; $P = 0.003$; Figure 5, Table 1]. After nocturnal wakefulness the proportion of falsely recognized theme words was on average 0.88 ± 0.02, i.e. subjects falsely recognized 88 % of the theme words, whereas after sleep and diurnal wakefulness false memory rate was 0.77 ± 0.03 and 0.75 ± 0.03, respectively [mean ± SEM; $t(27) = 3.40$, $P = 0.002$ and $t(27) = 4.01$, $P < 0.001$, for pair-wise comparisons]. Importantly, subjects did not produce more false memories in the "night sleep" group than in the "day wake" group, which would be expected if consolidation processes during post-learning sleep were critical for the development of false memories [$t(26) = 0.46$, $P > 0.60$]. There was no difference between the three groups in hit rates (correctly recognized words) [$F(2, 40) = 0.78$, $P > 0.40$] and false alarm rates (falsely recognized distractor words) [$F(2, 40) = 1.18$, $P > 0.30$; Table 1). To exclude that increased false memory generation after sleep deprivation merely resulted from enhanced baseline propensity to accept items, additional analyses were performed with the discrimination index P_r and the response bias index B_r according to the two-high threshold model of recognition memory as dependent variables (Snodgrass & Corwin, 1988; see Materials and Methods for details). In these analyses, sleep deprived subjects likewise exhibited significantly more false memories compared to both non-deprived control groups [$P_r = 0.67 \pm 0.04$, 0.50 ± 0.04 and 0.47 ± 0.04, for the "night wake", "night sleep" and "day wake" group, respectively; $F(2, 40) = 8.69$, $P = 0.001$], whereas correct recognition memory again did not differ between groups [$P_r = 0.51 \pm 0.04$, 0.40 ± 0.04 and 0.42 ± 0.04, for the "night wake", "night sleep" and "day wake" group, respectively; $F(2, 40) = 2.05$, $P > 0.14$]. The response bias, either for false recognition or correct recognition, also did not differ between groups [false recognition: $B_r = 0.63 \pm 0.06$, 0.55 ± 0.06 and 0.53 ± 0.06; correct recognition: $B_r = 0.40 \pm 0.04$, 0.45 ± 0.04 and 0.47 ± 0.04; both $F(2, 40) < 1.20$, $P > 0.30$].

This pattern of results indicates that sleep deprivation at retrieval, but not sleep after learning, critically enhances false memories. Experiments II and III were designed to further strengthen this conclusion by separating the two factors "sleep-deprived vs. non-deprived state at retrieval" and "sleep vs. wakefulness after learning", and carefully controlling for possible circadian influences.

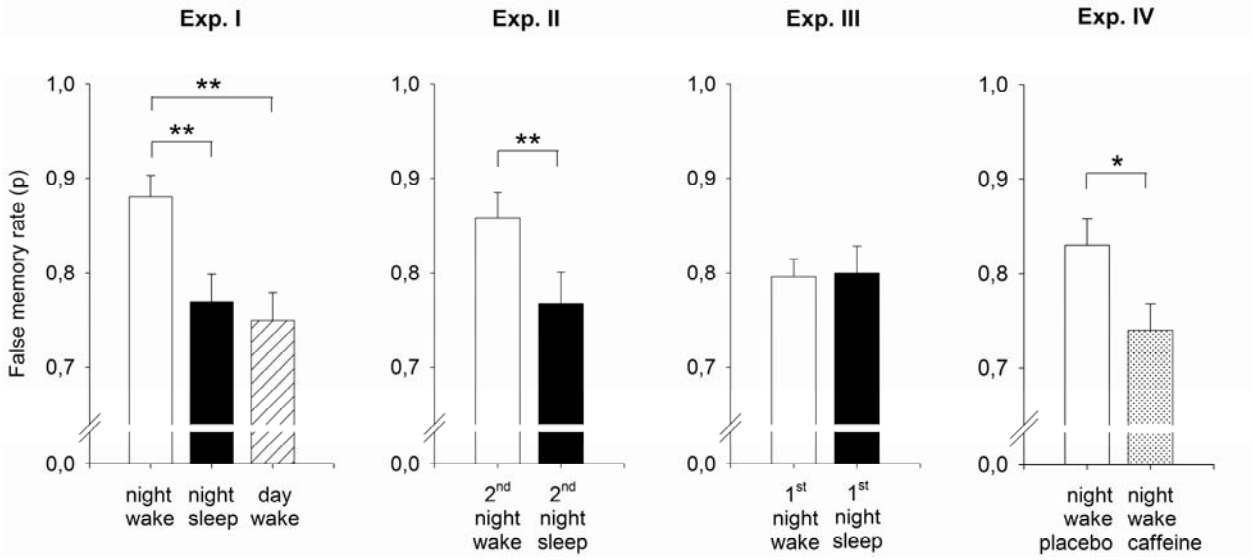

Figure 5. Proportion of false memories in the recognition test. Under sleep deprivation at retrieval false memory rate was significantly enhanced in Experiment I (higher false memory rate in the sleep deprived "night wake" group compared to both non-deprived groups), while sleep after learning compared to wakefulness did not increase false memories (no difference between the "night sleep" and "day wake" group). Experiments II and III further strengthen these findings in showing that sleep deprivation at retrieval also enhanced false memory rate when "sleep vs. wakefulness after learning" was held constant and subjects only were or were not sleep deprived at retrieval ("2nd night wake" vs. "2nd night sleep" in Experiment II), and that sleep after learning neither enhanced false memories when retrieval was tested after a recovery night and controlling for circadian phase ("1st night wake" vs. "1st night sleep" in Experiment III). The administration of caffeine one hour before retrieval testing in Experiment IV abolished the sleep deprivation-induced enhancement in false memories. False memory rate refers to the mean proportion of the judgment "old" to 18 theme words that were not presented during learning (mean ± SEM). * $P < 0.05$, ** $P < 0.01$

Experiment II

Only the factor "sleep-deprived vs. non-deprived state at retrieval" was manipulated, while the factor "sleep vs. wakefulness after learning" was held constant. Two groups of subjects learned in the evening and slept in the first night after learning. In the second night after learning, one group stayed awake to be sleep-deprived at retrieval testing on the next morning

("2nd night wake", n = 18), whereas the other group slept normally ("2nd night sleep", n = 19; Figure 4). In view of the results from Experiment I, we expected enhanced false memory retrieval under sleep deprivation, compared to the non-deprived state, also when retrieval testing took place one day later.

In fact, subjects who were sleep deprived at retrieval ("2nd night wake"), like in Experiment I, showed higher false memory rates than non-sleep deprived subjects [0.86 ± 0.02 vs. 0.76 ± 0.03; t (35) = 2.62, P = 0.007; Figure 5]. As in Experiment I, hit rate [t(35) = -0.85, P > 0.40] and false alarm rate [t(35) = 1.05, P = 0.30] did not differ between the groups (Table 1). False recognition corrected for baseline propensity to accept items was likewise higher in sleep deprived than in non-deprived subjects [P_r = 0.53 ± 0.04 vs. 0.48 ± 0.05, for the "2nd night wake" and "2nd night sleep" group, respectively; t(35) = 1.68, P = 0.05]. Like in Experiment I, correct recognition scores [P_r = 0.35 ± 0.03 and 0.42 ± 0.03, t(35) = -1.39, p > 0.17], as well as bias indices for both false recognition and correct recognition did not differ between groups [false recognition: B_r = 0.72 ± 0.04 and 0.54 ± 0.05; correct recognition: B_r = 0.50 ± 0.03 and 0.46 ± 0.04; both t(35) < 1.20, P > 0.20].

Experiment III

Only the factor "sleep vs. wakefulness after learning" was manipulated, while all subjects were not sleep-deprived at retrieval. Two groups of subjects learned in the evening, and in the subsequent night either slept normally ("1st night sleep", n = 15) or stayed awake ("1st night wake", n = 17). All subjects slept in the second night after learning and were tested for retrieval in the evening thereafter (Figure 4). In this way, not only were sleep/wake times and testing times paralleled between experimental groups, but times of learning and retrieval were also the same *within* subjects.

Confirming the results of Experiment I, false memory rate did not differ between subjects in the "1st night sleep" and the "1st night wake" groups [0.80 ± 0.02 vs. 0.80 ± 0.03; t (30) = -0.12, P > 0.90; Figure 5]. Again, the groups did not differ in hit rate [t(30) = -1.13, P > 0.20] and false alarm rate [t(30) = -0.51, P > 0.60; Table 1], as well as in baseline-corrected false recognition [P_r = 0.47 ± 0.04 and 0.44 ± 0.04, for the "1st night sleep" and "1st night wake" group, respectively; t(30) = 0.29, p > 0.70] and correct recognition [P_r = 0.28 ± 0.03 and 0.30 ± 0.04, t(30) = -0.16, p > 0.80]. Bias indices were also comparable between groups [false recognition: B_r = 0.60 ± 0.04 and 0.66 ± 0.05; correct recognition: B_r = 0.45 ± 0.05 and 0.51 ± 0.04; both t(30) < -0.50, P > 0.60].

Table 1. Recognition memory performance, confidence ratings and remember/know/guess judgments

	Exp. I			Exp. II		Exp. III		Exp. IV	
	night wake	night sleep	day wake	2nd night wake	2nd night sleep	1st night wake	1st night sleep	night wake placebo	night wake caffeine
Recognition									
False memories	**0.88±0.02**	0.77±0.03	0.75±0.03	**0.86±0.02**	0.76±0.03	0.80±0.03	0.80±0.02	**0.83±0.03**	0.74±0.03
Hits	0.72±0.03	0.67±0.02	0.70±0.03	0.68±0.02	0.70±0.02	0.66±0.03	0.61±0.03	0.73±0.02	0.66±0.04
False alarms	0.21±0.04	0.27±0.03	0.28±0.03	0.33±0.03	0.29±0.03	0.35±0.04	0.33±0.04	0.28±0.04	0.27±0.04
Confidence									
False memories	3.54±0.08	3.33±0.11	3.26±0.10	3.27±0.11	3.32±0.09	3.24±0.09	3.24±0.09	3.30±0.09	3.25±0.10
Hits	3.39±0.09	3.22±0.12	3.21±0.08	3.19±0.08	3.19±0.08	3.14±0.06	3.18±0.06	3.29±0.07	3.31±0.07
False alarms	2.70±0.15	2.45±0.14	2.28±0.12	2.65±0.13	2.61±0.08	2.49±0.12	2.37±0.12	2.41±0.12	2.47±0.14
Remember									
False memories	0.41±0.07	0.38±0.07	0.37±0.06	0.45±0.07	0.43±0.05	0.43±0.04	0.39±0.05	0.40±0.06	0.38±0.06
Hits	0.45±0.06	0.38±0.06	0.42±0.04	0.43±0.04	0.39±0.04	0.39±0.04	0.35±0.05	0.45±0.04	0.42±0.05
False alarms	0.11±0.04	0.06±0.03	0.08±0.03	0.25±0.04	0.18±0.03	0.19±0.04	0.14±0.04	0.13±0.05	0.18±0.06
Know									
False memories	0.39±0.05	0.38±0.06	0.35±0.03	0.33±0.06	0.36±0.05	0.35±0.04	0.38±0.05	0.34±0.05	0.34±0.05
Hits	0.30±0.04	0.29±0.05	0.29±0.02	0.31±0.05	0.37±0.04	0.35±0.04	0.40±0.04	0.28±0.03	0.32±0.03
False alarms	0.29±0.05	0.19±0.05	0.26±0.07	0.26±0.04	0.39±0.06	0.32±0.05	0.23±0.04	0.27±0.03	0.29±0.07
Guess									
False memories	0.20±0.04	0.29±0.05	0.28±0.05	0.22±0.04	0.21±0.04	0.24±0.05	0.23±0.05	0.26±0.05	0.27±0.05
Hits	0.25±0.03	0.33±0.04	0.30±0.04	0.23±0.03	0.24±0.03	0.25±0.03	0.26±0.02	0.27±0.03	0.26±0.04
False alarms	0.61±0.08	0.75±0.06	0.67±0.07	0.46±0.05	0.43±0.06	0.50±0.06	0.63±0.06	0.59±0.08	0.53±0.09

Recognition is indicated by the mean proportion of "old" judgments on theme words (= False memories), list words (= Hits) and distractors (= False alarms). Mean confidence ratings (ranging from 1 = "guess" to 4 = "sure") and proportions of Remember, Know and Guess judgments are displayed for words judged as "old". Means ± SEM are shown. Numbers in bold refer to significant differences compared to respective control groups within each experiment ($P < 0.05$).

Experiment IV

In view of the results from Experiments I to III, which consistently show that it is specifically sleep deprivation at retrieval that renders subjects susceptible to false memories, Experiment IV was performed to explore a possible neurophysiological mechanism underlying this effect. Adenosinergic activity is thought to play a key role in the emergence of sleepiness and impairment of executive cognitive functions after prolonged wakefulness (Basheer et al., 2000; Dunwiddie & Masino, 2001; Retey et al., 2006). Based on this background we hypothesized that caffeine, an adenosine receptor antagonist, reduces the occurrence of false memories after sleep deprivation. Two groups of subjects learned in the evening, stayed awake during the night and were tested again the next morning as in the "night wake" group of Experiment I (Figure 4). One group received 200 mg caffeine one hour before the start of retrieval testing ("night wake caffeine", n = 15) and the other group received placebo ("night

wake placebo", n = 18). Caffeine and placebo were administered according to a randomized, double-blind design.

The "night wake caffeine" group exhibited a significantly lower false memory rate when compared to the "night wake placebo" group [0.74 ± 0.03 vs. 0.83 ± 0.03; t(31) = -2.41, P = 0.022; Figure 5]. Again, in contrast to false memory rate, hit rate [t(31) = -1.47, P > 0.15] and false alarm rate [t(31) = -0.20, P > 0.80] did not differ between groups (Table 1), and again the same pattern occurred when baseline-corrected measures were used: False recognition was significantly reduced after caffeine administration [P_r = 0.47 ± 0.04 vs. 0.55 ± 0.03, for the "night wake caffeine" and "night wake placebo" group, respectively, t(31) = -2.43, P = 0.021], whereas scores of correct recognition did not differ between groups [P_r = 0.39 ± 0.03 vs. 0.45 ± 0.04, t(31) = -0.76, P > 0.40]. The response bias per se, like in the previous experiments, did not differ between groups, neither for false recognition nor for correct recognition [false recognition: B_r = 0.49 ± 0.05 and 0.61 ± 0.06; correct recognition: B_r = 0.44 ± 0.06 and 0.48 ± 0.05; both t(31) < -0.20, P > 0.70].

Confidence ratings and remember/know/guess judgments in recognition memory

All subjects tested in Experiments I to IV gave confidence ratings for their answers in the recognition memory test, as well as remember/know/guess judgments for the positive answers (Roediger, III & McDermott, 1995; Gardiner et al., 2002). Confidence ratings were in all experiments distinctly higher for theme words and list words when compared to distractors (main effects "word type", all P < 0.001; pair-wise comparisons, all P < 0.001). Also the proportion of "remember" judgments was higher for theme words and list words than for distractors in all experiments (main effects "word type", all P < 0.001; pair-wise comparisons, all P < 0.001). However, in none of the experiments differed the groups significantly in these variables (main effects "group" and interactions "group x word type", all P > 0.10; Table 1), indicating that sleep deprived subjects did not exhibit higher confidence or more remember judgments on false memories, hits or false alarms compared to non-deprived controls.

Control variables

Subjective ratings

Subjects in all experiments rated their subjective sleepiness, activation, motivation and concentration immediately before learning and recognition testing. As expected, sleep-

deprived groups (i.e., the "night wake" group in Experiment I and the "2nd night wake" group in Experiment II) scored higher at retrieval in subjective ratings of sleepiness, and lower in motivation and concentration than the respective non-sleep deprived groups (all $P < 0.05$; Table 2). In Experiment I, at learning subjects in the "night sleep" group were also sleepier and less activated than the "night wake" and "day wake" group ($P < 0.05$), possibly because subjects anticipated they would be allowed to sleep soon. In Experiment IV, caffeine administration after sleep deprivation significantly reduced subjective sleepiness and increased feelings of activation and motivation compared to placebo ($P \leq 0.05$; Table 2).

Table 2. Subjective ratings at learning and retrieval

	Exp. I			Exp. II		Exp. III		Exp. IV	
	night wake	night sleep	day wake	2nd night wake	2nd night sleep	1st night wake	1st night sleep	night wake placebo	night wake caffeine
Learning									
Sleepiness	2.53±0.32	**3.36±0.25**	2.00±0.26	2.11±0.21	2.33±0.21	2.47±0.23	3.20±0.30	2.17±0.20	2.13±0.27
Activation	3.33±0.19	**2.57±0.29**	3.36±0.23	3.39±0.20	3.50±0.23	3.00±0.21	2.60±0.13	3.67±0.20	3.40±0.19
Motivation	3.40±0.19	3.36±0.20	3.57±0.20	3.61±0.22	3.94±0.13	3.06±0.18	3.07±0.23	3.67±0.18	3.47±0.17
Concentration	3.00±0.17	2.93±0.22	3.57±0.23	3.50±0.20	3.22±0.15	3.00±0.17	2.93±0.15	3.33±0.23	3.67±0.23
Retrieval									
Sleepiness	**3.67±0.30**	2.36±0.27	1.93±0.29	**4.17±0.25**	2.26±0.25	1.94±0.29	1.80±0.20	4.50±0.26	**3.20±0.35**
Activation	**2.07±0.18**	3.14±0.21	3.57±0.29	**1.78±0.15**	3.53±0.21	3.23±0.25	3.53±0.17	2.22±0.22	**3.07±0.32**
Motivation	**2.80±0.17**	3.64±0.17	3.50±0.29	**2.00±0.20**	3.47±0.16	3.35±0.21	3.53±0.22	2.33±0.24	**3.07±0.27**
Concentration	**2.27±0.12**	3.29±0.13	3.21±0.24	**2.22±0.21**	3.37±0.14	3.35±0.26	3.53±0.24	2.33±0.18	2.73±0.25

Subjective ratings ranged from 1 = "not at all" to 5 = "very much". Bold numbers refer to significant differences compared to respective control groups within each experiment ($P < 0.05$).

Sleep data

For experimental conditions involving sleep, quality of sleep was controlled by standard polysomnography (Experiments I and III) and sleep questionnaires (Experiments II and III). In Experiment I, polysomnographic recordings of the "night sleep" group revealed normal sleep patterns with a total sleep time of 411.3 ± 4.4 min (mean ± SEM; sleep stage 1, 4.4 ± 0.80 %; sleep stage 2, 55.8 ± 1.7 %; slow wave sleep, 18.5 ± 1.7 % and rapid eye movement sleep, 20.8 ± 1.5 %). In Experiment II, subjects slept at home during the first night after learning and according to sleep questionnaire data, subjects in the "2nd night sleep" and "2nd night wake" group did not differ significantly in the time they went to bed (23:57 h ± 18 min vs. 00:39 h ± 13 min) or total sleep time (7.64 ± 0.32 h vs. 7.86 ± 0.25 h; $P > 0.05$). In the second night, subjects in the "2nd night sleep" condition went to bed on average at 00:42 h ±

17 min and slept for 6.54 ± 0.28 h. In Experiment III, subjects of the "1st night sleep" group slept in the sleep laboratory during the first night after learning and recordings revealed normal sleep (total sleep time, 441.7 ± 7.7 min; sleep stage 1, 4.3 ± 0.54 %; sleep stage 2, 49.1 ± 2.9 %; slow wave sleep, 21.3 ± 3.0 %, rapid eye-movement sleep, 23.8 ± 2.0 %). In the second night (recovery night for subjects in the "1st night wake" group) all subjects slept at home and filled in sleep questionnaires. Subjects in the "1st night wake" group went to bed significantly earlier than the "1st night sleep" group (22:53 ± 32 min vs. 00:04 ± 44 min, $P < 0.05$). The groups did not differ significantly in mean sleep time (9.97 ± 0.50 h vs. 8.95 ± 0.38 h for "1st night wake" and "1st night sleep" groups, respectively; $P > 0.10$).

Salivary Cortisol

Salivary cortisol concentrations were measured at retrieval in Experiment I on the background of previous studies indicating substantial influences of corticosteroids on memory retrieval (e.g., de Quervain et al., 2000) and of psychosocial stress on false recognition (Payne et al., 2002; but seeSmeets et al., 2006a). Cortisol concentrations (in nmol/l and collapsed across measurements before, during and after retrieval) differed significantly between the groups [$F(2, 40) = 23.97$, $P < 0.01$] with a mean of 23.66 ± 2.88 in the "night sleep" group, 11.12 ± 2.06 in the "night wake" group, and 5.45 ± 0.77 in the "day wake" group. The differences reflect the typical circadian variation in salivary cortisol levels and the cortisol response after awakening in the night sleep group (Pruessner et al., 1997; Wilhelm et al., 2007). Individual cortisol concentrations did not correlate with false memory rate, hit rate or false alarm rate ($r < 0.14$, $P > 0.30$). Thus, sleep deprivation is unlikely to have affected false memories by stress-associated alterations.

Discussion

We investigated sleep-associated mechanisms of false memory generation in the DRM false memory paradigm. A series of experiments was performed to test whether consolidation sleep following learning increases false memories, and/or whether acute sleep deprivation at retrieval testing does so. Results from Experiments I to III provide strong evidence for the latter rather than the former hypothesis. Sleep deprivation at retrieval testing, but not sleep after learning, critically enhanced the rate of false memories. In addition, Experiment IV

showed that this effect can be neutralized by administration of caffeine before retrieval testing.

It could be argued that false memory rates were higher in sleep deprived subjects simply due to loss of motivation or reduced compliance. If this were true, however, hit rate and false alarm rate should have been similarly affected. This was not the case. Moreover, lower confidence ratings and more judgments of guessing would be expected with reduced motivation to engage in the task. Also in these variables, the sleep deprived subjects did not differ from the non-sleep deprived subjects. Sleep deprivation likewise did not change the response criterion subjects adopted to make old-new decisions in the recognition task, and sleep deprivation also enhanced false memories when corrected for response bias, indicating that higher false memory rates in sleep deprived subjects are not attributable simply to a more liberal response criterion (although a minor contribution of this factor cannot be entirely ruled out). Thus, we conclude that the observed differences primarily derive from changes in brain functions genuinely linked to the sleep deprived state. This conclusion is further supported by the finding that blocking adenosine receptors by caffeine at retrieval counteracts false memory enhancement in sleep-deprived subjects.

Ample evidence indicates that sleep deprivation strongly affects cognitive functions essentially relying on the integrity of the prefrontal cortex (PFC; Horne, 1993; Drummond et al., 2000; Harrison & Horne, 2000b; Durmer & Dinges, 2005; Yoo et al., 2007). Notably, the PFC has been specifically implicated in false recognition (Schacter & Slotnick, 2004; Slotnick & Schacter, 2004; Kubota et al., 2006). False memories, as compared to true memories, show greater activation in prefrontal regions, especially in the right PFC (Schacter et al., 1996b). These regions have been associated with effortful aspects of retrieval involving inhibition, post-retrieval monitoring, criterion setting and decision making about the sense of familiarity or recollection associated with false recognition (Rugg et al., 1996; Schacter et al., 1996b; Henson et al., 1999; Dobbins et al., 2002). One study suggested that PFC activation is required to limit or avoid false recognition (Curran et al., 2001). In this study, Curran and colleagues compared event-related potentials (ERP) in subjects who discriminated well between studied and non-studied items (good performers) and subjects who did not (poor performers). Good performers were characterized by a more positive late right frontal ERP than poor performers. This finding possibly reflects retrieval monitoring processes that are more likely engaged in good performers than in poor performers. The impairment of prefrontal lobe function after sleep deprivation may derogate these kinds of reality monitoring, which are necessary to determine whether or not a word was actually encountered

before or internally generated (Johnson et al., 1993; Mitchell et al., 2004). Assuming that sleep deprivation specifically impairs the ability to discriminate previously encountered words from new words, it could be expected that not only false memories, but also false alarms on distractors that are not semantically associated should be enhanced following sleep deprivation. This was not the case here. However, discriminating presented list words from highly associated theme words is much more difficult than distinguishing old list words from non-associated distractors and thus is possibly more prone to cognitive impairments associated with sleep loss.

Regarding the underlying neurophysiological mechanisms, our caffeine experiment points to adenosine as one factor involved in the decline of these cognitive functions under sleep deprivation. This notion is in line with previous data pointing to a key role for adenosinergic neuromodulation in the emergence of sleepiness and impairment of neurobehavioral functions after prolonged wakefulness (Basheer et al., 2000; Dunwiddie & Masino, 2001; Retey et al., 2006). Caffeine acts as an antagonist at adenosine receptors (Fredholm et al., 1999). By blocking adenosine A_1 receptor-mediated neuronal inhibition, caffeine increases cortical and hippocampal activity (Fisone et al., 2004), and studies in rats showed that it induces acetylcholine release in prefrontal areas (Acquas et al., 2002). Such mechanisms may underlie the enhanced effectiveness in prefrontal functioning after caffeine administration and might in this way have mediated the caffeine-induced reduction of false memories in sleep-deprived subjects.

It has to be noted, however, that changes in prefrontal functioning are not the only possible explanation for the occurrence of false memories after sleep loss. Indeed, other brain regions and cognitive functions related to memory are likewise negatively affected by sleep loss (Durmer & Dinges, 2005; Boonstra et al., 2007). Specifically, sustained attention and arousal, relying on a prefrontal-parietal network as well as on the basal forebrain and thalamus, are substantially reduced under sleep deprivation and are known to be implicated in memory functions (Thomas et al., 2000; Sarter et al., 2001; Chun & Turk-Browne, 2007; Chee et al., 2008). It is presently not clear how arousal and attention interact specifically in relation to false memory generation. False memories have recently been shown to be enhanced when attentional resources at retrieval are reduced (Knott & Dewhurst, 2007). On the other hand, false memory rates are lower with reduced arousal and enhanced in high arousal conditions, e.g. following psychosocial stress (Payne et al., 2002) or emotional arousal (Corson & Verrier, 2007). Caffeine increases arousal and enhances attentional resources (Bonnet et al., 2005), as confirmed also by the subjective data here, which could at

least partly account for the reduced occurrence of false memories with caffeine. Because we did not test the specificity of the observed effect for caffeine, it remains to be elucidated whether acting on arousal and attention by other stimulants not specifically targeting the adenosinergic system (e.g., modafinil) can similarly reduce false memories.

In contrast to the acute retrieval-related effects induced by sleep deprivation, our findings do not point to a critical contribution of system consolidation during post-learning sleep to the generation of false memories. Sleep after learning did not increase false memories compared to post-learning wakefulness even when cognitive state at retrieval and circadian influences were controlled for (Experiment III). It has to be noted, however, that not only false memory rate, but also hit rate (true recognition) was unaffected by post-learning sleep when compared to wakefulness. One possible reason is the kind of memory testing used here, i.e., recognition memory. Although consolidation effects of sleep following learning were previously found within recognition memory tasks (Wagner et al., 2007) some studies suggest that recognition memory appears to be less affected by post-learning sleep than free recall or cued recall (Drosopoulos et al., 2005; Hu et al., 2006). Thus, it is conceivable that effects of post-learning sleep on the generation of false memories could be revealed with more sensitive testing procedures. Study 2 directly addressed this issue by using a free recall procedure in the same experimental paradigm as used here.

In sum, we found that acute sleep deprivation increases false memories, while sleep after learning did not influence false memory formation. Although false memories are formally a kind of memory distortion, for proper adaptation it might be useful especially in situations of restricted cognitive control (as in a state of sleep deprivation) to rely on the gist of a memory, i.e. the broader semantical network associated with actually experienced events. In other cases, however, an exact distinction between closely related memory representations is crucial, e.g. in eyewitness testimony. Apart from other factors that can produce distortions of memory retrieval (e.g., suggestive interview procedures; see Loftus, 2003 for an overview), our results clearly show that sleep deprivation is another critical factor that must be avoided in such situations.

Study 2 – The role of sleep and sleep deprivation for false memory formation in free recall

Published as: Diekelmann, S., Born, J. & Wagner, U. (2010). Sleep enhances false memories depending on general memory performance. *Behavioural Brain Research*, *208(2)*, 425-429.

Introduction

Sleep is known to play a critical role in memory formation, in particular by benefiting the consolidation of previously acquired memories, i.e., the off-line phase of processing and strengthening of new memory representations that takes place in the time interval between initial encoding (learning) and later retrieval (Smith, 1996; Peigneux et al., 2001; Stickgold, 2005; Diekelmann et al., 2009). A current model holds that the beneficial effect of sleep on memory consolidation relies on a covert reactivation of the newly encoded memory traces leading to a redistribution of these memories to other brain regions together with an integration into pre-existing knowledge networks (McClelland et al., 1995; Born et al., 2006). Sleep-dependent reorganization during consolidation can qualitatively change pre-existing memory representations (Wagner et al., 2004; Fischer et al., 2006; Diekelmann & Born, 2007; Ellenbogen et al., 2007; Payne et al., 2008), a process that may under certain conditions lead to the development of distorted and false memories. In this way, sleep could promote false memories as a consequence of a reorganization process during memory *consolidation* (Payne et al., 2009).

However, false memories could also result from disturbances of memory *retrieval*. In this case, acute *loss* of sleep (sleep deprivation) is expected to enhance false memories. Ample evidence indicates that sleep deprivation can strongly impair various cognitive functions, including memory retrieval (Harrison & Horne, 2000b; Durmer & Dinges, 2005). The same mechanisms hampering retrieval (and associated processes of monitoring and decision making) may concomitantly favor the generation of false memories (Curran et al., 2001; Schacter et al., 2001; McDonough & Gallo, 2008).

Thus, sleep-related effects on the generation of false memories are expected to occur at two stages of memory formation, consolidation and retrieval. Using a recognition memory

procedure, we found evidence for the latter but not the former effect (Study 1): Sleep deprivation at retrieval acutely enhanced the occurrence of false memories, whereas sleep during the consolidation period appeared to exert no substantial influence on false memory generation (Diekelmann et al., 2008). However, these results do not completely rule out an effect of sleep during consolidation, as such an effect could have been masked by the specific retrieval test used, i.e., recognition memory, where subjects indicate for each word whether or not it was presented at learning. In fact, previous studies have suggested that recognition tests are less sensitive to effects of sleep on memory consolidation than free recall procedures (Drosopoulos et al., 2005; Wagner et al., 2007). In free recall, in contrast to recognition tests, memory is probed without any cues given by the experimenter, but the subject generates his/her own retrieval cues. Compared with recognition, free recall benefits to a greater extent from an easier accessibility of a memory that may result from a broader integration of the newly acquired representations into pre-existing knowledge networks (Gardiner, 1988; Kahana et al., 2005). This integration process could specifically benefit from sleep.

To test this idea, we assessed here the effects of sleep and sleep deprivation on false memory generation using a free recall rather than recognition procedure. To induce false memories, we used the Deese-Roediger-McDermott (DRM) procedure in which subjects learn lists of highly associated words lacking the strongest common associate or "theme" word (see Methods, for details). At retrieval, subjects were asked to write down as many of the learned list words as possible without receiving any cues. Because of previous evidence that sleep-dependent consolidation depends on the subject's general level of memory performance (Kuriyama et al., 2004; Drosopoulos et al., 2007; Tucker & Fishbein, 2008), this was an additional factor of interest in our analyses.

Methods

Participants

Fifty-five healthy subjects [age 22.81 ± 3.07 (mean ± SD), range 18–33 years, 28 females] with regular sleep-wake cycles (≥ 6 hours sleep per night) and no shift work for at least six weeks prior to the experiments participated in the study. Subjects were not allowed to ingest any caffeine or alcohol from the day before until the end of the experiments. Prior to experimental nights, subjects in the sleep group spent an adaptation night in the sleep laboratory. All subjects gave written informed consent and were paid for participation in the study, which was approved by the local ethics committee of the University of Lübeck.

Design and procedure

Subjects participated in one of three conditions (Figure 6). In the "night sleep" (n = 18) and "night wake" (n = 19) group subjects learned at 22:30 h. Thereafter, subjects in the "night sleep" group were allowed to sleep from 23:00 to 07:00 h in the sleep laboratory with standard polysomnographic recordings. Subjects in the "night wake" condition stayed awake in the laboratory and were allowed to read, watch TV and play simple games. Retrieval testing in both groups was performed at 07:30 h. For the "day wake" group (n = 18) learning and retrieval occurred at 07:30 h and 16:30 h, respectively. During the retention interval subjects of this group engaged in everyday activities, which they reported in a questionnaire afterwards. According to this design, effects of sleep during consolidation can be specifically revealed by differences between the "night sleep" and the "day wake" condition, whereas acute effects of sleep deprivation at retrieval would specifically affect the comparison between the "night wake" and the "day wake" condition.

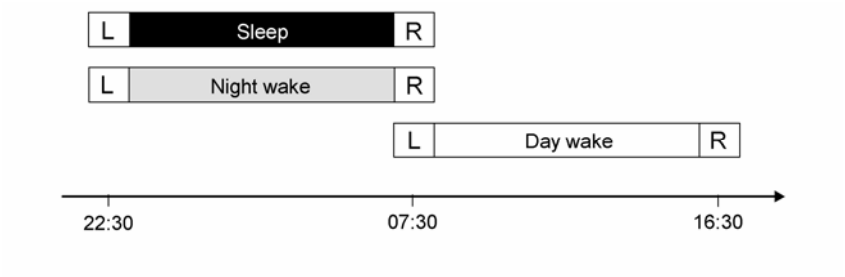

Figure 6. Experimental design. Subjects in the "night sleep" and "night wake" group learned in the evening and recall was tested the next morning after a full night of sleep or wakefulness. The "day wake" group learned in the morning and recall was tested in the evening after a normal day of wakefulness. L = learning, R = recall testing.

Materials

The standard DRM procedure as described in Diekelmann et al. (2008) was applied in a shortened version (for adapting a free recall procedure). Briefly, at learning, subjects studied 8 DRM lists (selected from Stadler et al., 1999) in a German version, each consisting of 12 strongly associated words (e.g., "night", "dark", "coal", etc.), with the strongest common associate, i.e., the "theme" word of the list, being not included (e.g., "black", in this example). For each list, words were presented in the order from strongest to weakest associative strength (with regard to the theme word). List words were recorded electronically in a male voice and were presented sequentially with one word every 3 seconds and a break of 20 seconds

between lists. At retrieval testing, subjects were asked to write down all the words they remember from the learning session. They were instructed not to guess and to write down only those words for which they were fairly sure that they actually occurred during learning.

To control for unspecific effects of sleep homeostatic and circadian factors on general cognitive performance level, prior to learning and retrieval testing subjects completed a word fluency test (Aschenbrenner et al., 2000) and rated their subjective sleepiness, activation, concentration and motivation on 5-point Likert-scales with 1 indicating “not at all” and 5 indicating “very much”.

Statistical analysis

Memory results were analyzed using the number of falsely recalled theme words (false memories), the number of correctly recalled list words (absolute recall) and the number of falsely recalled unrelated words (intrusions). Additionally, the number of correctly recalled list words (absolute recall) was adjusted for false recall of unrelated words (adjusted recall = absolute recall – intrusions), in order to take into account inter-individual differences in the general tendency to write down many or only few words. High and low performers were defined post-hoc according to a median split in adjusted recall of actual list words. This procedure resulted in sub-samples of n = 7, n = 7 and n = 14 subjects in the “night sleep”, “day wake” and “night wake” group for the low performers and n = 11, n = 11 and n = 5 subjects for the high performers, respectively.

Statistical analyses were performed using analyses of variance (ANOVA) with the factors “sleep/wake condition” (night sleep, night wake, day wake) and “high/low performers”, followed by separate analyses for high and low performers using one-way ANOVAs and post-hoc t-Tests where appropriate. Greenhouse-Geisser correction of degrees of freedom was applied when appropriate. The level of significance was set to $P = 0.05$.

Results

Effects of both sleep during consolidation and sleep deprivation at retrieval on false memory generation, while not present in the overall sample, occurred depending on the individual level of memory performance, i.e., sleep/wake conditions differentially affected false memories in low and high performing subjects [$F(2, 49) = 6.16$, $P = 0.004$, for the interaction sleep/wake condition x high/low performers]. Specifically, only in low performers, both sleep

deprivation (night wake) and post-learning nocturnal sleep (night sleep) yielded greater amounts of false memories in comparison with performance after daytime wakefulness [day wake, $F(2, 25) = 4.69$, $P = 0.019$, for main effect sleep/wake conditions; Figure 7]. Low-performing subjects who were allowed to sleep right after learning falsely recalled 2.86 ± 0.50 words whereas this rate was only 1.00 ± 0.50 words after a retention interval filled with daytime wakefulness [$t(12) = -2.41$, $P = 0.041$]. After nocturnal sleep deprivation false memory generation was enhanced to a rate of 2.71 ± 0.35 words [$t(19) = 3.38$, $P = 0.003$, for the comparison with the day wake group]. False recall in high-performing subjects, on the other hand, did not differ significantly between sleep/wake conditions [$F(2, 24) = 1.63$, $P = 0.22$; Table 3, Figure 7].

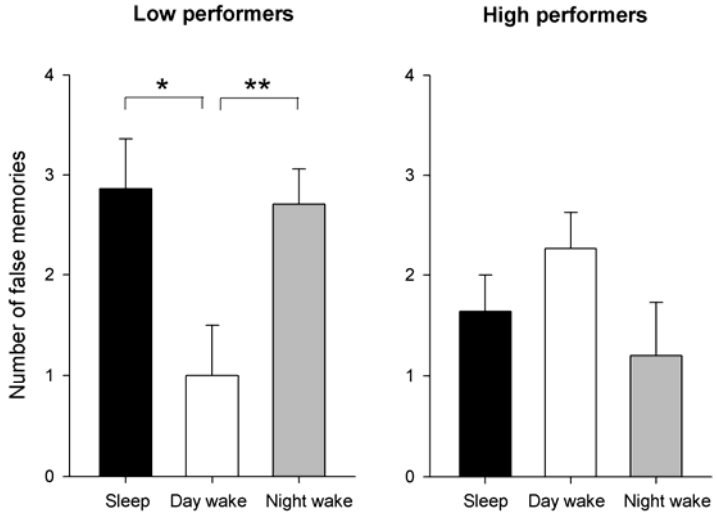

Figure 7. Number of false memories. In low performers, sleep after learning as well as sleep deprivation at retrieval enhanced the occurrence of false memories compared to diurnal wakefulness. False memories were not affected by sleep or sleep deprivation in high performers. Means ± SEM are shown. * $P < 0.05$, ** $P < 0.01$

The number of correctly recalled list words (absolute recall as well as adjusted recall) and also the number of intrusions did not differ between sleep/wake conditions in low performers and high performers (all $P > 0.12$; Table 3). Generally, reflecting the median split according to performance level in correct recall, high performers remembered about twice as many list words than low performers in absolute (44.56 ± 1.93 vs. 23.21 ± 1.87) as well as in adjusted recall (40.90 ± 1.92 vs. 19.09 ± 1.86; $P < 0.001$ for both comparisons). Notably, false memories for the non-presented theme words were not correlated with correct memory recall for the actually presented list words (correlation with absolute recall: $r = -0.02$, $P > 0.80$: with

adjusted recall: r = -0.087, P > 0.50), excluding that the observed differences between sleep/wake conditions in low performers occurred simply due to a selection bias with respect to the critical dependent variable (false memories) as a consequence of the median split by correct recall.

Table 3. Recall performance for low and high performers

	Low performers			High performers		
	sleep	day wake	night wake	sleep	day wake	night wake
False memories	2.86 ± 0.50[a]	1.00 ± 0.50	2.71 ± 0.35[a]	1.64 ± 0.36	2.27 ± 0.36	1.20 ± 0.53
Intrusions	4.71 ± 1.09	4.43 ± 1.09	3.21 ± 0.77	2.82 ± 0.87	4.18 ± 0.87	4.00 ± 1.30
Absolute recall	25.14 ± 3.54	21.43 ± 3.54	23.07 ± 2.51	43.73 ± 2.83	50.36 ± 2.83	39.60 ± 4.19
Adjusted recall	20.43 ± 3.53	17.00 ± 3.53	19.86 ± 2.49	40.91 ± 2.81	46.18 ± 2.81	35.60 ± 4.17

False memories = false recall of related theme words, Intrusions = false recall of unrelated words, Absolute recall = correctly recalled list words, Adjusted recall = Absolute recall – Intrusions. Means ± SEM are shown. [a] Significant difference compared to day wake group.

Performance in the word fluency test, indicating subject's current general capability to retrieve semantic information from memory revealed a lower performance of night wake compared to day wake subjects at retrieval (P = 0.012; see Table 4 for detailed results). Independent of sleep/wake conditions, high-performing subjects generated more words in the word fluency test than low performers (19.92 ± 1.00 vs. 16.70 ± 0.96, P = 0.024).

Table 4. Word fluency and subjective ratings at learning and retrieval

	Learning			Retrieval		
	sleep	day wake	night wake	sleep	day wake	night wake
Word fluency	19.39 ± 1.67	18.89 ± 1.13	15.79 ± 1.06	19.22 ± 1.10	21.22 ± 1.58	16.47 ± 0.89[b]
Sleepiness	3.28 ± 0.29[a]	2.11 ± 0.14	2.63 ± 0.11[b]	2.44 ± 0.22	2.22 ± 0.19	4.68 ± 0.25[a]
Activation	2.83 ± 0.23[b]	3.67 ± 0.16	3.26 ± 0.17	3.39 ± 0.22	3.50 ± 0.20	2.00 ± 0.15[a]
Concentration	3.11 ± 0.18	3.67 ± 0.16[a]	3.16 ± 0.14	3.50 ± 0.19	3.78 ± 0.19	2.11 ± 0.13[a]
Motivation	3.35 ± 0.21	4.11 ± 0.16[a]	3.26 ± 0.24	3.56 ± 0.18	3.78 ± 0.22	2.53 ± 0.18[a]

Means ± SEM are shown. [a] Significant difference compared to both other groups, [b] Significant difference compared to day wake group.

Subjective ratings were not differentially affected by performance level and therefore were combined for high and low performers (P > 0.27, for all interactions sleep/wake condition x high/low performers). Subjects in the night sleep group scored higher in sleepiness and lower

in activation, concentration and motivation during learning (possibly due to anticipation because subjects knew that they were allowed to sleep soon), whereas subjects of the night wake group scored higher in sleepiness and lower in activation, concentration and motivation at retrieval, reflecting their increased sleep pressure ($P < 0.05$; see Table 4 for detailed results). None of the subjective ratings, either during learning or at retrieval, correlated significantly with the number of false memories ($-0.21 < r < 0.03$, all $P > 0.12$).

Polysomnographic recordings in subjects of the night sleep group showed normal sleep patterns during the experimental night (total sleep time, 453.00 ± 7.25 min; wake, 2.06 ± 0.61%; S1, 3.50 ± 0.56%; S2, 55.56 ± 1.57%; SWS, 17.41 ± 1.33%; REM sleep, 20.13 ± 1.20%). This pattern did not differ between high and low memory performers ($P > 0.50$, for all sleep parameters).

Discussion

Our results show that sleep-associated consolidation can contribute to the formation of false memories in the DRM paradigm when subjects are tested with a free recall procedure rather than a recognition test. We also show that acute sleep deprivation increased freely recalled false memories, which agrees with previous data indicating a similar increase of false memories in a recognition test after sleep deprivation (Diekelmann et al., 2008). Of note, both effects were observed only in subjects with a low general level of memory performance.

The sleep-related effects cannot be explained simply by higher sleepiness and reduced motivation and concentration, either during learning (as observed in sleep subjects) or at retrieval (as observed in sleep deprived subjects). If so, they should have occurred similarly in both subjects with low and high memory performance, which was not the case. Moreover, none of the subjective ratings, either during learning or at retrieval, significantly correlated with the number of false memories. Differences in false memory generation are also unlikely due to circadian variation, as again such an influence should have affected low and high performers in the same manner instead of increasing false memories selectively in low performers. Of note, two recent studies found no differential effects of circadian variation on the generation of false memories (Murphy et al., 2007; Payne et al., 2009). In particular, Payne and colleagues, using a very similar procedure as in the present study, found that the amount of false recall was comparable between subjects tested in the morning or in the evening, respectively. It is further unlikely that the effects of sleep deprivation on false memories occurred due to possible stress-related cortisol elevations following sleep

deprivation. Although there is evidence that the stress-associated cortisol rise can enhance false memories (Payne et al., 2002; but see Smeets et al., 2006a; Smeets et al., 2008a), substantial increases in cortisol after acute sleep deprivation have not been found in a previous experiment using similar timing and deprivation procedures as in the present study (Diekelmann et al., 2008). We also did not find any significant correlation between endogenous cortisol levels and the number of false memories in that study (Diekelmann et al., 2008).

It has been proposed that sleep supports memory in a system consolidation process that leads to a reorganization of recently acquired memory representations along with the integration of the representations into pre-existing networks of long-term memories (Wagner et al., 2004; Ellenbogen et al., 2007). These processes that under normal circumstances help to efficiently integrate new information, might favor the formation of false memories in conditions such as the DRM paradigm, where the memories acquired are semantically highly related. Sleep, by reorganizing newly acquired memory representations, might facilitate the extraction of the gist of the newly encoded information and thus promote an abstraction and generalization of these representations, as reflected by the non-learned theme words of the DRM paradigm (Payne et al., 2009).

This effect observed here is well in line with recent findings by Payne and colleagues likewise showing greater amounts of false memories in the DRM paradigm after sleep compared to diurnal wakefulness, also using a free recall procedure (Payne et al., 2009). Interestingly, the effect did not occur in previous studies showing either no effect or even reduced false memories with a similar DRM procedure but employing a recognition test (Diekelmann et al., 2008; Fenn et al., 2009). One possible explanation for these divergent findings relates to the fact that retrieval operations fundamentally differ in free recall and recognition memory (Tulving & Madigan, 1970). The direct presentation of items in recognition procedures presumably reinstates the context of encoding and reactivates associated sensory details of studied list words (Cabeza et al., 2001). Such sensory information of contextual details is not available for non-studied theme words. Sleep might specifically strengthen sensory details of studied items which benefits the ability to discriminate between studied and non-studied words and thereby might prevent false *recognition* of theme words (Curran et al., 1997). Free recall, on the other hand, is characterized by the virtual absence of external memory cues at retrieval. During free recall, subjects generate their own cues to reinstate the original items. This process of "self-cueing" is thought to reflect to a greater extent the accessibility of a memory, presumably benefiting

more from a broader integration of new memories into pre-existing knowledge networks and the extraction of generalized features during sleep (Tulving & Madigan, 1970), which might promote higher rates of false *recall* after sleep. Both effects might be reconciled by considering that sleep, in a process of system consolidation, integrates the encoded stimuli in pre-existing knowledge networks by reactivating and reorganizing the underlying memory representations, thereby strengthening specific details of the single studied items and simultaneously extracting the common gist of the highly associated items. Free recall and recognition procedures, by relying on different retrieval operations, appear to target specifically at these concomitant effects of sleep-dependent system consolidation.

"Self-cueing" in free recall also leaves space for a great variety of individual strategies. This may be one reason why the effects here were confined to low performing subjects: High performers, in contrast to low performers, may have adopted specific mnemonic strategies that not only improved general memory performance, but also prevented the effects of sleep and sleep deprivation on false memory generation. It can be speculated that high performers encoded the list words very literally, thus preventing the generalized processing that in other participants leads to the creation of a schema representation and consequently to false recall of the associated theme words. However, since we did not directly assess or manipulate the mnemonic strategies adopted by our subjects here, the possible influence of such strategies needs to be investigated more systematically in future studies.

Our finding that sleep effects were confined to subjects with generally low memory performance fits well with previous studies indicating that the benefit of sleep on memory consolidation is greater for weak than strong memory traces (Kuriyama et al., 2004; Drosopoulos et al., 2007). The inferior recall in the low performing subjects in fact reflects that memory traces in these subjects were generally weaker, thus gaining preferential access to sleep-dependent consolidation (Diekelmann et al., 2009). Contrasting with this view, a recent study reported greater sleep-dependent benefits for high than low performing subjects (Tucker & Fishbein, 2008). However, a closer look suggests that the absolute performance level in the high performing subjects of that study were more comparable to the low than the high performers of the present study. Similarly, general memory performance of subjects in the study by Payne and colleagues (Payne et al., 2009) closely matches the performance level of the low performers in the present study. Since these authors used a very similar experimental design and likewise observed greater numbers of false memories when subjects slept during consolidation, it is tempting to speculate that in the present study low rather than high performers represent the "normal" level of memory performance. More generally, these

findings together suggest an inverted u-shape relationship between performance level and consolidation-related sleep effects, with maximal effects in the middle range of memory performance.

Sleep deprivation at retrieval also enhanced false memories produced in free recall, which is consistent with Study 1 using recognition testing (Diekelmann et al., 2008). Apparently, the effect of acute sleep deprivation on retrieval of false memories is more robust and less sensitive to changes in the testing procedure than the effect of sleep during consolidation. Nevertheless, this effect was again confined to low performing subjects, in line with our interpretation that high-performing subjects may have used deliberate strategies to prevent false memories. Although sleep deprivation at retrieval exerted the same enhancing effect on false memories as post-learning sleep during consolidation, the underlying mechanisms, of course, differ fundamentally. Whereas sleep-dependent consolidation enhances false memories through an active process of reorganization of memory traces, an acute state of sleep deprivation is thought to enhance retrieval of false memories due to acutely impaired cognitive control processes that transiently disturb the access to stored memories (Harrison & Horne, 2000b; Durmer & Dinges, 2005). Sleep deprivation strongly affects cognitive processes that essentially rely on the integrity of the PFC. Especially effort-related aspects of retrieval involving retrieval monitoring and judgments about recollection and familiarity (Henson et al., 1999; Dobbins et al., 2002), which serve to minimize retrieval of false memories (Curran et al., 2001; Schacter et al., 2001; McDonough & Gallo, 2008), critically depend on the PFC and are particularly sensitive to sleep deprivation (Horne, 1993). Thus, sleep deprivation may lead the subject to adopt a more schema-driven retrieval strategy, accepting also words as learned that are semantically highly associated with actually learned words.

Although false memories are highly undesirable in several instances (e.g., in eyewitness testimony; Loftus, 2003), it may be sufficiently adaptive in everyday life settings to create a schema representation of the learned information during sleep, or to retrieve memories on the basis of a schema following sleep deprivation when cognitive resources are reduced. False memories might thus reflect the cost of an otherwise adaptive memory system that is able to extract general knowledge from single encountered events (Schacter, 1999).

Study 3 – The effect of elevated cortisol at retrieval on false memory formation

Published as: Diekelmann, S., Wilhelm, I., Wagner, U. & Born, J. (2011). Elevated cortisol at retrieval suppresses false memories in parallel with correct memories. *Journal of Cognitive Neuroscience*, *23(4)*, 772-781.

Introduction

One of the most intriguing features of human memory is the ability to extract the general meaning or the gist of single encountered events in an adaptive process (Bartlett, 1932; Loftus et al., 1995; Schacter et al., 1998). People after learning single exemplars of one category subsequently vividly remembered having encountered the prototype of that category which actually was never presented during learning, i.e., they generated a false memory (Posner & Keele, 1968; Bransford & Franks, 1971; Roediger, III & McDermott, 1995). Generally, the term "false memory" refers to instances in which people claim to remember events that in fact never happened. As described above, a classical approach to the study of false memory generation is the Deese-Roediger-McDermott (DRM) paradigm, in which subjects learn lists of highly associated words like “white”, “night”, “cat” and “dark” etc., while the common theme or gist word of the list, in this example “black”, is not presented during learning (Deese, 1959; Roediger, III & McDermott, 1995). On a later retrieval test subjects frequently and with high confidence falsely remember having encountered the gist word (McDermott, 1996; Payne et al., 1996; Toglia et al., 1999; Thapar & McDermott, 2001; Seamon et al., 2002; Roediger, III et al., 2004). Such “false” memories are highly undesirable in situations where it is essential to rely on veridical memory, e.g., in eyewitness testimony (Loftus, 2003); but it can also be useful to remember the gist or general concept of what had been experienced instead of specific details. It has been proposed that false memories might be unwanted by-products of the human memory system that acts to adaptively change memory representations and extract general knowledge, i.e., the gist from single learned exemplars (Schacter, 1999). Along this line, so-called gist-based (or schema-based) views of false memory generation assume that all the single learned exemplars share common features with the gist whereby the gist, through the overlapping features of the encoded exemplars becomes simultaneously

activated and stored in parallel with the actually encoded exemplars, with both types of memories sharing common mechanism (Posner & Keele, 1968; Bransford & Franks, 1971; McClelland et al., 1995; Reyna & Brainerd, 1998; Brainerd & Reyna, 2001). However, evidence for a common neurophysiological mechanism producing both false and veridical memories is scarce.

In fact an influential alternative view on false memory generation (i.e., the so-called monitoring theories) holds that the memory for the gist word is generated already in the phase of encoding which consequently produces a sense of familiarity when the gist word is presented at retrieval testing (Gallo & Roediger, III, 2002; Marsh & Bower, 2004). In this view, false memories result from a failure in retrieval monitoring, when the subject mistakenly attributes this sense of familiarity for having encountered the gist word at learning (Johnson et al., 1993; Mitchell & Johnson, 2009). Here, to examine the different views on false memory generation, we used a pharmacological approach, i.e., we administered cortisol which is well-known to reliably impair the retrieval of correct memories (de Quervain et al., 2000; Wolf et al., 2001; de Quervain et al., 2003; Kuhlmann et al., 2005). If false memories are due to an impaired retrieval monitoring, a cortisol-induced impairment of retrieval should enhance false memory generation whereas reduced rates of false memory generation are expected under cortisol if, as assumed by gist-based theories, false memories are formed as a by-product of correct memories basically relying on similar neurophysiological mechanisms.

There have been several attempts to characterize the effects of cortisol on false memory generation based on the investigation of stress-induced release of glucocorticoids. Payne et al. (2002) as well as Smeets et al. (2006a) introduced psychosocial stress, i.e., the Trier Social Stress Test (Kirschbaum et al., 1993), before encoding of DRM word lists and retrieval was tested immediately thereafter. Whereas the occurrence of false memories was significantly increased in the Payne et al. (2002) study, Smeets et al. (2006a) found no change in false memory rate following stress. Yet, both studies applied stress already before encoding, which prevents a clear-cut dissociation of effects of cortisol on retrieval from those on encoding. Unlike retrieval, encoding can be even enhanced by cortisol (Buchanan & Lovallo, 2001; Abercrombie et al., 2003; Rimmele et al., 2003). In a recent study, Smeets et al. (2008a) introduced a physiological stressor, i.e., cold pressor stress, either before encoding, immediately after encoding (i.e., before consolidation), or before retrieval testing of DRM word lists and found no significant effects in neither condition but even slightly decreased false memory rates. Yet, the pharmacological interpretation of these findings is still difficult because stress, beyond stimulating cortisol release, concurrently affects numerous

other processes that are implicated in memory functions like sympatho-adrenal responses, mood and different cognitive functions and thus possibly confound the effects of cortisol (de Kloet et al., 2005; Lupien et al., 2007; Ulrich-Lai & Herman, 2009).

In the present study, we were interested in dissociating the effect of cortisol on the generation of false memories compared to correct memories at retrieval to determine whether false memories compared with correct memories would be affected by cortisol in the same or opposite way. We directly administered cortisol (vs. placebo) to exclude possible concurrent effects of stress on false memory formation. Substance administration took place shortly before testing retrieval and more than seven hours after encoding to exclude effects of cortisol on encoding or consolidation.

Methods

Participants

12 healthy male subjects [age 22.67 ± 2.90 (mean ± SD), range 18–29 years] were recruited at the University of Lübeck to participate in the study. All subjects were non-smokers, free of any medication and had no history of neurological, psychiatric or endocrine disorders. They were not allowed to ingest any caffeine or alcohol on the days of the experiments. All subjects gave written informed consent and were paid for participation in the study, which was approved by the local ethics committee of the University of Lübeck.

Design and procedure

All subjects participated in two treatment conditions (cortisol and placebo) according to a double-blind cross-over design, with the order of conditions balanced across subjects (Figure 8a). The two treatment conditions for each participant were separated by at least two weeks. Each condition started at 10:30 h with the subject learning the false memory task. Following learning, subjects left the laboratory to engage in their everyday activities and returned at 15:00 h. Two venous catheters were then placed into the subject's forearms for substance administration and blood sampling. Intravenous infusion of cortisol or placebo started at 18:00 h, i.e., ~ 7 hours after learning of the false memory task. A total of 13 mg cortisol (Hydrocortisone 100-Rotexmedica, Rotexmedica, Germany; dissolved in 100 ml saline solution), or placebo (100 ml saline solution), were infused over 2 h at a rate of 100 ml/h during the first 30 min and 35 ml/h during the remaining time. Between 18:00 – 19:30 h

subjects were engaged in standardized activities (playing simple games). False memory retrieval testing took place between 19:30 and 20:00 h, i.e., 1.5 h after the start of substance administration. Subjects were instructed not to take any naps during the retention interval to exclude possible effects of sleep on the generation of false memories (Payne et al., 2009; Diekelmann et al., 2010). Adherence to this instruction was ensured by a post-experimental questionnaire and constant supervision by the experimenter between 15:00 and 20:00 h.

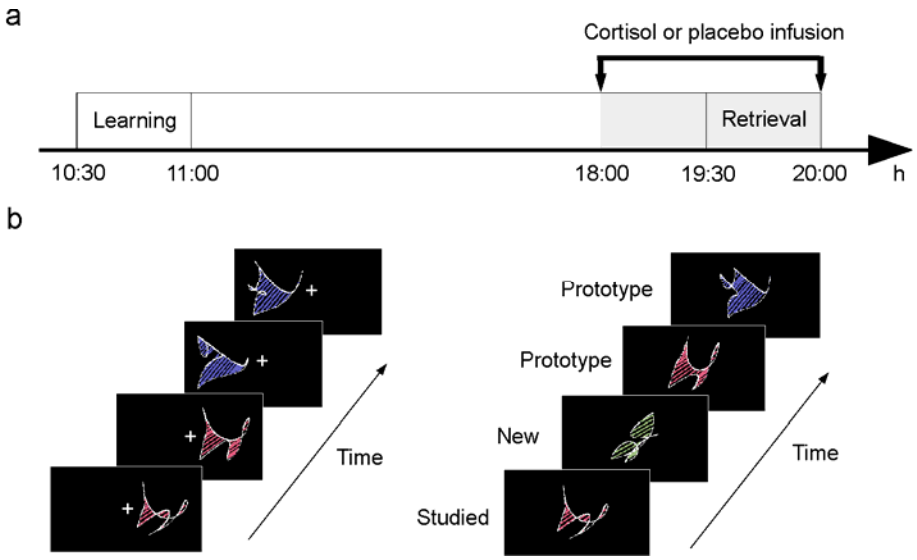

Figure 8. Experimental design and false memory task. a) Subjects participated in two treatment conditions according to a double-blind cross-over design. In each condition, learning took place in the morning and intravenous infusion of cortisol or placebo started in the evening ~1.5 hrs before retrieval testing (arrow-marked field indicates period of substance infusion). b) During learning (left panel), subjects studied 16 sets of colored shapes presented either on the left or right side of the screen. Each set consisted of 10 shapes (2 shown here) derived from one prototype that was not presented during learning. At retrieval testing (right panel), subjects were presented with studied shapes, new shapes and prototypes, and had to indicate for each shape whether or not it had been presented during learning.

Materials

To induce false memories we used a non-verbal version of the Deese-Roediger-McDermott paradigm (Deese, 1959; Roediger, III & McDermott, 1995) which was developed by Slotnick and Schacter (for a detailed description of the materials see Slotnick & Schacter, 2004). We applied the non-verbal version instead of the standard verbal DRM paradigm to prevent subjects from using deliberate mnemonic strategies to memorize the learning material because such strategies could not only affect correct memory retrieval but also the generation of false memories (Libby & Neisser, 2001; McCabe & Smith, 2006). The materials comprised two

parallel versions that were counterbalanced across subjects and treatment conditions. During learning, subjects studied 16 sets of abstract shapes, each set consisting of 10 shapes filled with a specific color and line orientation (Figure 8b). The 10 shapes of each set were derived from a prototype that was not presented during learning. Shapes were presented consecutively on a black background for 2.5 sec each with an inter-trial interval of 3 sec, with shapes of the same set presented in succession. Sets of shapes alternated in presentation between the left and right side of the screen and subjects were instructed to memorize the shapes and their spatial location.

At retrieval testing, subjects were presented with three types of shapes: studied shapes (32; 2 from each set), new shapes (32; from non-studied sets) and prototypes (16; 1 from each studied set). Each shape was presented at the center of the screen and subjects had to indicate whether or not it had been presented during learning and whether it was located on the left or right side of the screen during learning ("old left", "old right", or "new"). For each response subjects additionally rated their confidence on a 4-point scale ranging from 1 ("I had to guess") to 4 ("absolutely sure") and gave a remember/know/guess judgment for the items identified as "old" (Gardiner et al., 2002). Subjects were instructed to indicate that they "remembered" a shape if they "explicitly recalled the presentation of the shape and had some recollection of the specific context, e.g., what they thought in that moment". In contrast, they should state that they "know" the shape if they "were sure that the shape had been presented at learning but could not recollect specific details of the situation". "Guess" should be indicated if they "were not entirely sure but had the feeling that the shape was presented before". There was no time limitation for all responses.

Blood sampling and biochemical analyses

Blood was sampled every 30 to 45 min between 16:30 h and 21:00 h (Figure 10). Hormone concentrations were determined in serum samples that were stored at -80 °C until assay. Serum cortisol concentrations were assessed via Immulite [DPC Biermann, Bad Nauheim, Germany, intra- and interassay coefficients of variation (CV) < 10 %]. Additionally, adrenocorticotropic hormone (ACTH) was assessed in plasma via Lumitest [Brahms Diagnostica, Hennigsdorf, Germany, interassay CV 2.8 %, intra-assay CV 1.6 %]. ACTH (released from the pituitary) is the major secretagogue of adrenal cortisol and becomes suppressed as a consequence of the inhibitory feedback influence cortisol exerts on the hypothalamo-pituitary-adrenal system.

Statistical analysis

Memory results were analyzed using the signal detection measure d' as a bias-corrected measure of recognition performance in order to take into account inter-individual differences in the baseline propensity to accept items (Snodgrass & Corwin, 1988). The calculation of d' was based on three recognition memory measures: hit rate = old responses to studied shapes, false alarm rate = old responses to new shapes, false memory rate = old responses to prototypes. We calculated d' separately for correct memories [z(hit rate) – z(false alarm rate)] and false memories [z(false memory rate) – z(false alarm rate)]. In this procedure, false memory rate is treated as "hit rate" in order to provide a false memory measure corrected for response bias (Seamon et al., 2002). Additionally, to exclude that cortisol administration affected response bias per se, we calculated the bias index C, again separately for correct memories [-0.5*(z(hit rate) + z(false alarm rate))] and false memories [-0.5*(z(false memory rate) + z(false alarm rate))].

Statistical analyses were performed using analyses of variance (ANOVA) for repeated measures with the factors "cortisol/placebo" and "false/correct memories" for the memory measures. As the ability to remember whether shapes were presented at the left or right side of the screen (i.e., spatial source memory) did not significantly differ between the cortisol and placebo condition for false memories (63.48 ± 5.88 vs. 68.54 ± 5.18 %, $P > 0.40$) or correct memories (64.55 ± 4.58 vs. 73.05 ± 1.99 %, $P = 0.10$; chance level = 50 %), "old left" and "old right" responses were collapsed for the present analyses. ANOVA performed on cortisol and ACTH concentrations included a "time" factor in addition to the "cortisol/placebo" factor. Post-hoc t-tests were used to specify significant main effects and interactions. The Greenhouse-Geisser correction of degrees of freedom was applied where appropriate. The level of significance was set to $P = 0.05$. For analyses of confidence ratings and remember/know/guess judgments multiple t-Tests were applied with the level of significance adjusted according to the Bonferroni correction.

Results

False memories and correct memories

Cortisol infusion before retrieval testing profoundly reduced the susceptibility to false memories. The probability of falsely recognizing non-studied prototypes was 0.87 ± 0.10 in the placebo condition and 0.49 ± 0.13 following cortisol treatment [$t(11) = -2.81$, $P = 0.017$;

Figure 9a]. Thus, false memories were reduced by 44 % when cortisol was enhanced during retrieval testing compared to placebo. As expected from previous reports, retrieval of correct memories (of studied items) was also reduced when cortisol was infused before retrieval testing. The correct recognition score was 0.72 ± 0.08 in the placebo condition and 0.40 ± 0.14 after cortisol administration [$t(11) = -2.44$, $P = 0.033$; Figure 9a], resulting in a similar 44 % reduction. Indeed there was no evidence for a differential influence of cortisol on false and correct memories ($P > 0.60$, for the interaction cortisol/placebo x false/correct memories, $P = 0.009$, for the main effect cortisol/placebo across both types of memory). The response bias C was not affected by cortisol administration and was comparable for false memories and correct memories (all $P > 0.15$; Figure 9a). Above all, the occurrence of false memories was positively correlated with correct memory retrieval when averaged across the treatment conditions ($r = 0.66$, $P = 0.02$) as well as in both conditions separately (cortisol: $r = 0.54$, $P = 0.07$; placebo: $r = 0.64$, $P = 0.026$; Figure 9b).

Raw measures of recognition not accounting for response biases, i.e., false memory rate, hit rate and false alarm rate, are displayed in Table 5. Only false memory rate tended to be reduced with enhanced cortisol levels ($P = 0.065$) suggesting that the parallel reduction of false and correct memories after cortisol in the bias-corrected measure d' partly relied on an increased false alarm rate, in addition to the decreases in false memory rate and hit rate which per se did not reach significance (hit rate: $P = 0.15$, false alarm rate: $P = 0.37$).

Table 5. Recognition memory performance

	Cortisol	Placebo	P
Proportion (p)			
False memory rate	0.69 ± 0.06	0.77 ± 0.05	**0.065**
Hit rate	0.65 ± 0.06	0.72 ± 0.03	0.153
False alarm rate	0.51 ± 0.04	0.47 ± 0.04	0.368
Recognition index (d')			
False memories	0.49 ± 0.13	0.87 ± 0.10	**0.017***
Correct memories	0.40 ± 0.14	0.72 ± 0.08	**0.033***
Response bias index (C)			
False memories	0.27 ± 0.13	0.35 ± 0.11	0.421
Correct memories	0.23 ± 0.14	0.27 ± 0.10	0.713

Recognition is indicated by the mean proportion (p) of old responses to prototypes (= false memory rate), studied shapes (= hit rate), and new shapes (= false alarm rate) as well as the recognition index d' for false memories (false memory rate with reference to false alarm rate) and correct memories (hit rate with reference to false alarm rate). The response bias index C is indicated separately for false memories and correct memories. P values are given for the comparison between the effects of cortisol and placebo. Means ± SEM are shown. * $P < 0.05$

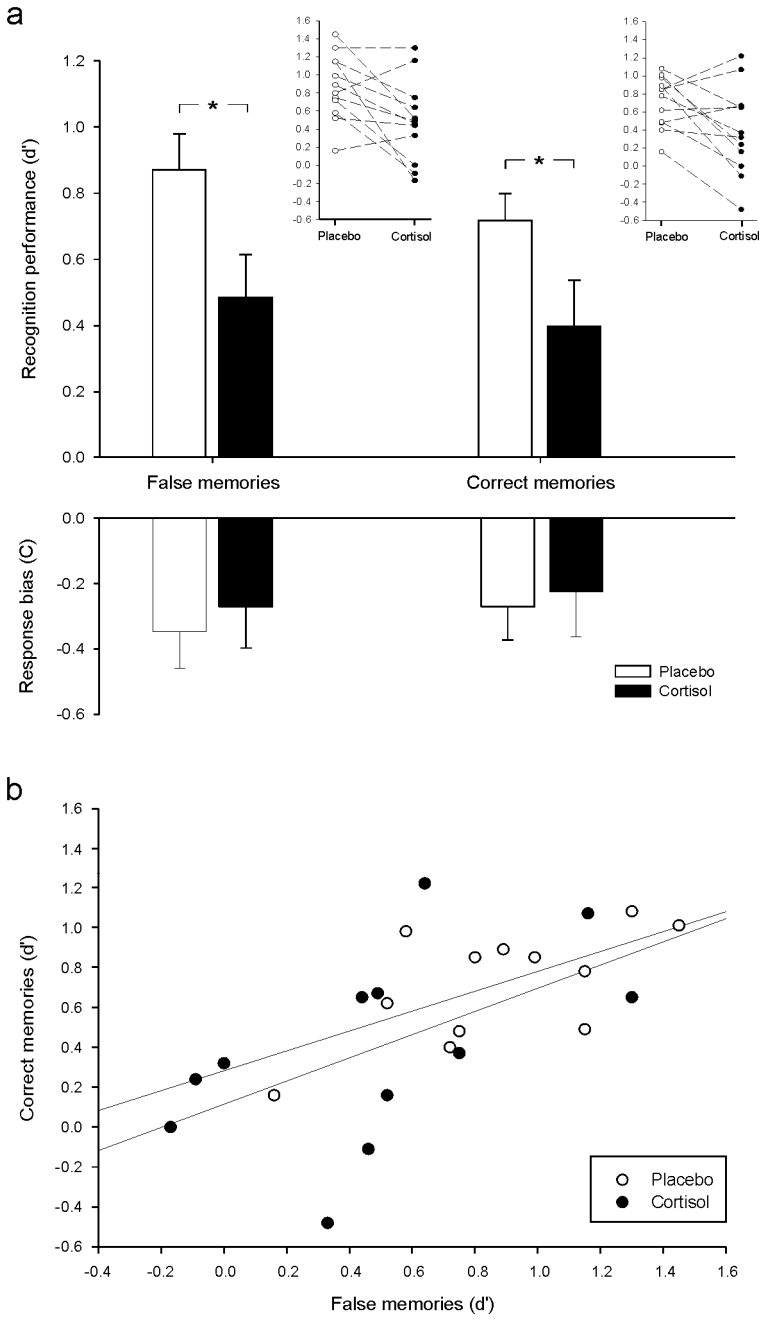

Figure 9. Recognition performance. a) Enhanced cortisol levels at retrieval reduced the occurrence of false memories (old responses to prototypes) and impaired correct memory retrieval (old responses to studied shapes; means ± SEM are shown). Individual recognition data for each subject in the placebo and cortisol conditions are depicted for false memories (upper left panel) and correct memories (upper right panel), respectively. Cortisol enhancement did not affect the overall response bias. b) The occurrence of false memories was correlated with correct memory retrieval following cortisol infusion (filled dots) as well as under placebo conditions [empty dots; r = 0.54 in the cortisol condition (lower regression line) and 0.64 in the placebo condition (upper regression line)]. * $P < 0.05$

Confidence ratings as well as remember, know and guess judgments did not differ between the cortisol and placebo condition (Table 6). Independent of cortisol enhancement, subjects were more confident on hits and false memories than on false alarms, and guess judgments were more frequent for false alarms than for hits and false memories (all $P \leq 0.001$).

Table 6. Confidence ratings and remember/know/guess judgments

	Cortisol	Placebo	P
Confidence			
False memories	2.67 ± 0.12	2.78 ± 0.09	0.216
Hits	2.71 ± 0.08	2.63 ± 0.08	0.161
False alarms	2.39 ± 0.07	2.32 ± 0.06	0.538
Remember			
False memories	0.24 ± 0.07	0.23 ± 0.06	0.915
Hits	0.22 ± 0.06	0.18 ± 0.05	0.223
False alarms	0.17 ± 0.05	0.19 ± 0.07	0.688
Know			
False memories	0.43 ± 0.03	0.53 ± 0.06	0.110
Hits	0.43 ± 0.04	0.42 ± 0.05	0.877
False alarms	0.39 ± 0.05	0.27 ± 0.05	0.045
Guess			
False memories	0.33 ± 0.06	0.23 ± 0.07	0.119
Hits	0.35 ± 0.07	0.39 ± 0.07	0.448
False alarms	0.44 ± 0.06	0.54 ± 0.08	0.154

Mean confidence ratings (ranging from 1 = “guess” to 4 = “sure”) and proportions of remember, know and guess judgments are displayed for items judged as “old”. P values are given for the comparison between the effects of cortisol vs. placebo. Means ± SEM are shown.

Cortisol and ACTH concentrations

Cortisol levels were distinctly enhanced following cortisol infusion ($P < 0.001$; for cortisol/placebo main effect and interaction with time). During false memory retrieval testing (i.e., 19:30 – 20:00 h) cortisol concentrations were 3- to 4-fold higher compared to the placebo condition ($P < 0.001$; Figure 10). Additionally, and consistent with the well-known inhibitory feedback cortisol exerts on the hypothalamo-pituitary-adrenal system, cortisol infusion significantly decreased ACTH concentrations (main effect cortisol/placebo, $P < 0.001$; cortisol/placebo x time interaction, $P = 0.004$; at retrieval testing, $P < 0.002$; Figure 10). While this decrease confirms effective (feedback) inhibition of ACTH by cortisol, it can be excluded as a mediator of the observed effects on memory retrieval, as ACTH per se has no strong effects on memory functions (Born et al., 1986).

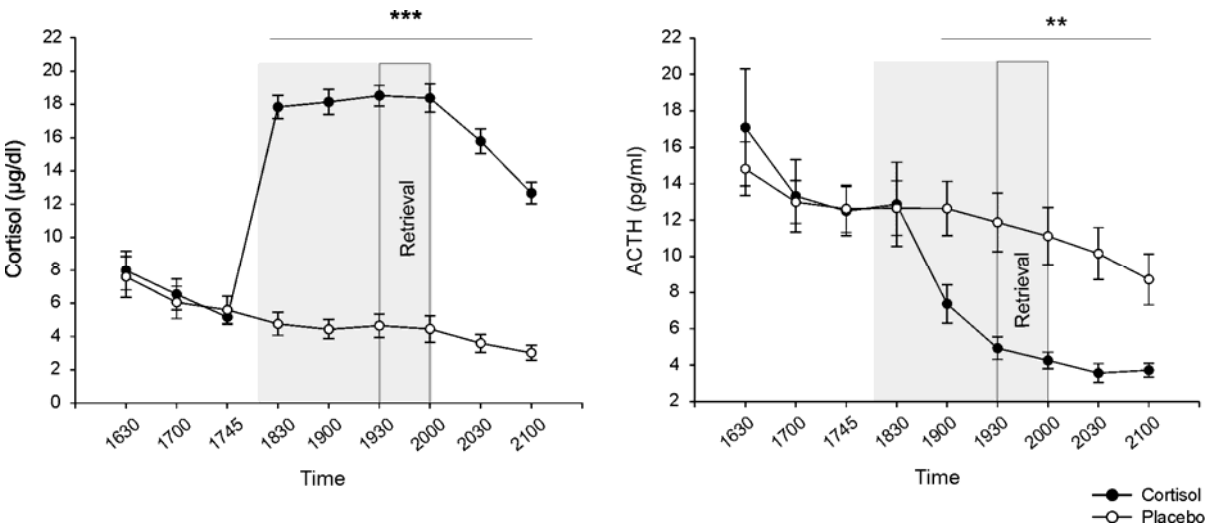

Figure 10. Cortisol and ACTH concentrations. During retrieval testing, subjects displayed distinctly enhanced cortisol levels and reduced ACTH concentrations following cortisol infusion compared to placebo (gray fields indicate period of substance infusion). ** $P < 0.01$, *** $P < 0.001$

Discussion

Our results demonstrate that elevated cortisol levels at retrieval distinctly reduce the generation of false memories. In parallel, cortisol impaired retrieval of correct memories. This latter result confirms findings from several previous studies in humans and animals of a glucocorticoid induced impairment of retrieval function (de Quervain et al., 2000; Wolf et al., 2001; McGaugh & Roozendaal, 2002; de Quervain et al., 2003; Het et al., 2005; Lupien et al., 2005; Kuhlmann et al., 2005). Both effects occurred in the absence of changes in general response bias. Also confidence ratings and remember/know/guess judgments were not affected by cortisol. The present study is the first to directly and selectively manipulate cortisol concentrations at retrieval in relation to false memory formation. As cortisol was administered shortly before retrieval and more than seven hours after initial learning the observed effect is specifically on retrieval whereas effects on encoding and consolidation can be excluded.

Whereas the effects of cortisol on false memory generation have not been investigated so far, several foregoing studies investigated the influence of stress on false memories which amongst others is characterized by profound release of endogenous cortisol. Yet, those studies reported mixed results, with either no changes or enhanced rates of false memories following psychosocial stress (Payne et al., 2002; Smeets et al., 2006a). As these studies introduced stress before encoding, effects of stress on retrieval could not be dissociated from those on

encoding or consolidation. A recent study separately testing the effects of cold pressor stress on these memory processes found, in line with the present results, slightly decreased false memory rates if stress accompanied retrieval (Smeets et al., 2008a). Nevertheless, the patterns observed in these studies of stress, in principle, remain difficult to interpret in relation to cortisol because stress substantially affects numerous endocrine and cognitive parameters other than cortisol (de Kloet et al., 2005; Lupien et al., 2007; Ulrich-Lai & Herman, 2009).

Our finding of reduced false memory rates in parallel with impaired correct memory retrieval has implications for the current theorizing on the formation of false memories. Of the two main theoretical frameworks currently discussed, the retrieval monitoring theories assume that subjects during learning consciously or unconsciously generate the prototype of the single exemplars which are all highly associated with the prototype. This internal generation of the prototype produces a sense of familiarity at subsequent retrieval testing. The cause for the occurrence of a false memory is assumed to be a failure of retrieval monitoring, i.e., the subject mistakes this sense of familiarity for having actually encountered the prototype during encoding (Johnson et al., 1993; Mitchell & Johnson, 2009). Effective retrieval monitoring, i.e., the ability to discriminate between familiarity due to external presentation or internal generation, has been shown to be essential for avoiding false memories (Curran et al., 2001). Retrieval monitoring critically relies on the prefrontal cortex (Dobbins et al., 2004; Turner et al., 2008; Mitchell & Johnson, 2009) and false memory generation is likewise associated with increased prefrontal cortex activity (Schacter, 1996; Schacter & Slotnick, 2004; Kubota et al., 2006). Retrieval monitoring can be also improved by acute psychosocial stress (Smeets et al., 2006b; Smeets et al., 2008b). Because the prefrontal cortex, in addition to other brain areas, is a significant target of glucocorticoids (Sanchez et al., 2000; Lupien & Lepage, 2001; Radley et al., 2004; Wang et al., 2005), it could be speculated that cortisol acts on the prefrontal cortex to improve retrieval monitoring, thus reducing the occurrence of false memories. However, this view of an improved retrieval monitoring would not integrate the opposite, i.e. impairing, effect of cortisol on retrieval of correct memories.

Gist or schema-based theories, on the other hand, propose that subjects remember the gist (i.e., the concept or schema) of single events rather than the specific details of the individually learned exemplars (Posner & Keele, 1968; Reyna & Brainerd, 1998). Each of the single exemplars reveals a specific pattern of activation in the associative network during encoding (Posner & Keele, 1968; Bransford & Franks, 1971; McClelland et al., 1995; Gallo & Roediger, III, 2002). Since all of the exemplars are derived from one prototype, they share

common features resulting in the activation of overlapping representations which, most importantly, also overlap with regard to networks that represent the prototype. During encoding the networks representing the prototype thus become automatically activated due to spreading activation from the individual exemplars and, paradoxically, even receives the greatest activation (because it has the most features in common with all single exemplars), although it was never encountered by the subject as individual pattern. The more the subject relies on the gist or schema of what he/she experienced during learning the more he/she falsely remembers the prototype of the learned exemplars (Brainerd & Reyna, 2001; Gallo & Roediger, III, 2002). It is assumed that in the course of memory formation the two features of an episode, i.e., the actually encountered exemplars and the common schema or gist of these exemplars, both become stored as distinct representations, i.e., whenever subjects encounter an event, specific details of the individual exemplars are stored as single entities in the associative memory network but, simultaneously, common features of these exemplars, i.e., the prototype, become stored as the gist representation. Thus, correct memories of the exemplars and false memories of the prototype refer to discrete entities represented in separate memory traces, though sharing some overlapping features. Although little is known about the neuronal correlates of gist representations, there is some evidence that both representations of the gist and of the specific events depend on hippocampal and medial temporal lobe regions (Schacter et al., 1996b; Garoff-Eaton et al., 2006). These brain regions express a high density of glucocorticoid receptors and are well-known to be particularly sensitive to the effects of cortisol (de Kloet et al., 1998; Lupien & Lepage, 2001; Joels, 2001; Lupien et al., 2007). Assuming that false and correct memories are stored in the same networks but as separate representations, retrieval of false memories would be expected to be reduced by high cortisol levels to the same extent as retrieval of correct memories. Our present findings indeed indicate that both retrieval of correct and false memory was markedly decreased by elevated cortisol, with the magnitude of the decrease being comparable for both types of memory. Finally, we found the reduction of false memories to be strongly correlated with the impairment of correct memory retrieval, a finding in line with the gist-based view on false memories, suggesting that effects of cortisol on both false and correct memories rely on the same mechanism basically impairing retrieval operations.

Thus, our results essentially support gist-based theories of false memory formation rather than retrieval monitoring theories. To be noted, we applied a non-verbal version of the DRM paradigm using abstract shapes instead of word lists which have been more commonly employed in previous studies. It has been argued that the use of abstract shapes prevents

subjects from internally generating the gist representation at encoding which might also prevent subsequent retrieval monitoring (Koutstaal & Schacter, 1997). Although this possibility cannot be completely ruled out without further testing, in our view it is not likely that the occurrence of retrieval monitoring essentially depends on the stimulus material because the basic process promoting the encoding of a gist representation is the activation of overlapping representations of the single exemplars during the learning phase. This activation of overlapping representations, resulting in an internal "generation" of the gist representation, presumably occurs similarly with abstract shapes and words (although only in the case of words it may occasionally occur that activation of a specific gist representation enters consciousness). Importantly, in this view gist representations of both words and abstract shapes similarly produce a sense of familiarity at subsequent retrieval testing provoking failures in retrieval monitoring. Hence, if false memories were due to erroneous retrieval monitoring, this indeed should have been detected in the present study using abstract shapes. Rather than pointing towards an impaired retrieval monitoring as cause of false memories, our data speak for the notion that such false memories are generated as part of the process leading to the formation of correct memories, with common underlying neurophysiological (i.e., cortisol-dependent) mechanisms. It will be an intriguing issue of future studies to further specify the particular brain circuitry by which cortisol impacts retrieval of false and correct memories. Since it is well-known that glucocorticoid receptors are expressed throughout both the prefrontal cortex and hippocampus, one outstanding question centers around understanding the relative contributions of these two structures to correct memory retrieval and false memory suppression within the context of elevated cortisol.

In sum, our finding of a parallel modulation of false memories and correct memories by elevated cortisol suggests that both types of memory share common general mechanisms, with false memories possibly being the cost of an otherwise adaptive memory system that is able to extract general knowledge from single encountered events (Schacter, 1999). This view is eventually supported also by studies in amnesic patients who do not only display impaired memory for true events but likewise exhibit in parallel a distinctly reduced production of false memories in comparison with healthy controls (Schacter et al., 1997c; Koutstaal et al., 2001), possibly due to a diminished capability of these patients to extract a gist representation from the learned exemplars (Verfaellie et al., 2002). Thus, false memories appear to be tightly linked to the formation of correct memories with both types of memory relying on basically similar neurophysiological mechanisms.

Conclusions and general discussion

The purpose of the three studies reported in the present thesis was to discover the role of sleep and sleep deprivation, as well as that of the neuromodulators adenosine and cortisol for the generation of false memories. The mechanisms underlying the generation of false memories are presently obscure although it is particularly important to understand such mechanisms for two reasons. First, memory distortions and false memories can be extremely harmful in situations where it is essential to rely on veridical memories, e.g., in eyewitness testimony or falsely "recovered" memories of childhood abuse (Loftus, 2003). Second, as false memories are presumably created as a by-product in the normal process of memory formation, understanding the mechanisms of false memory formation will considerably advance our knowledge on processes of memory formation in general (Schacter, 1999). Together, Studies 1, 2, and 3 revealed that *(i)* false memories can be generated during sleep in a process of system consolidation, which is *(ii)* only observed when free recall procedures are applied at memory testing and in subjects with relatively low general memory performance. False memories are *(iii)* enhanced by acute sleep deprivation at retrieval testing through an impairment of strategic retrieval monitoring processes, an effect that *(iv)* can be reversed by the application of the adenosine antagonist caffeine before retrieval testing. False memories are *(v)* reduced in parallel with correct memories by elevated cortisol levels at retrieval testing, suggesting that false memories rely on the same basic mechanisms as correct memory formation.

These results provide novel evidence that the generation of false memories is tightly linked to the general processes of memory formation. The same physiological mechanisms that promote the highly adaptive and dynamic nature of memory can lead to memory distortions and false memories. Sleep is particularly well-known to benefit the consolidation of memories for long-term storage in an active process of reorganization and integration (Peigneux et al., 2001; Smith, 2001; Maquet, 2001; Stickgold, 2005; Diekelmann & Born, 2010). These active consolidation processes have been shown to enhance the long-term retention of memories and can even promote the generation of new explicit knowledge (Wagner et al., 2004; Fischer et al., 2006; Ellenbogen et al., 2007). False memories in the DRM paradigm can be likewise considered a kind of explicit knowledge, i.e., gist knowledge (Reyna & Brainerd, 1998; Brainerd & Reyna, 2001). In the DRM paradigm, subjects learn lists of highly associated words and subsequently "falsely" remember the gist word or schema

of the single lists that were never presented during learning. Such false memories can be interpreted in two different ways. On the one hand, remembering the gist word (e.g., black) after learning specific singular words (e.g., white, night, cat, dark) can be considered a "false" memory because the word "black" actually never occurred in the learning situation. Such false memories are highly undesirable if it is essential to accurately remember the specific details of a situation and not to rely on a general schema or gist of an encountered event. On the other hand, it is often rather useful and adaptive, with regard to limited cognitive resources, to just remember the gist of what was learned instead of all the single highly similar exemplars. It has even been suggested that it is a specific advantageous feature of human memory to extract general knowledge from single learned exemplars (Posner & Keele, 1968; McClelland et al., 1995; Schacter, 1999). Study 1 and Study 2 together show that sleep-dependent processes of active consolidation indeed increase the formation of false "gist" memories in the DRM paradigm (see also Payne et al., 2009; Darsaud et al., 2010).

During sleep such false memories presumably become extracted from the single highly associated words learned from each list during the study phase. Newly encoded memory representations are repeatedly reactivated during subsequent sleep, specifically during SWS (Wilson & McNaughton, 1994; Peigneux et al., 2004; Rasch et al., 2007; Ji & Wilson, 2007). In a process of system consolidation, this covert reactivation of fresh memory traces leads to the gradual redistribution of memories from the temporary hippocampal store to neocortical sites for long-term storage (Marr, 1971; Buzsaki, 1998; Diekelmann & Born, 2010). The hippocampus thereby acts as an internal trainer of the neocortex to strengthen cortico-cortical connections such that these memories become increasingly independent from the hippocampus (Rasch & Born, 2007). New memories are not only strengthened in this process but are reactivated in conjunction with older memories in the pre-existing neocortical knowledge network. This conjoint reactivation of new and associated older memory representations provides the integration of fresh memories in the pre-existing memory network and the adaptive reorganization of both new and older memories. This adaptive reorganization process might lead to the extraction of false memories, i.e., the gist knowledge, from the single encoded memory representations. According to gist-based views of false memory generation, all the single learned exemplars share common features with the gist whereby the gist, through the overlapping features of the encoded exemplars, becomes simultaneously activated. The gist thereby paradoxically receives even the greatest activation because all of the single exemplars are highly associated with the gist representation (Brainerd & Reyna, 2001; Gallo & Roediger, III, 2002). By the repeated reactivation and

associated adaptive integration of newly encoded memories in pre-existing knowledge networks, sleep might even further increase the activation of the gist representation and thus facilitate the generation of false memories. Several studies using fMRI revealed that sleep indeed fosters a transfer and reorganization of memories from the hippocampus to neocortical storage sites (Takashima et al., 2006; Rasch & Born, 2007; Gais et al., 2007). A recent study observed that false memories in the DRM paradigm were associated with activations in the hippocampus and retrosplenial cortex after sleep, but not after wakefulness, suggesting that the system consolidation process in hippocampo-neocortical networks can promote the generation of false memories during sleep (Darsaud et al., 2010).

The finding of a facilitated extraction of the gist representation during sleep adds to the growing evidence that new memory representations are actively manipulated and reorganized during sleep, leading not only to a quantitative strengthening of memory traces but also to qualitative changes in memory representations. Previous studies found that sleep can facilitate the gain of explicit knowledge about an underlying sequence in an implicitly trained serial reaction time task (SRTT; Fischer et al., 2006) as well as the gain of insight into hidden structures of a complex problem solving task (Wagner et al., 2004). The finding of a sleep-dependent enhancement of false memory generation significantly adds to these studies in providing a more comprehensive view on sleep and memory consolidation. The increase of false memories after sleep extends our present understanding of sleep-dependent memory consolidation in showing that the active processes of memory transformation and reorganization during sleep do not in any case provide beneficial effects, e.g., new insights and generalized knowledge. Rather, as an unwanted by-product, sleep can under some circumstances lead to the generation of distorted and false memories.

Importantly, Studies 1 and 2 further revealed two significant constraints on the enhancing effect of sleep on false memories. The increase of false memories after sleep was only observed when memory retrieval was tested using a free recall procedure (Study 2), but not with a recognition test (Study 1), and only in subjects who displayed relatively low general memory performance (Study 2). The finding of the sleep-dependent increase of false memory being restricted to free recall procedures is in line with recent evidence revealing higher amounts of false memories following sleep in a free recall test (Payne et al., 2009), but even slightly reduced false memory rates in a recognition procedure (Fenn et al., 2009). Several studies on veridical memory further suggest that recall procedures are generally more sensitive to the effect of sleep on memory than recognition procedures (for an overview see Diekelmann et al., 2009). The system consolidation process taking place during sleep might

specifically facilitate the self-initiated generation of items in recall procedures. System consolidation integrates and interlinks newly encoded memories with pre-existing knowledge networks. Thereby, memories are embedded in a richer network of neighboring associations providing different possible access routes for the to-be-remembered memory (Diekelmann & Born, 2007; Diekelmann & Born, 2010). This effect would be even more pronounced in the recall of false memories in the DRM paradigm, since all of the single learned words of each list provide a potential recall cue that can activate the highly associated gist word, thereby increasing the likelihood of false recall.

The second constraint, i.e., false memories being only enhanced after sleep in subjects who display relatively low general memory performance, is consistent with previous studies on veridical memory indicating that sleep benefits depend on the strength of the memory trace at initial encoding (Ekstrand, 1967; Kuriyama et al., 2004; Hauptmann et al., 2005; Drosopoulos et al., 2007; Tucker & Fishbein, 2008). Recently, it has been proposed that the sleep benefit follows an inverted u-shaped function depending on the strength of the underlying memory associations. Both very weak and very strong memories might fail to benefit from sleep, while those with intermediate levels of initial encoding might show the greatest benefit (Stickgold, 2009). Low-performing subjects in Study 2 can indeed be considered "intermediate" performers since their performance is comparable to the performance observed in similar studies (Payne et al., 2009). High-performing subjects in Study 2, on the other hand, show extraordinarily good memory retention, suggesting that these subjects applied deliberate mnemonic strategies that improved general memory performance and concurrently prevented the increase in false memories.

While sleep enhances false memories through active reorganization processes in the *consolidation* period, sleep deprivation enhances false memories through fundamentally different processes at *retrieval* (Study 1 and 2). Sleep deprivation can be assumed to enhance the occurrence of false memories at retrieval due to acutely impaired cognitive control processes that disturb the access to stored memories. Sleep deprivation substantially impairs various cognitive functions (for reviews see Harrison & Horne, 2000b; Durmer & Dinges, 2005; Boonstra et al., 2007; Lim & Dinges, 2010) and especially effort-related aspects of retrieval involving retrieval monitoring and judgments about recollection and familiarity (Horne, 1993; Drummond et al., 2000; Harrison & Horne, 2000b; Chee & Choo, 2004). Failures in retrieval monitoring have been proposed to increase the likelihood of false remembering (Johnson et al., 1993) and successful retrieval monitoring is neccessary to counteract the generation of false memories at retrieval (Curran et al., 2001; Schacter et al.,

2001; McDonough & Gallo, 2008). Such processes of retrieval monitoring critically depend on the PFC, a brain structure that is particularly sensitive to sleep deprivation (Horne, 1993; Jones & Harrison, 2001). The PFC has also been implicated in false memory retrieval (Schacter & Slotnick, 2004; Slotnick & Schacter, 2004; Kubota et al., 2006), presumably subserving retrieval monitoring, inhibition, and discrimination processes (Rugg et al., 1996; Schacter et al., 1996b; Henson et al., 1999; Dobbins et al., 2002). Thus, the derogation of prefrontal lobe function after prolonged wakefulness presumably impairs the kinds of retrieval monitoring processes that are necessary to discriminate actually encountered words from those that were internally generated, leading to an increase in false remembering (Johnson et al., 1993; Mitchell et al., 2004). The neuromodulator adenosine could reflect one potential neurophysiological mechanism underlying the decline of retrieval monitoring under sleep deprivation (Study 1). Adenosinergic neuromodulation plays a central role in sleepiness, reduced arousal/activation, and the impairment of cognitive functions after sleep deprivation (Basheer et al., 2000; Dunwiddie & Masino, 2001; Retey et al., 2006). Caffeine blocks adenosine A_1 receptor-mediated neuronal inhibition and thereby increases cortical and hippocampal activity including activity in prefrontal areas (Acquas et al., 2002; Fisone et al., 2004). Such mechanisms may have increased effectiveness in prefrontal functioning after caffeine administration by improving prefrontal retrieval monitoring which consequently reduced the generation of false memories in sleep-deprived subjects.

Interestingly, contrary to the sleep-dependent enhancement of false memories, the increase in false memory rate under acute sleep deprivation was independent of the applied retrieval test: false memories were enhanced in both recognition (Study 1) and free recall procedures (Study 2). This finding indicates that the monitoring processes necessary to inhibit false memories at retrieval testing are required in recognition and free recall to the same extent. There is indeed evidence that recognition and recall are comparable with regard to strategic retrieval monitoring processes. According to the “generate-recognize” theory, recall involves two stages: the generation of possible responses and a recognition test to decide whether each of these generated responses was actually learned or not, whereas recognition is characterized by the absence of the first stage (Bahrick, 1970). Thus, while processes that specifically affect the first (generation) stage are expected to be only detectable with recall procedures (like the sleep-dependent enhancement of false memories in Study 2), processes that affect the second (recognition) stage should be found in both recognition and recall tests.

Together, studies 1 and 2 show that sleep and sleep deprivation affect the generation of false memories at different stages of memory formation and through different underlying

processes. While sleep enhances false memories by fostering the extraction of gist knowledge in an active reorganization process during consolidation, acute sleep deprivation derogates monitoring processes that are necessary to prevent false memories at retrieval. Both findings are consistent with one of the two main theoretical frameworks on the generation of false memories currently discussed, i.e, gist-based and monitoring accounts, respectively. Both processes might occur independent of each other and target different stages of memory formation.

Study 3, by administering the stress hormone cortisol before retrieval testing in the rested wake state, further extends these findings, directly testing whether false memories in a non-verbal DRM paradigm are generated during consolidation by gist extracting or at retrieval by monitoring failures. Cortisol is well-known to specifically impair the retrieval of accurate memories (de Quervain et al., 2000; Wolf et al., 2001; de Quervain et al., 2003; Het et al., 2005; Wolf, 2009). Importantly, gist-based and monitoring theories would make different predictions on the effects of cortisol at retrieval on false memory generation: while according to gist-based theories cortisol should decrease false memories to the same extent as correct memories (because gist and item-specific memories are processed similarly), monitoring theories would expect an increase in false memories due to impaired retrieval monitoring processes. Consistent with gist-based theories, but contrary to monitoring theories, increased cortisol levels at retrieval distinctly reduced the occurrence of false memories and this reduction was significantly correlated to a parallel decrease in correct memory retrieval (Study 3). These findings suggest that the gist representation was extracted during encoding/consolidation and was stored in the same way as actually encoded memories, with both veridical and gist representations being similarly susceptible to cortisol-dependent blockade of the access to stored memories. However, these findings do not preclude that retrieval monitoring processes can be critically involved in false memory formation under different conditions, as for example shown in the verbal DRM paradigm following sleep deprivation (Study 1 and 2).

Although the findings of the present thesis substantially advance our understanding of the neurophysiological mechanisms underlying the generation of false memories in the general process of memory formation, several challenging issues remain to be further elucidated. A key topic for future research will be to identify specific conditions under which false memories are generated and to find determining factors for the generation of false memories primarily by gist extraction or by retrieval monitoring failures. The present findings show that false memories are generated through gist extraction by sleep during the

consolidation period and by cortisol administration at retrieval testing, but also through impairment in retrieval monitoring after sleep deprivation. It will be important to further specify the underlying neurophysiological mechanisms of these effects. For example, one question to be addressed in the future is whether gist extraction during sleep-dependent consolidation depends on a specific sleep stage. Studies investigating the reactivation of memory traces during sleep in rodents and humans would lead to the assumption that the generation of gist representations specifically depends on SWS rather than REM sleep (Wilson & McNaughton, 1994; Rasch et al., 2007; Ji & Wilson, 2007). Functional brain imaging techniques (like fMRI) should further be used to reveal the underlying neuronal mechanisms of false memory generation during sleep and sleep deprivation. It would be expected that the generation of gist representations during sleep is characterized by a hippocampo-neocortical reorganization of activations associated with the learned exemplars. Further, specific differences following sleep as compared to wakefulness would be expected in activation patterns during false recall of the gist representation. A prefrontal deactivation should be seen, on the other hand, during false memory retrieval specifically after sleep deprivation. Also, using fMRI, possible neuronal mechanisms at encoding should be examined to determine whether or not false memories will be generated during sleep or sleep deprivation. Additionally, there are various neuromodulators that are well-known to affect the formation of accurate memories, e.g., noradrenaline, acetylcholine, insulin, and cannabinoids (Hasselmo, 1999; Kobayashi & Yasoshima, 2001; Ranganathan & D'Souza, 2006; Benedict et al., 2007). It remains to be elucidated whether these and other neuromodulators are also functionally implicated in the generation of false memories.

Importantly, false memories in the DRM paradigm, as investigated in the present thesis, are a specific type of false memories relying on strong associations between words or non-verbal items in the associative memory network. Although the DRM paradigm has most frequently been applied in the research on false memories, there are also other kinds of false memories and memory distortions. For example, memories can be distorted by post-learning misinformation or misleading questioning and false memories of entire events that never happened can be implanted by imaginations and suggestions. Future research will have to specify whether sleep and sleep deprivation as well as specific neuromodulators likewise play a role in the occurrence of other types of false memories and memory distortions.

Abstract

Human memory is not a literal record of the world but memories can be changed and distorted in a reconstructive process, sometimes even leading to the generation of false memories. False memories are defined as memories of events that actually never happened. Although the occurrence of false memories under different conditions is well described in the literature, the neurobiological mechanisms underlying this phenomenon remain largely unknown. Sleep has been shown to benefit the consolidation of accurate memories in a process of active reactivation and reorganization, i.e., system consolidation. Acute sleep deprivation, on the other hand, substantially impairs cognitive functions that are essential for memory retrieval. Apart from sleep and sleep deprivation, several neuroendocrine modulators are known to considerably affect processes of memory formation. The present thesis aimed at characterizing the role of active processes of consolidation during sleep, as well as the effects of sleep deprivation at retrieval testing, and the modulating influence of specific neuroendocrine factors in the generation of false memories. Three studies were performed, revealing that sleep, as well as sleep deprivation, and the neuromodulators adenosine and cortisol, critically affect false memory formation. Sleep-dependent processes of active system consolidation distinctly increased the generation of false memories, which was primarily observed when free recall procedures were applied at memory testing, but not with recognition procedures, and only in subjects with relatively low general memory performance (Study 1 and 2). False memories were likewise enhanced by acute sleep deprivation at retrieval testing, in both free recall and recognition tests, and this effect was abolished by the application of the adenosine antagonist caffeine before retrieval testing (Study 1 and 2). Finally, elevated levels of the stress hormone cortisol at retrieval testing reduced the occurrence of false memories in parallel with a diminished recall of correct memories (Study 3). Together, these findings indicate that the generation of false memories is tightly linked to the general processes of memory formation, relying on the same basic neurophysiological mechanisms.

Zusammenfassung

Das menschliche Gedächtnis stellt keine exakte Abbildung des Erlebten dar, sondern entspricht vielmehr einem (re-)konstruktiven Prozess, in dem es unter Umständen zur Entstehung von fehlerhaften und falschen Erinnerungen (so genannten „False Memories“) kommen kann. Als False Memories werden Erinnerungen an Ereignisse bezeichnet die tatsächlich nie stattgefunden haben. Obwohl das Auftreten von False Memories unter verschiedenen Bedingungen in der Literatur gut beschrieben ist, sind die diesem Phänomen zu Grunde liegenden neurobiologischen Mechanismen weitgehend unbekannt. Es ist gut belegt, dass Schlaf nach dem Lernen die Gedächtniskonsolidierung im Rahmen eines aktiven Reaktivierungs- und Umstrukturierungsprozesses fördert. Akute Schlafdeprivation führt hingegen zu einer Beeinträchtigung kognitiver Funktionen, die eine zentrale Rolle für den Gedächtnisabruf spielen. Neben Schlaf und Schlafdeprivation sind zudem verschiedene neuroendokrine Faktoren bekannt, die die Gedächtnisbildung entscheidend beeinflussen. Ziel der vorliegenden Arbeit war es, die Rolle von Prozessen der aktiven Gedächtniskonsolidierung im Schlaf, sowie die Auswirkung von Schlafdeprivation beim Gedächtnisabruf und die modulierende Funktion von bestimmten Neuromodulatoren für die Entstehung von False Memories zu charakterisieren. Es wurde gezeigt, dass sowohl Schlaf, als auch Schlafdeprivation und die Neuromodulatoren Adenosin und Cortisol einen bedeutenden Einfluss auf die Entstehung von False Memories ausüben. Schlafabhängige Prozesse der aktiven Konsolidierung führten zu einem verstärkten Auftreten von False Memories, wobei dieser Effekt nur unter Verwendung eines freien Gedächtnisabrufs, nicht jedoch eines Wiedererkennungstests, und nur für Probanden mit einer relativ geringen generellen Gedächtnisleistung gezeigt werden konnte (Studie 1 und 2). Schlafdeprivation zum Zeitpunkt des Gedächtnisabrufs bewirkte ebenfalls eine erhöhte Rate an False Memories, wobei dieser Effekt sowohl für den freien Gedächtnisabruf als auch für die Wiedererkennungsleistung auftrat und durch die Gabe des Adenosin-Antagonisten Koffein vor der Abruftestung eliminiert werden konnte (Studie 1 und 2). Die Erhöhung des Stresshormons Cortisol während des Gedächtnisabrufs führte schließlich zu einer Reduktion von False Memories die mit einer parallelen Abnahme der korrekten Erinnerungsleistung einherging (Studie 3). Die Ergebnisse der drei Experimente zeigen, dass die Entstehung von False Memories eng mit dem generellen Gedächtnisbildungsprozess verknüpft ist und auf den gleichen grundlegenden neurophysiologischen Mechanismen beruht.

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Acknowledgments

I am deeply grateful to Prof. Jan Born whose constant encouragement, supervision and support enabled me to develop fundamental research skills as well as an understanding of the basic principles of the scientific community, whilst allowing me the room to work in my own way. During the numerous stimulating discussions we had, he provided a motivating, enthusiastic, and critical atmosphere that exceptionally inspired me and enriched my growth as a researcher. I invaluably benefited from his immense knowledge and his true passion in science, as a mentor and friend. I am deeply indebted to him more than he knows.

I want to express my deepest thanks to my colleagues and friends who all have invaluably contributed to this thesis and who have made the last five years the best time of my life. In particular, I would like to thank Ullrich Wagner for helping me in writing the papers underlying this thesis as well as the challenging research that lies behind it. His friendship, support and guidance from the first day on, as well as his crucial scientific contribution, made him a backbone of this research. My sincere thanks go to Ines Wilhelm and Sabine Groch for their endless and friendly scientific as well as emotional support and for being a family for me during the last years. Furthermore, I am grateful to Björn Rasch, Manfred Hallschmid, Sebastian Schmid and Til Ole Bergmann for their invaluable help and support. Many thanks to all of these people for the great fun we had over the years with inspiring scientific discussions, amazing sailing trips, sporty cycling tours, playing card games, exciting vacations and lots of other great adventures.

I further want to thank all of the rest of my colleagues at the Department of Neuroendocrinology for providing such a stimulating and fun environment which made this institute a very special place and home over the past years. Special thanks go to Anja Otterbein for coordinating almost everything and for keeping the institute running, to Heidi Ruf and Ingrid von Lützau for technical assistance with the hormone assays, as well as to the doctoral students Katja Sevenich, Bettina Seidel, Alice Speidel, and Johannes Schneeweiß for their highly motivated help with data collection. Finally, I am grateful to Ullrich Wagner and Daria Antonenko for proofreading this thesis.

Lastly, I want to thank my family, especially my mother and my sister, who have given me the freedom to make my own decisions and supported me in any possible way.

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Studies and degrees

10/2001 – 03/2006	Studies in Psychology at the Dresden University of Technology (Germany), Diploma degree in Psychology ("with distinction")
10/2000 – 09/2001	Studies in Media and Communication Studies, Psychology, and Business and Economics at the Free University of Berlin (Germany)

Research positions

04/2006 – present	PhD position at the Department of Neuroendocrinology, University of Lübeck (Germany), Supervisor: Prof. Dr. Jan Born
10/2005 – 03/2006	Student research assistant at the Department of Neuroendocrinology, University of Lübeck (Germany), Supervisor: Prof. Dr. Jan Born
04/2004 – 06/2005	Student research assistant at the Department of Biological Psychology, Dresden University of Technology (Germany), Supervisor: Prof. Dr. Clemens Kirschbaum
04/2003 – 09/2005	Student research assistant at the Department of Cognitive Psychology, Dresden University of Technology (Germany), Supervisor: Prof. Dr. Thomas Goschke

Publications

Original articles

Diekelmann S, Büchel C, Born J, Rasch B. Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nat Neurosci*. 2011; in press.

Wilhelm I, **Diekelmann S**, Molzow I, Ayoub A, Mölle M, Born J. Sleep selectively enhances memories of future relevance. *J Neurosci*. 2011; in press.

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Diekelmann S, Born J. Slow wave sleep takes the leading role in memory reorganization. *Nat Rev Neurosci*. 2010 Mar;11(3):218.

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[*] Shared first authorship

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Presentations at conferences (selected)

Diekelmann S, Wilhelm I, Wagner U, Ayoub A, Born J (2010). Die Rolle von Intentionen für die schlaf-abhängige Gedächtnisbildung. Talk presented at the 9th *Tagung der Österreichischen Gesellschaft für Psychologie (ÖGP)*, Salzburg, Austria.

Diekelmann S, Wilhelm I, Wagner U, Born J (2009). Der Einfluss von Schlaf auf die prospektive Gedächtnisbildung. Talk presented at the *Psychologie & Gehirn*, Leipzig, Germany.

Diekelmann S, Landolt H-P, Lahl O, Born J, Wagner U (2008). Sleep loss produces false memories. Poster and datablitz talk presented at the 6th *FENS Forum of European Neuroscience*, Geneva, Switzerland.

Diekelmann S, Landolt H-P, Lahl O, Born J, Wagner U (2008). Sleep loss produces false memories. Poster and datablitz talk presented at the 19th *Congress of European Sleep Research Society* (*ESRS)*, Glasgow, Scotland.

Diekelmann S, Wilhelm I, Schneeweiß J, Wagner U, Born J (2008). Elevated cortisol at retrieval reduces the occurrence of false memories. Poster presented at the *Psychologie & Gehirn*, Magdeburg, Germany.

Diekelmann S, Groch S, Wilhelm I, Schneeweiß J, Wagner U, Born J (2008). Elevated cortisol at retrieval reduces the occurrence of false memories. Poster presented at the 39th *Annual Conference of the International Society of Psychoneuroendocrinology* (*ISPNE)*, Dresden, Germany.

Diekelmann S, Wagner U, Seidel B, Lahl O, Pietrowsky R, Landolt H-P, Born J (2007). Caffeine counteracts the sleep deprivation-induced enhancement of false memories. Poster presented at the *Psychologie & Gehirn*, Dortmund, Germany.

Diekelmann S, Wagner U, Sevenich K, Wilhelm I, Lahl O, Pietrowsky R, Born J (2006). Does sleep facilitate the formation of false memories? Poster presented at the *Psychologie & Gehirn*, Dresden, Germany.

Diekelmann S, Schuster M, Lößner R, Kirschbaum C (2005). Impact of sexual orientation and social support on cortisol and subjective responses to acute psychosocial stress. Poster presented at the 36th *Annual Conference of the International Society of Psychoneuroendocrinology* (*ISPNE)*, Montréal, Canada.