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## Wake and be fine?

### The effect of sleep on emotional memory

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A painting of a woman with dark skin, wearing a vibrant, multi-colored striped dress and a pink headscarf, lying on her back and playing a stringed instrument. She is smiling peacefully. To her left, a large, shaggy, brown creature with a white mane stands looking towards her. In the background, there are rolling hills under a dark blue night sky with a large, full moon. The overall mood is serene and contemplative.

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PER DAVIDSON

FACULTY OF SOCIAL SCIENCES | DEPARTMENT OF PSYCHOLOGY LUND UNIVERSITY





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Per Davidson



**LUND**  
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DOCTORAL DISSERTATION

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Lund University, Sweden.

To be defended in Edens Hörsal, Lund on the 20<sup>th</sup> of January  
2017 at 13:15.

*Faculty opponent*

Edward Pace-Schott, Harvard Medical School

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Title and subtitle: Wake and be fine? The effect of sleep on emotional memory.		
<p>Abstract: The aim of this thesis was to examine the effect of sleep on emotional memories. The first two studies examined the role of sleep in the generalization of fear learning and the third study examined how sleep affected the forgetting of unwanted emotional memories.</p> <p>In study 1, participants first underwent fear conditioning with a small and a large circle as the CS+ and the CS-. Next, after either a nap or an equal amount of time spent awake, participants viewed these two circles again, as well as eight novel circles that gradually varied in size in-between the former two. The results showed that fear conditioning was successful and that there was a tendency towards the larger responses to the CS+ as compared to the CS- having been preserved during the delay interval but that there was no group difference. Analyzing responses to the novel stimuli revealed that fear responses increased as a function of their similarity to the CS+. This increase did however not differ between the groups, thus there was no support for that sleep or wake would differently affect the generalization of fear learning.</p> <p>In study 2, a similar design was used, but with electric shocks instead of the aversive sound, in order to elicit a stronger fear response. The results revealed that in the wake group, fear responses were larger to the CS+ compared to the CS-, whereas no such effect was observed after sleep. Similar results were evident for fear responses to the novel circles, indicating that after sleep, similarity to the CS+ was no longer a predictor of the degree of fear responding. The groups did not differ in general responsivity, but only in how their responses were distributed across the stimuli.</p> <p>In study 3, participants first learned associations between neutral words and images that were either negative or neutral. Then, in the Think/No-Think phase, a subset of these words were shown without the images, and participants were asked to either try to think of the image that they had previously been associated with (Think items) or to avoid all thoughts of the associated image (No-Think items). Then, memory was tested for all the items. Results revealed significant below baseline forgetting of the No-Think items in the group that was tested right after the conclusion of the No-Think phase. This forgetting effect had however disappeared after a longer delay interval, regardless of if it had contained sleep or wake, regardless of the emotionality of the images. Thus, we found no support that sleep and wake would differently affect the duration of this forgetting effect.</p>		
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Per Davidson



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# Abstract

The aim of this thesis was to examine the effect of sleep on emotional memories. The first two studies examined the role of sleep in the generalization of fear learning and the third study examined how sleep affected the forgetting of unwanted emotional memories.

In study 1, participants first underwent fear conditioning with a small and a large circle as the CS+ and the CS-. Next, after either a nap or an equal amount of time spent awake, participants viewed these two circles again, as well as eight novel circles that gradually varied in size in-between the former two. The results showed that fear conditioning was successful and that there was a tendency towards the larger responses to the CS+ as compared to the CS- having been preserved during the delay interval but that there was no group difference. Analyzing responses to the novel stimuli revealed that fear responses increased as a function of their similarity to the CS+. This increase did however not differ between the groups, thus there was no support for that sleep or wake would differently affect the generalization of fear learning.

In study 2, a similar design was used, but with electric shocks instead of the aversive sound, in order to elicit a stronger fear response. The results revealed that in the wake group, fear responses were larger to the CS+ compared to the CS-, whereas no such effect was observed after sleep. Similar results were evident for fear responses to the novel circles, indicating that after sleep, similarity to the CS+ was no longer a predictor of the degree of fear responding. The groups did not differ in general responsivity, but only in how their responses were distributed across the stimuli.

In study 3, participants first learned associations between neutral words and images that were either negative or neutral. Then, in the Think/No-Think phase, a subset of these words were shown without the images, and participants were asked to either try to think of the image that they had previously been associated with (Think items) or to avoid all thoughts of the associated image (No-Think items). Then, memory was tested for all the items. Results revealed significant below baseline forgetting of the No-Think items in the group that was tested right after the conclusion of the No-Think phase. This forgetting effect had however disappeared after a longer delay interval, regardless of if it had contained sleep or wake, regardless of the emotionality of the images. Thus, we found no support that sleep and wake would differently affect the duration of this forgetting effect.

# Sammanfattning

Tidigare forskning har visat att sömn har en stärkande effekt på minnet. Det har även visats att sömn inte enbart ”lagrar” information, utan även aktivt bearbetar den, vilket till exempel tillåter oss att under sömnen dra slutsatser utifrån sådant vi lärt oss. Vidare har det visats att de delar av hjärnan som behandlar emotioner i hög grad är aktiva under sömnen och flera studier har hittat att sömn har en starkare effekt på emotionella minnen än på neutrala. Tidigare studier har även visat att sömn och vakenhet i olika utsträckning kan påverka våra emotionella responser till ett stimulus.

Syftet med denna avhandling var att kombinera dessa olika typer av forskningsfynd och undersöka hur sömn konsoliderar och bearbetar emotionella minnen. De första två studierna undersökte hur sömn, jämfört med vakenhet, generaliserar rädslainläring. Att kunna generalisera sådant vi är med om till liknande situationer är en viktig egenskap. Detsamma gäller för generalisering av rädslainläring. Om vi till exempel har haft en negativ erfarenhet där vi blivit jagade av en björn är det förmodligen väldigt användbart att vi kan generalisera rädslan som björnen gett upphov även till andra björnar, även om vi inte haft några negativa erfarenheter med de björnarna specifikt. Genom att resonera att andra björnar också är farliga eftersom de delar så pass många likheter med den tidigare björnen, kan vi helt enkelt undvika fara. Ett överdrivet generaliserande är dock väldigt problematiskt och något som även är vanligt förekommande i ångesttörningar. Om vi till exempel är med om en bilolycka och sedan får för oss att alla bilar nu är farliga har vi generaliserat vår rädslainläring till en punkt där det inte längre är adaptivt. Eftersom sömn stärker emotionella minnen samt i flera studier har visats vara ett bättre stadié än vakenhet för att dra slutsatser och se samband, ville vi studera vilken roll sömn hade i generaliserandet av rädslainläring. Detta skulle till exempel hjälpa oss att svara på frågan om det är gynnsamt att sova direkt efter en negativ händelse, eller om det finns risk att vi i så fall i högre grad än vid vakenhet generaliserar händelsen även till liknande situationer som inte är farliga.

Vi undersökte sömnens roll i bevarandet och generaliserandet av emotionella minnen med hjälp av klassisk rädslobetningning. I delstudie 1 fick försöksdeltagarna först upprepade gånger se bilder av en stor och en liten cirkel. En av dessa två cirklar visades samtidigt som ett obehagligt ljud spelades upp i ett par hörlurar. Detta leder till att den cirkeln som varit hopparad med ljudet snart börjar väcka en rädslarespons (i det här fallet uppmätt via svettningar), enbart i sig själv, alltså även i avsaknad av ljudet. Den andra cirkeln var aldrig hopparad med ljudet. Efter betingningsfasen fick hälften av deltagarna ta en tupplur medan den andra halvan förblev vakna. Vid ett senare test visades båda dessa cirklar igen,

tillsammans med åtta ytterligare cirklar som deltagarna inte hade sett förut, och som stegvis varierade i storlek mellan den lilla och den stora cirkeln. Detta test visade att deltagarnas rädsleresponser till cirklarna ökade som en funktion av likhet till den cirkel som tidigare varit hopparad med det obehagliga ljudet, men att denna ökning inte skiljde sig åt mellan grupperna, vilket innebär att vi inte hittade något stöd för att sömn och vila i olika utsträckning skulle generalisera rädslolinläring.

Delstudie 2 använde sig av en liknande metod som den första studien, med skillnaden att vi istället för det obehagliga ljudet parade ihop en av cirklarna med en elchock i syfte att få till större rädsleresponser. Resultatet denna gång visade att vakengruppen hade större responser till cirkeln som tidigare varit hopparad med ljudet jämfört med den cirkel som inte hade varit det. Sömngruppen visade dock på lika höga responser till båda cirklarna. Den totala mängden och styrkan på responserna skiljde sig inte åt mellan grupperna, enbart hur de var distribuerade. Analysen som även involverade de nya cirklarna visade på liknande effekter, där rädsleresponsen i vilogruppen ökade som en funktion av visuell likhet med den ursprungligen farliga cirkeln, medan responserna till den farliga cirkeln i sömngruppen inte skiljde sig åt från responserna till någon annan cirkel. Återigen var det inte så att grupperna skiljde sig åt i allmän reaktivitet. Sömnens roll i generalisering av rädslolinläring är fortfarande mycket kontroversiell och är ett område där mycket vidare forskning behövs. Tidigare studier har hittat resultat åt olika håll, där sömn har resulterat i att graden av generalisering både har ökat och minskat. Generalisering av en respons från ett stimulus till ett annat kan vidare vara baserad på flera olika faktorer utöver visuell likhet, så som kategorisk likhet, eller att två stimulin påträffats tidsmässigt nära varandra. En viktig uppgift för vidare forskning är att undersöka ifall sömn spelar olika roller för dessa olika typer av generalisering.

Den tredje delstudien utgick från de fynd som visat att sömn har en gynnsam effekt på minnet och att denna effekt i flera har studier visat sig vara större för emotionellt material jämfört med neutralt. Betydligt mindre är dock känt om hur sömn påverkar minnet för sådant som vi försökt undvika att tänka på. I denna studie ville vi undersöka om sömnen skulle stärka dessa försök till bortträngning, eller om det tvärtom var så att sömnen ”reparerar” dessa minnen och gör dem mer tillgängliga för oss. Vi ville även se om effekten var större för negativt jämfört med neutralt material. Vi undersökte detta genom det så kallade Think/No-Think-paradigmet, som tidigare använts för att inducera glömska för material som deltagare försökt undvika att tänka på i samband med att de exponerats för en påminnelse om det. I vår version av detta paradigm fick deltagarna först lära sig associationer mellan neutrala ord och bilder, som antingen var negativa eller neutrala. Nästa steg var Think/No-Think-fasen. I denna fas fick deltagarna se enbart orden skrivna på skärmen, i antingen röd eller grön text. Om ett ord visades

i grönt uppmanades deltagarna att försöka tänka på den bild som det tidigare varit associerade med (Think-items) och om ordet var skrivet i rött uppmanades deltagarna att försöka undvika alla tankar på den tidigare associerade bilden (No-Think-items). Några av orden visades inte alls under denna fas (Baseline-items). Deltagarna delades sedan upp i tre olika grupper; en grupp som gjorde minnestestet direkt (No Delay-gruppen), samt två andra grupper som gjorde minnestestet några timmar senare, efter antingen sömn eller vila. Vid minnestestet fick deltagarna se samtliga ord igen och ombads ange vilken bild de tidigare hade visats tillsammans med. Flera studier som använt sig av detta paradig har tidigare visat på försämrad minnesprestation för No-Think-items jämfört med Baseline-items. Resultaten i vår studie visade på en sådan glömskeffekt i No Delay-gruppen och att denna glömske-effekt framförallt var drevs av sänkt minnesprestation för de negativa No-Think-bilderna. För de två grupper som gjorde minnestestet efter lite längre tid fanns dock ingen sådan glömske-effekt, oavsett emotion. Det fanns inte heller någon skillnad mellan sömn- och vilogruppen. Detta är i linje med tidigare studier som hittat att denna glömske-effekt avtar över tid och, vi fann inget stöd för att den skulle avta vare sig mer eller mindre om denna tid innehållit sömn. Sömn har tidigare visats både öka och minska skillnaden i minnesprestation mellan objekt som deltagare av olika skäl kan förväntas glömma bort jämfört med objekt de kan förväntas komma ihåg. I ljuset av detta, i kombination med att den glömske-effekt som ofta hittas med hjälp av vårt paradig i tidigare forskning har visat sig snabbt försvinna över tid, var vår brist på en skillnad mellan grupperna inte särskilt förvånande. Vidare forskning om hur sömn påverkar minnet för sådant vi helst vill glömma är mycket viktig då både sömnstörningar och påträngande, oönskade tankar och minnen är ett stort problem i många affektiva störningar så som i depression eller vid post-traumatisk stress.



## List of Papers

- I. Davidson, P., Carlsson, I., Jönsson, P., & Johansson, M. (2016). Sleep and the generalization of fear learning. *Journal of Sleep Research*, 25(1), 88-95. doi:10.1111/jsr.12339  
(Published article reprinted with permission from John Wiley & Sons, Ltd)
- II. Davidson, P., Carlsson, I., Jönsson, P., & Johansson, M. (submitted). A daytime nap generalizes fear responses.
- III. Davidson, P., Hellerstedt, R., Jönsson, P., & Johansson, M. Both sleep and wake reduce suppression-induced forgetting.

## Abbreviations

CS	Conditioned stimulus
CS-	A neutral stimulus that has not been paired with an aversive stimulus
CS+	A neutral stimulus that has been paired with an aversive stimulus
CS+E	A neutral stimulus that has first been paired with an aversive stimulus and has subsequently undergone fear extinction
DW/NS	Daytime Wake / Nighttime Sleep
EMG	Electromyography
NREM	Non-REM sleep (all sleep stages that are not REM sleep combined)
PSG	Polysomnography
PTSD	Post-traumatic stress disorder
REM	Rapid Eye Movement sleep (the sleep stage)
REMs	Rapid eye movements (the actual eye movements)
SCRs	Skin conductance responses
SWS	Slow wave sleep
T/NT	Think / No-Think
TSD	Total sleep deprivation
TST	Total sleep time
vmPFC	ventromedial Prefrontal Cortex
WASO	Wake after sleep onset



# 1. Introduction

The aim of the three studies in this doctoral thesis was to contribute to the knowledge about how emotional memories are differently processed during sleep compared to during wake. The first two studies examined how sleep, as compared to wake, preserved the memory of conditioned fear. They also examined how sleep is involved in generalizing the learned fear response from a specific stimulus that has been associated with danger to other stimuli that are visually similar to it. The third study investigated how sleep affected the forgetting of unwanted emotional memories, that we have tried to avoid to think about.

The first chapter will commence with a brief introduction to sleep and the relationship between sleep and memory. Then follows an introduction to the link between sleep and affect. The complexity of this bidirectional relationship is important to keep in mind when interpreting the results of studies on sleep and emotional memory. The last part of this chapter will then bring up the concept of sleep as a potential trait marker, and then present an overview of the sleep manipulation paradigms that are most commonly used. The following chapters after that will be an extensive review of the previous research that is relevant for when attempting to determine how sleep affects the memory of an emotional experience. This is followed by a summary of the empirical studies in this thesis. The final chapter will be a general discussion where the results of our studies will be presented and discussed in the context of the previous literature. In the final chapter, there will also be a discussion of the importance and the possible applications of studies on this topic.

To be able to say anything about the role of sleep in the generalization of fear learning, and about what role it will have on the consolidation of unwanted emotional memories, we basically need to know four things. First, we need to know how sleep and wake differently affect how well we will remember emotional material. It has been suggested that sleep has a stronger effect on emotional memories compared to neutral ones. That is the topic of chapter 2. Then, it is of equal importance to know how sleep, compared to wake, after an emotional experience will alter the affective tone associated with the memory, and the emotional reactivity to cues that are associated with it. Research on how sleep affects emotional reactivity will be discussed in chapter 3. Further, in order to be able to say how sleep will affect memory consolidation for memories that we had

tried not to think about, it is also important to know how sleep and wake differently affects what is remembered and what is not, depending on the perceived relevance of the material and instructions during encoding. The literature examining if sleep and wake have different “algorithms” for sorting which memories that will be consolidated is reviewed in chapter 4. Beyond just passively storing information sleep has also been found to actively process, and to allow us to draw conclusions from it. This literature is discussed in chapter 5.

## Sleep – an introduction

Sleep is defined as a reversible state of relatively less activity and relatively less receptivity to stimuli from the world surrounding us (Carskadon & Dement, 2011). Sleep should not be viewed as just the brain and body shutting down. On the contrary, the brain has to work to keep the brain asleep, just as other areas of the brain have to work in order to keep the brain awake. Sleep it thus not a passive, but an active state.

Humans sleep for about eight hours per day, which means that we spend about a third of our total lives asleep. Yet, we do still not know exactly why we do this. One would however think that there ought to be some very important reason because otherwise it is a behavior that would have been eradicated by evolution, considering how dangerous it is to just shut oneself down. Especially in species that are under high predatory pressure where sleeping is associated with a direct threat to their survival. There are several good candidate suggestions for what purposes sleep serves. These include saving energy (Berger & Phillips, 1995), clearing out waste products accumulated during wake (Xie et al., 2013), thermoregulation (Rechtschaffen & Bergmann, 1995), tissue repair (Oswald, 1980) and optimizing immune system functioning (Lange, Dimitrov, & Born, 2010).

Beyond the physiological consequences, lack of sleep also has several psychological and cognitive consequences. When we have not gotten a sufficient amount of sleep, the most obvious consequence is that we become more tired and that alertness and vigilance decrease. When it comes to cognition, sleep loss severely impairs performance on tasks that require sustained attention and working memory, whereas there are more inconsistencies in the findings regarding more tasks (Killgore, 2009). See Lim and Dinges (2010) for a meta-analysis of the effects of sleep deprivation on cognition.

## Sleep stages

Just as wake is not a unitary state, the same goes for sleep. Sleep consists of several different stages and additionally involves several different “micro events” which are all based on different degrees of activation in different brain regions and varying neurochemical activity. Below follows a brief overview of the different sleep stages and their underlying physiological basis. One must keep in mind that the sleep stages are defined arbitrarily depending on rules determined by humans and the borders between them are probably not as sharp as suggested by these clear definitions.

Sleep staging is assessed using polysomnography (PSG) which combines three different measurements; electrodes attached to the scalp that measure electroencephalography (EEG); electrooculography (EOG) - electrodes above and below the eyes that measure eye movements and electromyography (EMG) - electrodes that measure muscle activity, normally placed below the chin. Sleep staging is based on the criteria set up by the American Academy of Sleep Medicine (Iber, Ancoli-Israel, Chesson, & Quan, 2007). For an overview of sleep monitoring and scoring, see Keenan and Hirshkowitz (2011).

### *Stage 1*

The first stage after falling asleep is viewed as a transition state between sleep and wake. It does not really conserve energy and the sleeper is still quite receptive to outside stimuli.

### *Stage 2*

In Stage 2, sleep gets deeper, which means more relaxation of the brain and body and the sleeper becomes harder to wake up. This stage is also characterized by micro-events such as sleep spindles, which are quick bursts of low frequency activity in the EEG (de Gennaro & Ferrara, 2003; Lüthi, 2013). About 50 % of a normal night of sleep is spent in Stage 2.

### *Slow Wave Sleep (SWS)*

As sleep becomes even deeper, we enter Slow Wave Sleep (SWS). Here, the body and brain continue to get more relaxed. The EEG activity in this stage is defined by delta waves, or slow waves, with low frequency and high amplitude. This is the stage where we are the least alert when we are woken up from it. About 12.5 - 20 % percent of a normal night of sleep is spent in this stage. Most of the SWS takes place during the first half of the night whereas the degree of SWS decreases during the second half. Sleep spindles are present during this stage as well. This stage was previously divided into two different stages where the definition of Stage 3 was at

least 20 % delta activity during a 30 second epoch, whereas Stage 4 was defined by at least 50 % delta activity during a 30 second epoch.

### *Rapid Eye Movement (REM) sleep*

In Rapid Eye Movement (REM) sleep, the muscles of the body become completely relaxed and the sleeper enters a stage of muscle atonia. The brain however does not go into deeper relaxation. On the contrary, brain metabolism increases to about the same levels as during wake. However, the areas of the brain that are active during REM sleep are quite different from those that are active during wake. During REM sleep, prefrontal regions show very low activity whereas for example the limbic system shows high activity. For a summary of studies about regional changes in activity between wake, REM and NREM, see Pace-Schott, Germain and Milad (2015a).

REM sleep is further characterized by the eyes occasionally moving from side to side. A variable that is sometimes discussed in the literature review in this thesis is REM density which is quantified as the number of eye movements divided by the time spent in REM sleep. There is quite little REM sleep during the first half of the night and more during the second half. 20 – 25 % of the night is spent in this sleep stage.

A frequently discussed feature of REM sleep when it comes to emotional processing is REM fragmentation. How is defined varies somewhat between studies but it is mostly conceptualized as how coherent the REM epochs are. A higher degree of changes into and out of REM during the night is classified as REM being fragmented. More awakenings from REM is often included in this definition as well. REM fragmentation is believed to reflect higher physiological arousal during REM, which has been suggested to be associated with impaired emotional processing (e.g. Spoormaker & Montgomery, 2008).

The stages that are not REM sleep (Stage 1, 2 and SWS) are together called Non-REM (NREM) sleep. In animals, sleep is normally only divided into REM and NREM sleep, even though there are sometimes mentionings of light and deep sleep in animal studies as well.

During NREM sleep, the levels of acetylcholine and norepinephrine (noradrenaline) are decreased compared to during wake. When entering REM, there is a further decrease of serotonin and norepinephrine. but an increase in the levels of acetylcholine. Cortisol levels are also high during REM. For reviews of the neurochemical regulation of sleep, see Pace-Schott and Hobson (2002) and Steiger (2007).

## Sleep and memory

Since the first controlled experiment, which showed less forgetting of nonsense syllables after sleep (Jenkins & Dallenbach, 1924), a large and rapidly increasing body of experimental studies has revealed that memory performance is enhanced if the time between encoding and the memory test is spent asleep, compared to if it is spent awake. For an extensive review on sleep and memory, see Rasch and Born (2013).

There are several different theoretical accounts of why sleep during the consolidation period is more beneficial for memory than time spent awake. One explanation could simply be that during sleep, one is exposed to less novel impressions than while awake, and therefore sleep enhances memory performance simply by protecting what has been learned from interference. Sleep, or any of the neurobiological processes that occur during it, would thus not have an active role more than reducing outside interference. This is certainly a contributing factor. Naturally, less interference would be beneficial for subsequent memory performance. There is however now an increasing amount of empirical evidence supporting that the lack of interference is far from the only factor in the beneficial role of sleep on memory consolidation. There are studies showing that wake participants that have been exposed to very little outside interference during the delay interval still show worse memory performance compared to participants who were allowed to sleep (McDevitt, Duggan, & Mednick, 2015; Schönauer, Pawlizki, Köck, & Gais, 2014). Sleep seems not just to be a state where forgetting temporarily stops due to decreased interference. Instead, sleep also appears to make memories less vulnerable to interference also after the sleep interval is over, suggesting that the memory has been stabilized. An example of sleep stabilizing memories, in addition to just passively protecting them, is a study that found sleep to make memories less vulnerable to retroactive interference presented after the delay interval, but before the memory test (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). Further, if sleep would just passively store information, we would not see the effects of sleep being more beneficial than wake in drawing conclusions from a studied material. Neither would we find that sleep and wake would differently sort which information that is remembered and which that is forgotten. This kind of findings suggest that new learning is actively processed during sleep and are discussed in chapters 4 and 5.

Another approach that suggests a more active role for sleep in memory consolidation is that the neural activity present during learning is replayed again during sleep. This would then allow for additional learning. The first study to show this was Wilson and McNaughton (1994) who found that the neural activity of rats while running through a maze was replayed during subsequent NREM



sleep. Similar results in humans were reported for the first time by Maquet et al. (2000), who found that neural activity during the acquisition of a motor task was repeated during subsequent REM sleep. Additional support for replay of waking experiences during sleep having an active role in memory consolidation comes from studies that have examined targeted memory reactivation through repeating stimuli that were presented during learning during subsequent sleep. Repeating sounds or odors that were present during learning, as well as repeating the actually studied words out loud during sleep, has in several studies been found to increase memory performance for different kinds of memory tasks (e.g. Antony, Gobel, O'Hare, Reber, & Paller, 2012; Rasch, Büchel, Gais, & Born, 2007; Rudoy, Voss, Westerberg, & Paller, 2009; Schreiner, & Rasch, 2015). But see also Cordi, Diekelmann, Born, and Rasch (2014) for a null finding. For a review, see Oudiette and Paller (2013).

The beneficial effect of sleep on memory has also been explained by the active systems consolidation hypothesis (Born & Wilhelm, 2012), which suggests that during sleep, newly formed memories are transferred from short term storage in the hippocampus to long term storage in the neocortex (Buzsaki, 1996). Sleep is suggested to be a preferred state for this because of the lack of interference from novel outside impressions, which allows for the transferring of information from the hippocampus to the neocortex in a state where the hippocampus is not needed to encode novel information. Support for this was found by Takashima et al. (2006) who showed that SWS made accurate recognition memory less dependent on activation of the hippocampus. Gais et al. (2007) however found sleep after learning to result in more hippocampal activity during the re-test. Still, this study found that sleep after learning leads to long lasting changes in the neural representations of memories which would argue that sleep is involved in transferring where in the brain a memory is stored. Hippocampal-cortical interaction during sleep has recently been shown to have a causal role in memory consolidation (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016).

Another theory for the role of sleep in memory consolidation is the synaptic downscaling hypothesis (Tononi & Cirelli, 2006) which states that during SWS, there is a general downscaling of synapses in order to conserve the energy that is expended while upholding these synapses. All synapses are suggested to go through a similar downscaling, which would make the weakest disappear completely which would then result in a larger signal to noise ratio for the synapses that remain.

## **The active mechanisms during sleep**

So what is it that happens during sleep that consolidates memories which does not also happen during wake? One way of examining this is to look at which sleep stages and other events during sleep that have been associated with memory consolidation. There are several theories regarding exactly what events during sleep that are causal for its beneficial effect on memory consolidation. In the literature in general, it has often been suggested that SWS and Stage 2 sleep strengthen declarative and explicit memories, whereas REM sleep is involved in strengthening implicit memories such as procedural or emotional memory (for a review of sleep stages and memory consolidation, see Diekelmann, Wilhelm, & Born, 2009).

Other sleep events that have been associated with memory consolidation are sleep spindles and slow wave activity (e.g. Clemens, Fabo, & Halasz., 2005; Marshall, Helgadottir, Mölle, & Born, 2006). It has also been found that reducing theta activity during REM impaired memory consolidation in rats (Boyce, Glasgow, Williams, & Adamantidis, 2016). The low amount of acetylcholine during SWS has been found to be necessary for memory improvement during this stage (Gais & Born, 2004). However, results regarding which sleep stages that are involved in different kinds of memory consolidation are not conclusive. For example, one study found that pharmacologically reducing REM sleep resulted in an improvement in procedural memory (Rasch, Pommer, Diekelmann, & Born, 2009), and time spent in sleep stage 2 has been found to be positively correlated with memory performance for motor learning (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). The effects of different sleep stages are replicated in far from every study, which will be evident throughout the different literature overviews. An extended discussion on which events during sleep that are involved in the consolidation of emotional memories specifically is found in chapter 2.

Finally, one can of course ask if the question whether the effects of sleep on memory matters beyond basic research, considering that a person eventually has to sleep. That would mean that at some point, we will get the sleep related memory benefit anyway. But beyond finding that getting sufficient sleep is important for memory, studies have shown that the timing of sleep is important as well. It has been shown that sleep is more beneficial for memory when it takes place right after learning compared to when it is delayed, even though both groups have had the same amount of sleep between encoding and re-test (Gais, Lucas, & Born, 2006; Payne, Chambers, & Kensinger, 2012). Payne et al. (2015) found that a nap improved memory performance even when it was followed by time spent awake to an extent so that the sleep and the wake group had spent an equal amount of time awake between learning and re-test. Furthermore, many sleep deprivation studies that have found sleep to have an effect on memory have often used additional

recovery nights after the initial sleepless night before the re-test and still found differences in memory performance. If learning is immediately followed by sleep or not has further been found to be associated with improved memory performance several years after encoding (Wagner, Hallschmid, Rasch, & Born, 2006), and with changes in neural responses when being re-exposed to images six months after initial encoding (Sterpenich et al., 2009). Thus, the timing of sleep after learning matters.

## **Disclaimer**

Before leaving the introduction of sleep and memory, it should be noted that sleep research has often been regrettably bad at controlling for multiple comparisons. This could be one of the explanations for the large degree of correlations between different memory effects and various sleep variables not being replicated. With studies using several different memory tests and then testing correlations between these with several different sleep stages as well as other sleep related events, there is of course always a risk that several significant correlations will be found just by chance. Furthermore, as will be discussed later, it is possible that these sleep related events are not causal for improved memory performance, but instead markers of successful learning or other individual factors that predict successful consolidation, such as intelligence. This is of course not only relevant for studies on memory consolidation but should be kept in mind for all sleep studies.

## **Sleep and affect**

The fact that there is a link between sleep and affect is not very surprising. If we are in immediate danger, it is not a good idea to fall asleep until we know that doing so is safe. To take an obvious example, if an animal has been exposed to a predator, it is probably a good thing that the arousal associated with that situation makes it difficult to fall asleep for a while afterwards, given that the predator might still be around. Thus, the fact that arousal from an emotional event keeps us awake has probably in many cases served an important survival function. The fact that we become more emotionally reactive when we have not slept sufficiently has probably also served such a survival function. If we have not slept, and thus have less energy for cognitive functions available, it might be a good thing that we become more reactive to everything that seems even remotely dangerous, adopting a “better safe than sorry” approach. This hyper reactivity could be viewed as a compensatory function in order to enhance survival when cognitive resources for the adequate processing of something’s fear relevance are limited.

However, for most humans these days, the stress we experience is not associated with predation but instead with other less directly urgent and often more chronic matters. Thus, sleep quantity and quality can be reduced during longer time intervals even when it serves no adaptive function. It is not like problems related to work or relationships will come and eat us if we happen to doze off. These stressors, however, still trigger many of the same arousal systems as a predator would, and thus they keep us awake even though it does not serve any adaptive function. On the contrary, it will just make us more reactive the day after, which will result in even more stress and less adaptive emotional processing, which risks resulting in a highly problematic vicious cycle.

This bidirectional relationship is very important to keep in mind when conducting research on sleep and emotional memories. When manipulating if someone sleeps or not in the delay interval between being exposed to emotional stimuli for the first and the second time, the results are quite clear cut to interpret, because in experimental designs we can easily decide who that will have a sleep opportunity between encoding and re-test and who that will not. It is however more difficult to manipulate the quality of the post-learning sleep and how much time that will be spent in each sleep stage. Some studies that are discussed in this thesis have attempted to manipulate sleep in various ways in order to be able to say something about causality. However, when we do manipulate sleep to contain more or less of something (such as a certain sleep stage or spindles), we cannot know if that is the only feature that we have manipulated or if this manipulation has also resulted in other changes. This issue will be further discussed throughout the text where it is relevant.

After an arousing event, it is harder to fall asleep than after a normal day and even when we do manage to fall asleep, the sleep we have is different from the sleep we would have during a normal night. Are the specific physiological events detected during sleep causal mechanisms in the processing of the emotional experience, or just markers of successful emotional learning or of the perceived subjective severity of the event? Further, it could be so that having a certain sleep architecture reflects a general trait marker in people who have difficulties in adaptively processing emotional experience. The role of sleep alterations in affective disorders and their implications for emotional processing will be discussed in the final chapter.

## **Sleep and mood**

Several studies have shown that experimental sleep deprivation has negative effects on our mood. The exact emotions and aspects of mood that have been affected have however varied between studies. A meta-analysis has revealed that

sleep deprivation had larger effects on mood than on both cognitive and motor performance (Pilcher & Huffcutt, 1996). Partially restricting participant's sleep to only 4-5 hours per night has been found to increase tension, confusion and total mood disturbance, but not depression or anger, for each day of sleep restriction (Dinges et al., 1997). One night of total sleep deprivation has been found to be associated with increases in general distress, depression and anxiety (Babson, Feldner, Trainor, & Smith, 2009; Babson, Trainor, Feldner, & Blumenthal, 2010). Another study found a decrease in positive affect, but no difference in negative affect after two nights of partial sleep deprivation compared to two nights of normal sleep, even though the sleep deprived group reported experiencing their most threatening worry to be more threatening (Talbot, McGlinchey, Kaplan, Dahl, & Harvey, 2010). Paterson et al. (2011) tested both the frequency and the intensity of various moods during sleep deprivation and found that after one or two nights without sleep compared to after normal sleep, participants felt happy less frequently and with less intensity. After one night of sleep loss, there was also a significant increase in the intensity of feeling of depression, but interestingly, that was also the case in the normal sleep group after two nights of sleep. Thus, the increase might have been caused by being in the sleep lab, which is something one must keep in mind when interpreting the results of sleep studies.

Other studies have used non-experimental methods to assess the link between sleep and affect. In these studies, participants were asked daily about their current affective state and how they slept during the preceding night for a limited time period. Also for these studies, it has varied exactly which aspects of mood that have been affected by variations in sleep quality. Lower sleep quality has been found to result in less positive and more negative affect during the next day (Simor, Krietsch, Köteles, & McCrae, 2015), a decrease in positive affect and an increase in negative affect, even though the effects were larger for positive affect (de Wild-Hartmann et al., 2013), as well as in a lower degree of several positive mood aspects during the following day, without any increase of negative affect (Kalmbach, Pillai, Roth, & Drake, 2014).

## **Sleep and emotional reactivity**

The two first studies in this thesis examined how sleep and wake would differently alter emotional reactivity to a stimulus that had been associated with either an aversive sound or an electric shock. If someone is less reactive when re-exposed to an emotional stimulus after sleep, it does not necessarily mean that that particular stimulus has been processed in a different way than during wake during the delay interval. It could also be a result of sleep leading to a general decrease of emotional reactivity, not related to that particular stimulus. Therefore, it is

important to keep in mind how sleep affects emotional reactivity to stimuli not seen before.

Without enough sleep, we become more reactive to emotional stimuli even though the exact effects have varied between studies. Some studies have found that sleep deprivation mainly affects the responses to negative stimuli, whereas some have found the lack of sleep to be mainly involved in making neutral stimuli being interpreted as more negative. Sleep deprivation, compared to normal sleep, has been found to lead to a decrease in functional connectivity between frontal regions of the brain, which are involved in downregulating negative affect, and the amygdala. This lack of functional connectivity increases emotional reactivity. This has been found when viewing images after one night of sleep deprivation (Yoo, Gujar, Hu, Jolesz, & Walker, 2007), after a week of partial sleep deprivation (Motomura et al., 2013) and during the resting state after one night of total sleep deprivation (Shao et al., 2014). One study found this decrease in connectivity after two nights of only three hours per sleep night compared to two nights of normal sleep during both the resting state and while watching unpleasant images (Motomura, Katsunuma, Itasaka, Yoshimura, & Mishima, 2016). This change in connectivity was driven by the change of REM duration between the sleep restricted nights and the control nights. A larger reduction of REM sleep during the sleep restriction nights was associated with a larger reduction of functional connectivity.

Other studies have found that lack of sleep has resulted in lower thresholds for when a stimulus is considered as negative. Sleep deprivation has been found to make participants rate neutral images as more negative without affecting the ratings of negative images (Tempesta et al., 2010). Another study found sleep deprivation to result in similar amygdala responses to negative and neutral distractors during an attention task, whereas there was more discriminated responses, with higher reactivity to negative distractors, after normal sleep (Simon et al., 2015). Sleep has also been shown to lead to more stress to a low demanding, but not to a high demanding, cognitive task (Minkel et al., 2012). Five days of partial sleep deprivation has further been shown to lead to higher amygdala reactivity to subliminal presentations of fearful faces (Motomura et al., 2014), indicating that the threshold for detecting threats might be lowered after sleep deprivation. Goldstein et al. (2013) had participants view cues that predicted either a negative or a neutral image and cues that were ambiguous, so that they could predict either a negative or a neutral image. This was done after either normal sleep or after a night of total sleep deprivation. Sleep deprivation increased amygdala reactivity to all cues regardless of type. After normal sleep, insula responses were highest for the ambiguous cues, whereas that was not the case in the sleep deprived group, who showed the strongest responses to the cues predicting negative images. This was interpreted as that after sleep, all cues were

viewed as potentially aversive. Further, trait anxiety predicted the degree of increased insula reactivity, indicating that people with high trait anxiety were also more sensitive to experience an increase of emotional reactivity after sleep loss.

Contrasting results have been found in other studies, with sleep deprivation leading to larger responses to negative compared to neutral images, and higher anticipatory responses during blocks of negative images (Franzen, Buysse, Dahl, Thompson, & Siegle, 2009), and to result in failure to inhibit responses to negative, but not to neutral, stimuli (Anderson & Platten, 2011).

Sleep deprivation has also been found to result in increasing responses to positive stimuli. Gujar, Yoo, Hu, and Walker (2011) had participants rate images as either neutral or positive after either a night of total sleep deprivation or after a night of normal sleep. Results revealed that the sleep deprived group rated a higher amount of stimuli as positive and that sleep deprivation amplified the responses to positive images in the brain's reward networks.

Other studies have found sleep deprivation to lead to decreased habituation of physiological stress responses during fear conditioning (Peters et al., 2014), to result in more panic symptoms in a situation that induced hyperventilation (Babson et al., 2009), and to increased perceived pain and heart rate during a task that consisted of putting the hand into ice water (Larson, Yang, Durocher, & Carter, 2014).

A non-experimental study found poor sleep quality during the preceding week to be associated with poorer ability to re-evaluate a sad video clip and re-interpret it in a more positive perspective (Mauss, Troy, & LeBourgeois, 2013).

## **The impact of affect on sleep**

### *Animal studies*

In general in animal studies, stressors decrease both the duration and the quality of sleep, with the largest effects being evident on REM sleep which becomes either decreased or fragmented. There are however many exceptions and a large variation in the findings that seem to be dependent on the specific kind of stressor that has been used, and to which degree the animals have been exposed to reminders of the stressor. In one study, there were even different effects when comparing different kinds of rats (DaSilva et al., 2011). For reviews of this literature, see Pawlyk, Morrison, Ross and Brennan (2008) and Suchecki, Tiba and Machado (2012). More recent studies have found that contextual fear learning changes the distribution of REM sleep during the night (Polta et al., 2013), that the percentage of time spent in REM is increased during several days after being exposed to a series of different stressors (Vanderheyden et al., 2015), and that

sleep fragmentation increases after the delivery of electric shocks, as well as after a reminder of the electric shocks have been presented and that these changes could still be observed 21 days later (Philbert et al., 2011). One study first found a decrease in REM sleep after acute stress and then a rebound effect with increased REM. This rebound effect was however slower if the rats had been exposed to contextual fear conditioning and reminded of it each day for 22 days prior to the acute stressor (Greenwood, Thompson, Opp, & Fleshner, 2014). Chemical deactivation of the amygdala has been found to decrease sleep latency and to increase slow wave activity (Tang, Yang, Liu, & Sanford, 2005). Lesku et al. (2008) found that rats, after having a simulated encounter with a predator, had less SWS and REM during the early half of their subsequent sleep period, with a rebound during the latter half. For a theoretical account of sleep under the risk of predation, see Lima, Rattenborg, Lesku, and Amlaner, 2005.

A very interesting finding on the effect of fear extinction on sleep is Wellman, Yang, Tang and Sanford (2008). In this study, rats were first exposed to contextual fear learning. Rats were then re-exposed to the conditioned context. Half of the rats were allowed to remain in the context until all signs of freezing had disappeared, whereas the other half were removed before that, that is, before full extinction had been achieved. Sleep was recorded at baseline, after conditioning and after extinction. After conditioning, there was a reduction of REM duration in both groups during the first hours of sleep. In the rats who did not receive full extinction training, the decrease of total sleep, both REM and NREM persisted during the next night, whereas sleep in the group that had received full extinction training returned to baseline. Similar results were reported by Deschaux et al. (2010).

### *Studies with humans*

For an extended review of how stress affects sleep, see Kim and Dimsdale (2007). Several studies, but not all of them, have found that negative affect, either occurring naturally or induced experimentally affects sleep. However, exactly how sleep is affected has, just as in the rodent studies, varied between different studies.

Gross and Borkovec (1982) found that telling participants that they would have to give a speech after a nap before going to bed prolonged the time it took to fall asleep and reduced total sleep time (TST). Tang and Harvey (2004) found similar results even though the effects were only evident in the subjective ratings of sleep and not in the objective measurements. One study looked specifically at the effects on REM sleep and showed that information about having to give a speech in the morning resulted in a slower increase of the number of REMs during the night, and in fewer REMs during the last REM epoch of the night, but in no other REM related differences (Germain, Buysse, Ombao, Kupfer, & Hall, 2003).



It has also been found that both the quality and the duration of sleep decreased after experimentally inducing feelings of failure in participants after an intelligence test (Vandekerckhove et al., 2011). Cohen (1975) found increased REM density in participants who had been treated poorly through lack of information, social isolation and being made to feel that they had performed poorly on an intelligence test. Of note however, this effect was only evident for participants with low neuroticism.

Other studies have manipulated affect by having participants watch a negative and a neutral film clip on different nights and then measure their subsequent sleep in counterbalanced designs. The negative film has been shown to result in more awakenings from REM, but not from NREM sleep, and to increase the number of REMs (Baekeland, Koulack, & Lasky, 1968), to eradicate the gradual increase of REM during the night (which is normally present) and to result in a tendency towards reduced time spent in REM sleep and an increase of the percentage of SWS (Talamini, Bringmann, de Boer, & Hofman, 2013). One study found no differences between the two movies except for a higher arousal index during REM after the negative movie (Werner, Schabus, Blechert, Kolodyazhniy, & Wilhelm, 2015).

In a fear conditioning study by Spoormaker et al. (2010), that will be further discussed in chapter 3, it was found that the group that had REM sleep during the post conditioning nap had larger skin conductance responses (SCRs), and a slower habituation, to the electric shocks themselves during conditioning. Thus is it possible that the amount of REM sleep, or at least REM latency, is dependent on baseline emotional reactivity. A higher intensity of the electric shock has been shown to result in more fragmented sleep during a post learning nap, even though REM sleep was not affected (Sturm, Czisch, & Spoormaker, 2013). The participants in this study who also had a fear extinction session had increased amount of Stage 4 sleep compared to those who only had fear learning.

Regarding the effect of viewing emotional images, Ward, Peters and Smith (2014) found no group differences in any sleep variable between groups that had encoded either positive, negative or neutral images.

The studies examining the relation between sleep and affect on a day-to-day basis that have been mentioned above also showed that positive, but not negative, affect during the day predicted better sleep quality during the subsequent night (de-Wild Hartmann et al., 2013; Kalmbach et al., 2014). In the Kalmbach et al. (2014) study, it was further shown that these effects were still significant when controlling for baseline depression and anxiety, as well as for sleep quality during the night before. Simor et al. (2015) found that high positive affect and low negative affect on average throughout the study was related to good sleep quality, but no influence of affect on sleep on a day-to-day basis.

Another study showing the complex bidirectional relationship between sleep and affect is Vahtera et al. (2007). They examined the relationship between sleep, anxiety and stressful life events in a five year longitudinal study. They found that experiencing a stressful life event was associated with developing sleep disturbances and that the degree of sleep disturbances was related to the severity of the event. People with higher levels of anxiety before the event were also more likely to experience sleep disturbances during the six months preceding the event, compared to those with lower levels of baseline anxiety. Guastella and Moulds (2007) tested college students during the same day as they had taken an important exam. Participants were first tested for trait rumination after which exam related ruminations were induced in half of the participants right before going to bed. Results revealed that participants with high levels of baseline rumination reported lower sleep quality after rumination induction. The rumination induction did not however cause any group differences among participants with low baseline rumination. Thus, it can be said that negative events or feelings have a stronger effect on sleep in participants who already have a high degree of negative affect at baseline.

## Sleep as a trait marker

Good sleep has often been linked to more healthy affective responses and better cognitive performance. But just because these factors often co-occur, it does not necessarily mean that there is a direct causal relationship between them. Perhaps sleep could also be viewed more as a trait marker, or as a sign of successful learning, rather than something that causally affects our emotions or cognitive ability on a day-to-day basis.

Regarding sleep spindles, which have been found to be correlated with overnight improvement in memory performance, studies have found that they are also correlated with general intelligence and thus might also serve as a marker of learning ability more than a causal factor. For a review, see Fogel and Smith, 2011.

Smith, Nixon and Nader (2004) found that the increase in REM density and the number of REMs during the night after learning a procedural task (compared to during a baseline night before learning) was associated with both memory improvement and higher IQ, whereas no baseline REM measures were correlated with either IQ or task performance. It has also been found that the amount of REM sleep during the post-learning night correlated with degree of learning achieved in a categorization task (Djonlagic et al., 2009). This means that REM sleep also could be a marker of learning rather than only a factor consolidating this learning.

There also seems to be interactions between sleep and various trait factors, meaning that everyone does not seem to gain equally from post learning sleep. Fenn and Hambrick (2015) found a positive correlation between general intelligence and memory improvement during sleep, but not during wake, suggesting that sleep does not have the same effect on memory for everyone. Similar results have also been found for baseline working memory ability where it predicted the degree of memory consolidation during sleep, but not during wake, even though there was no effect of working memory on performance during initial learning (Fenn & Hambrick, 2012).

Other findings that make it relevant to ask the question if a certain sleep feature is a causal factor influencing memory processing during the night, or just a trait variable or a marker will be discussed throughout the following chapters.

## Methods to study sleep

The problematic issue when studying the effect of sleep on anything is to determine what a relevant control condition is. If we compare the effect of sleep on processing a memory with time spent awake, how do we then know that the potential differences are caused by things that happen during sleep, and not by things that have happened during the time spent awake? And how do we disentangle the effects of being tired during the re-test from the absence of the processes that we expect to have taken place during the preceding sleep? Here follows an overview of the most commonly used experimental designs.

Some studies have used within-subjects designs where all participants are tested on two different occasions, once in the sleep condition and once in the wake condition. Other studies have used between-groups designs where the two groups consist of different individuals. This is of course a less preferred way of doing it because it adds the variance of individual differences but it is sometimes necessary when the task can only be used on a participant once.

### **Comparing daytime wake with nighttime sleep (DW/NS)**

One of the most common ways of manipulating sleep is to test the wake group in the morning, then let them go on with their normal activities during the day and then return to the lab for the re-test in the evening. The sleep group do the encoding in the evening and is then tested the next morning, after a night containing a normal sleep opportunity, either at home or in the lab. This kind of design, i.e. daytime wake/nighttime sleep (DW/NS), will be referred to as such throughout the text. An advantage with this design is that it is ecologically valid,

considering that most often sleep takes place during the night and wakefulness during the day. This design also assures that the wake group is not excessively sleepy during the re-test, which could be the case if they are deprived of their normal nightly sleep.

One of the flaws with this design is that participants are being tested at different points during the day. This is problematic considering that such factors as learning and memory have been shown to vary as a function of the circadian rhythm (e.g. Baddeley, Hatter, Scott, & Snashall, 1970; Pace-Schott et al., 2013). It can be difficult to disentangle the effect of circadian rhythms from the effects of sleep. Some studies have however controlled for this and this issue will also be mentioned in the literature review where it is necessary for interpreting the conclusions of a study. Some of the studies discussed here have used control groups that have done the re-test immediately after encoding at various time points during the day in order to control for circadian rhythms in encoding and retrieval. Such circadian differences are rarely found to be confounding factors and therefore, results from these groups will not be mentioned here unless necessary. Some studies have also combined a DW/NS design with an additional control group that do the encoding and retrieval at the same time points as the sleep group but spend the night awake. Another issue with DW/NS designs is that a wake group that go on with their normal daily activities during the day will be subjected to considerably more interference compared to the sleep group.

## **Nap designs**

In a nap design, participants are first tested during the day and are then divided into either a sleep group, who often gets a 90-120 minute sleep opportunity, or into a wake group that remain awake (most often in the lab, often watching some form of non-arousing movie). With this design, circadian rhythm is controlled for because both groups do the encoding and the re-test at the same time point during the day. Also, the sleep group will not be lacking any normal sleep, and sleepiness is thus less likely to be a confounding factor in the results. The disadvantage of this method is that just a two hour sleep opportunity is not always sufficient to detect any group differences. This is especially problematic because REM sleep is the stage that appears in the end of the sleep cycle. Thus, there will often be quite little REM time during a nap. In some studies however, as we will see below, even small amounts of time spent in REM sleep has been sufficient to detect interesting correlations.

## **Total sleep deprivation (TSD) designs**

In these designs, both groups normally do the encoding in the evening after which the sleep group goes to bed as normal and the wake group is deprived of sleep

during the first post-encoding night and normally during the preceding day as well. This controls for circadian factors and, unlike nap designs, also results in large manipulations of sleep. A problem with these kinds of designs is of course sleepiness in the sleep deprived group, even though this is often resolved by testing both groups after at least one additional night of recovery sleep. Sleep deprivation can also cause stress which could be a confounding factor. One can also question the ecological validity of a night with no sleep at all, something that is sometimes resolved by only subjecting participants to partial sleep deprivation, such as for example only allowing 4 hours of sleep on the post-encoding night.

Sleep deprivation can also be specific for different sleep stages so that participants are woken up each time they enter for example SWS or REM sleep. One critique of this method is that perhaps awakenings from different sleep stages are not equally stressful which thus enters a confound in this kind of studies where the difference in a dependent variable is not necessarily caused by lack of time spent in a certain sleep stage, but instead by stress related to the awakenings. Further, when trying to selectively deprive participants of one kind of sleep, either pharmacologically or through targeted awakenings, it is also possible that other sleep factors are affected as well, which makes it difficult to know exactly what has been manipulated.

### **Split night designs**

In split night designs, some participants first do the encoding in the evening, then sleep for a few hours (normally three) early in the night and then do the re-test right after waking up in the morning. Because the early night is dominated by SWS sleep and has relatively little REM sleep, this is a way of creating a condition where the participants have had plenty of SWS and very little REM sleep, without having to subject participants to awakenings. Other participants first sleep normally and are then awakened in the middle of the night to do the encoding. They then go back to sleep again, and do the re-test the next morning. The second half of the night has less SWS and more REM sleep. By comparing sleep during these two halves of the night, one can compare the effect of SWS rich sleep after learning to the effect of REM rich sleep. However, there are of course many confounds that makes it hard to say that the different prevalence of REM and SWS are the only thing that varies between these two conditions. There might for example be other physiological differences between early and late sleep beyond the prevalence of certain sleep stages and there is also the issue of circadian rhythms.

## 2. Sleep and emotional memory consolidation

A natural place to start when asking the question about what happens with an emotional memory during sleep compared to during wake is to see if sleep will result in better recall of the emotional event. This would be a natural expectation given the often found beneficial effect of sleep on memory consolidation in general. It has however also been suggested that emotional memories have a privileged role when it comes to which memories that get consolidated during sleep so that sleep will have a larger effect on emotional than on neutral material compared to wake. This is a central research question of the third study in this thesis, and it is also highly relevant for study one and two because it is important to know if the memory of fear conditioning is better retained after sleep compared to after wake, even though this chapter will focus solely on material that is intrinsically emotional. The role of sleep in fear conditioning is discussed in the next chapter.

The aim of this chapter is to summarize and discuss the scientific literature regarding if memory for emotional material will be strengthened more during a delay interval containing sleep compared to an equal amount of time only containing wake. If sleep strengthens emotional memories more than neutral ones, and if this difference is larger compared to the effect of time spent awake, this would further argue the importance of sleep in the processing of emotional memories. This chapter will solely focus on studies that have used behavioral outcome measures. Studies that have used emotional reactivity or physiological responses as the outcome measure will be discussed in the next chapter. Studies that have measured both emotional reactivity and behavioral memory performance in the same experiment will be divided and discussed separately, even though these two components can of course sometimes be difficult to disentangle from each other.

Most studies discussed in this chapter have included participants who have encoded both emotional and neutral material (images, video clips or words) for which memory performance has been tested after a delay interval that has either contained sleep or been spent awake. In other studies, the duration or timing of sleep has been manipulated.

This overview will commence by discussing studies that have looked at sleep in general, that is, studies that have compared a sleep and a wake group. Studies using simple contrasts between neutral and emotional material will be described first, followed by studies with more complex designs. The chapter will then continue with studies examining exactly what factors during sleep that are related to emotional memory consolidation, such as the contributions of specific sleep stages or other sleep related features. This could for example be examined with correlational studies where different sleep features are correlated with memory performance, or studies in which sleep has been manipulated in some way in order to try to isolate the underlying causal mechanisms.

The description of the different studies will on occasion be quite detailed. This is necessary because researchers have often used quite varying memory paradigms, sleep manipulations and variations of emotionality in the stimulus material. Therefore, one must get quite detailed in order to be able to explain in which ways the studies are comparable to each other and how they differ. Also, several studies have combined many different outcome measures for memory performance and it is important to report all of these in order not to exaggerate the degree of significant findings. Some of the studies have also included groups with various psychiatric conditions such as schizophrenia or ADHD. The results of these groups are beyond the scope of this thesis and will not be discussed here.

The ambition has been to make this literature review as systematic as possible. One way of doing this would be to calculate the effect sizes of the different studies and to present a weighted mean effect size for the different kind of memory tasks and sleep manipulations. Unfortunately, this has however not been possible because of the large variations in experimental designs and in how the results have been reported. This has mostly been a problem in studies with an absence of significant results in which case the exact statistics are not always reported in a sufficient manner in order to calculate the effect size. But even when significant results are found, effect sizes are rarely reported. This makes it problematic to summarize the findings. Reporting effect sizes is something that I would strongly urge researchers to do in future studies. Being able to summarize effect sizes from different studies is especially important in an emerging field like this with such a large variation of the findings.

## Methods to measure memory

In order to not have to repeat basic information about the different paradigms for all the studies, I will start by defining some important concepts regarding different ways of measuring memory. Other, more complex memory tasks, less frequently

used, will be described in more detail when discussing the study it has been used in. It should also be mentioned that many of the studies have used an immediate memory test right after learning as a baseline for the degree of forgetting over the delay interval, in order to assure equal initial learning during encoding between the groups. However, because no studies have reported any differences already at this stage, results from these pre-tests will not be mentioned further.

## **Recognition tasks**

In a recognition memory task, participants are exposed to the stimuli (almost always images in the studies discussed here) that were present during encoding, intermixed with some novel images that were not present during encoding. Participants are then asked to say if the image was present during encoding or not. Memory performance is then normally calculated by subtracting the number of images participants incorrectly claim to have seen before (false alarms) from the numbers of images correctly identified as having been seen before (hits).

## **Remember / Know tasks**

A Remember/know task is similar to recognition tasks but adds a degree of specificity about the degree of remembering. Just like in a recognition task, participants are exposed to the stimuli they saw during encoding, as well as some novel images, but instead of only being asked to say if they have seen the image before or not, they are asked to indicate if they have a clear recollection of seeing it before and can memorize some of the contextual details from when they saw it (*Remember*), or if they just know that they have seen it before but cannot recall in what context (*Know*). These responses are believed to be based on two separate memory systems where a 'Know' response would be a more shallow way of remembering, indicating only a feeling of familiarity, whereas a 'Remember' response would implicate a more elaborate memory where several different features of the original event have been combined into an integrated memory.

## **Other measurements - Cued recall, free recall and forced choice**

In a cued recall task, participants first learn to associate different cues with each other (e.g. word pairs). At the re-test, participants are presented with only one cue and are asked to say which other cue it was presented together with during the encoding.



In a free recall task, participants are not given any cues but are instead asked to freely describe what they remember from the encoding session. This can for example be listing which words that were present in a previously studied word list, or to write down all the details they remember from a previously seen movie or image.

Forced choice means that participants are asked questions about something they have previously seen or read while being forced to choose from different response alternatives. Depending on the structure of these questions, forced choice can sometimes be highly similar to recognition tasks.

## The effect of sleep on emotional memory consolidation

This section will cover studies that have compared emotional and neutral memory consolidation using a sleep and a wake control group. If studies beyond this have reported findings on the contribution of specific sleep stages, or manipulated sleep in some other way that does not allow for a clear sleep-wake comparison, those additional results will be discussed in the next section.

### **Studies using simple memory tasks**

#### *Recognition tasks*

The most frequent manner of measuring memory performance in the literature has been recognition tasks. Most studies that have used recognition as the memory measurement have not found support for sleep being extra beneficial for emotional memories. The absence of interaction effects between sleep/wake and emotion have been reported in DW/NS between-group designs (Baran, Pace-Schott, Ericson, & Spencer, 2012; Bennion, Mickley Steinmetz, Kensinger, & Payne, 2015; Bennion, Payne, & Kensinger, 2016; Jones, Schultz, Adams, Baran, & Spencer, 2016), DW/NS within-subjects designs (Göder et al., 2015; Morgenthaler et al., 2014; Wagner, Kashyap, Diekelmann, & Born, 2007; Wiesner et al., 2015) as well as in a within-subject TSD design (Tempesta, de Gennaro, Natale, & Ferrara, 2015). Most studies mentioned here compared memory for negative and neutral images except for two of the experiments in the Jones et al. (2016) study that used positive images instead of negative ones, the Wagner et al., (2007) study that used images of happy, angry and neutral faces and Tempesta et al. (2015) who used positive, negative and neutral images.

The only studies to clearly have revealed sleep to have a specifically beneficial effect on emotional memories have been conducted in children in DW/NS within-

subject designs using negative and neutral material (Prehn-Kristensen et al., 2009; Prehn-Kristensen et al., 2013). The latter study also had an adult group in which this effect was not present. This could possibly be explained by that the stimulus material was selected in order to be suitable for children, which means that it was less emotional than normally is the case when exposing adults to affective stimuli.

Nishida, Pearsall, Buckner and Walker (2009) found partial support for sleep affecting neutral and negative memories differently in a between-groups nap design. The sleep group showed better memory performance for emotional images that had been learned before sleep compared to emotional images that had been learned after sleep, whereas no such effect was found in the wake group or for the neutral items in any group. In a follow-up experiment, an additional group was added that performed four different encoding sessions, two before sleep and two after sleep and the effect was replicated again with memory for emotional images encoded before sleep being better than for emotional images encoded after sleep. No such effect was evident for the neutral items. The reason that this study can only be categorized as “partial support” is that the sleep groups did not perform better than the wake groups when it came to emotional memory. They just remembered more emotional items learned before the delay interval than emotional memories learned after it, which was not the case in the wake groups. If the recently learned material had not been included and if there would just have been learning and then a memory test after either sleep or wake, which is the case in most other studies described in this chapter, then this study would count as not finding support for a specific effect of sleep on emotional memory. Another study used a highly similar design that also included positive images but did not find the effect of sleep to be larger for emotional stimuli (Cellini, Torre, Stegagno, & Sarlo, 2016).

One remarkable finding is a study that let participants answer forced choice questions about a negative and a neutral text that they had read during another test four years earlier (Wagner et al., 2006, the initial test was a split night design, reported in Wagner, Gais, & Born, 2001 and will be discussed below). Still after such a long delay, there was a tendency towards a main effect of group, and a significant interaction effect. The sleep group remembered the negative text better than the wake group, whereas there was no group difference for the neutral text.

### *Remember/Know tasks*

All studies that have used Remember/Know tasks as the re-test have used positive, negative and neutral images. The only study that have found a specific benefit for sleep on emotional memory is Hu, Stylos-Allan and Walker (2006), who compared high arousing (both positive and negative) images with medium arousing images in a within-subject DW/NS design. In the sleep condition, there was better recognition accuracy for ‘Know’ responses for the arousing images

compared to in the wake condition. No such group difference was found for the neutral images, indicating that sleep does not strengthen neutral memory more than time spent awake. No differences were found for ‘Remember’ judgments, which were affected equally by sleep and wake regardless of arousal.

Sterpenich et al. (2007) found a trend towards an interaction effect of group and emotion for both ‘Know’ and ‘Remember’ responses combined in a between-subjects TSD design with the re-test 72 hours after encoding, in order to allow for additional recovery sleep. Surprisingly, this tendency was driven by better memory in the sleep group for positive and neutral memories whereas sleep deprivation did not impair the memory performance for negative items. This effect was only present for ‘Remember’, and not for ‘Know’ responses. An additional re-test taking place additionally six months later revealed no differences in memory performance between the groups for either response type (Sterpenich et al., 2009). Both these studies revealed differences in the neural responses when re-exposed to the images during the respective re-tests and will be further discussed in the next chapter. Another between-subject TSD design with the re-test one week after encoding, revealed no interaction effects between group and emotion for either response type (Atienza & Cantero, 2008).

In summary, one Remember/Know study has reported sleep to have larger effect on emotional memories. That study was also the one with the shortest delay between learning and re-test, only 12 hours, whereas the other studies had 72 hours or more between encoding and re-test. Two of the studies showed no interaction between sleep and memory, and one actually showed a tendency in the opposite direction, with negative images being less affected by sleep deprivation than neutral ones, even though sleep had the largest effect on the positive items.

### *Free recall tasks*

Free recall has been used as the memory task in four studies. Two of these have found the relevant interaction effect, one found no effect and one found an interaction in the opposite direction. Van Heugten-van der Kloet, Giesbrecht and Merckelbach (2015) found impaired memory performance for a positive video clip, but not for a neutral or a negative one, after a night of TSD in a between-subjects design with the re-test the next morning. Further, this study revealed no signs of TSD increasing either subjective or objective memory fragmentation (as measured by subjective reports and a temporal order test respectively) for any of the movie clips. One study found sleep to have a more beneficial effect on humorous material compared to non-humorous material in a between-subjects DW/NS design, but only in participants who had not seen the stimulus material before and when categorizing which stimuli that were humorous based on participants own ratings (Chambers & Payne, 2014a). Humor and arousal ratings

were highly correlated and therefore it is possible that the humor effect was driven by arousal.

McKeon, Pace-Schott and Spencer (2012) found an effect in the opposite direction in a DW/NS between-subjects design using negative and neutral words. There was no difference for the groups in memory for the negative items but the wake group showed better memory performance for the negative items. This study also examined the effect of sleep on false memory formation. Those results will be further discussed in chapter 4.

Ackermann, Hartmann, Papassotiropoulos, de Quervain and Rasch (2015) found no interaction between sleep and valence in a between-subjects DW/NS design using positive, negative and neutral images.

### *Cued recall*

Only two studies have examined the effect of sleep on emotional memory using cued recall. In a DW/NS study by Lehmann, Seifritz and Rasch (2016), participants first learned to associate neutral words with images that were either negative, neutral or positive. Results revealed no extra benefit for sleep on emotional memories compared to neutral ones. Alger and Payne (2016) found an effect in the unexpected direction, with a benefit of sleep only for neutral, but not for negative items. For relational memory, that is, associating two objects that had been presented together with the same third object, without ever having been presented together, there was no effect of emotion.

## **More complex memory tasks**

This section will focus on studies with more complex designs than simply comparing the differences between neutral and emotional memory performance between a sleep and a wake group. This could for example be to examine if sleep is involved in transforming an emotional memory in a qualitative way.

### *The emotional trade-off paradigm*

The aim of the emotional trade-off paradigm is to examine if memories for emotional details of scenes are strengthened whereas the neutral backgrounds that they are presented on are weakened. By adding sleep to this paradigm, it is possible to see which effect it has, not just on the difference in memory performance between emotional and negative items, but also on memory for the different components within a scene, depending on their emotionality. If sleep strengthens the emotional components of a scene, while not affecting the neutral components, this would imply a role of sleep in “unbinding” the emotional objects from the non-emotional backgrounds they are presented on.

The role of sleep in transforming emotional memory is a highly relevant research question for this thesis and it has important clinical implications. After a negative experience, it is for example very important that contextual details are remembered so that a person understands that something is dangerous in only a very specific context, in combination with certain other stimuli. For example a loud startling sound is certainly a relevant cue of danger in a war zone, but less so on New Year's Eve. For more on the importance of being able to use contextual cues as predictors of fear relevance, see for example the review by Kheirbek, Klemenhagen, Sahay and Hen (2012). However, after learning that something is safe, such as for example after exposure therapy for people suffering from spider phobia, de-contextualization is necessary so that the client does not constrain their safety learning only to the individual spider used during the therapy session, or only to the therapist's office. In this case, de-contextualization would be desired in order to understand that this learning is applicable also in other contexts than the one where the learning took place. Studies of the role of sleep in the generalization of learning will be further discussed in chapters three and five.

Studies of the role of sleep in de-contextualizing memories that have only used neutral material have revealed contrasting findings. Cairney, Durrant, Musgrove and Lewis (2011) found that sleep, compared to wake, removed the beneficial effect of being tested in the same context as encoding took place in. Other studies found no effect of sleep on de-contextualization of learning (Cox, Tijdens, Meeter, Sweegers, & Talamini, 2014; Jurewicz, Cordi, Staudigl, & Rasch, 2016) and van der Helm, Gujar, Nishida and Walker (2011) even found that a nap, compared to wake, improved memory for in which one of two lists different words had been presented.

Payne, Stickgold, Swanberg and Kensinger (2008) developed a paradigm where participants viewed scenes consisting of an object placed on a neutral background image. Half of the objects were negative and the other half were neutral. The re-test was a recognition task where the objects and backgrounds were shown separately. Results revealed improved memory performance in the sleep group only for the negative objects, and not for the neutral objects or for any of the backgrounds. It is notable that the backgrounds that had contained the negative objects were not strengthened by sleep, suggesting that sleep helped to "unbind" the negative objects from their respective backgrounds, meaning that the whole scene containing a negative object was not strengthened in its entirety. These results have been replicated in two DW/NS designs (Payne & Kensinger, 2011; Payne, Chambers, & Kensinger, 2012) as well as in a nap design (Payne et al., 2015). In the Payne et al. (2012) study, sleep was further associated with a decrease in memory for backgrounds of negative objects compared to the backgrounds of neutral objects. This indicates that sleep could be involved in the active forgetting of these backgrounds (the role of sleep in forgetting will be

further discussed in chapter four). This study also included two groups that had a 24 hour interval between encoding and re-test, one that first slept and then spent the rest of the time before the re-test awake, and one that was first awake and then slept. The effects were larger in the 'sleep first' group, indicating that the timing of sleep in relation to learning is important as well.

Cunningham, Chambers and Payne (2014) also found increased memory performance for negative, but not for neutral, objects compared to their backgrounds after sleep, but not after wake (this was the case for participants not expecting a re-test, which is similar to all the other emotional trade-off studies mentioned in this section. The results from the manipulation of re-test expectancy in this experiment will be discussed in chapter 4).

Two DW/NS studies have only provided partial support to these findings. Cunningham, Crowell et al. (2014) found that the sleep group showed better memory performance for the negative objects compared to their backgrounds whereas there was no such effect in the wake group, even though no interaction effect was reported. Chambers and Payne (2014b) used a similar paradigm but with positive objects instead of negative ones, and a remember/know task as the re-test. The study did not reveal the same interaction effects as described above for either 'Remember' or 'Know' answers, indicating no difference in the trade-off effects between the sleep and the wake group. However, despite the lack of an interaction effect, post hoc tests revealed that the sleep group, for 'Remember' responses, remembered positive objects better than the wake group, whereas no such effect was evident for neutral objects or any of the backgrounds. No group differences were found for 'Know' responses.

In a slightly different paradigm, Lewis, Cairney, Manning and Critchley (2011) used a between-subjects DW/NS design in which participants first viewed neutral objects imposed on either a negative or a neutral background. At re-test, participants viewed only the objects as well as some novel objects not seen before and were asked which kinds of contexts that they had been previously been shown on. Results revealed no interaction effect of emotion and group, indicating that sleep strengthened memory for which context the objects had been imposed on regardless of the background's emotion. These effects were also replicated in a second experiment which used a nap design reported in the same article, as well as in another nap design (Cairney, Durrant, Jackson, & Lewis, 2014). In summary, these results would also argue against sleep being involved in unbinding an object from the negative background it has previously been presented in more than it unbinds neutral backgrounds and objects from each other.

In two other studies, participants first viewed video clips containing either motor vehicle accidents or normal traffic. During the re-test, after either normal sleep or TSD, they viewed images from these videos as well as some novel images not

seen before and were asked to indicate if they had seen the images before, and in that case if they came from the clip with the accidents or from the normal traffic clips. Results revealed no effect of TSD on performance in this memory task (Kuriyama, Honma, Yoshiike, & Kim, 2013; Kuriyama, Soshi, & Kim, 2010). These studies also contained measurements of emotional reactivity and will be further discussed in the next chapter .

Another paradigm that has been used in order to examine if sleep unbinds memories from the emotional context in which they were encoded was used by Deliens, Gilson, Schmitz and Peigneux (2013). In this within-subject TSD design, participants were induced with either a sad or a happy mood and then learned associations between neutral word pairs. Before the subsequent cued recall re-test taking place after two additional nights of normal sleep, participants were induced with either the same or with the opposite mood as they had encoded the material in. When only using the participants whose mood had been effectively altered by the mood induction, the results revealed a significant interaction effect of sleep and interference (being tested in the same/different mood as during encoding). The TSD group benefited from being tested in the same mood as they had encoded the words in, whereas no such beneficial effect observed in the sleep group. Thus, after sleep, correct recall is less dependent on reactivating the encoding context. These effects were not replicated by Deliens and Peigneux (2014) who did not find an interaction effect between sleep and interference using a DW/NS design and slightly different mood conditions. This suggests that one night of sleep might not be sufficient for these unbinding effects to occur. The mood manipulation was also slightly weaker which might have made it less important as a contextual cue.

### *Sleep and intrusive memories*

Whereas most studies have examined the voluntary recall of emotional memories, another factor that is very important to gain further knowledge of is how sleep affects intrusive involuntary recall of emotional events. This is a question with high clinical relevance considering that such intrusions are a common feature of post-traumatic stress disorder (PTSD)

Porcheret, Holmes, Goodwin, Foster and Wulff (2015) measured the effect of TSD on intrusive memories of a traumatic film. Participants viewed a film with traumatic content in a between-subjects TSD design. Then, for the following six days, participants were asked to write down the number of intrusive memories related to the traumatic film in a diary. The sleep deprived group reported less intrusive memories during the first two days after having watched the film. After that, the degree of intrusions was quite low for both groups. Explicit memory for the films was not measured in this study. These results were replicated in a subsequent study which also found an effect of sleep resulting in better explicit memory compared to TSD (Porcheret et al., 2016).

Another study showed completely opposite results however, and found that sleep after a traumatic film reduced the degree of intrusive memories during the following week (Kleim, Wysokowsky, Schmid, Seifritz, & Rasch. 2016). The increased degree of intrusions after wake compared to after sleep was found both in a group that was sleep deprived during the first post-encoding night, as well as in a group that viewed the film in the morning and then spent the rest of the day awake. The decrease of intrusions in the sleep group was the largest during the end of the week.

## **Summary**

Several studies have found sleep, as compared to wake, to have a specific benefit on the consolidation on emotional items compared to neutral ones. However, an equally large body of studies have not revealed such an effect. The proportion of null findings becomes even larger if one considers studies only finding partial support, such as the studies where an effect of emotion has only been present in one of several memory tests that has been used. The three studies finding a larger effect of sleep on neutral memories compared to emotional ones further makes it questionable if we can really claim that emotional memories are preferentially benefited by sleep.

Whether a study has found an interaction of sleep and emotion or not does not seem to depend on if it is a within- or a between-subjects design, if the study has included positive images or not, the kind of memory task used, or on the type of sleep study (DW/NS, TSD or naps). The majority of studies finding a significant effect of sleep specifically on emotional memory have used the trade-off paradigm, which has been repeatedly replicated, even though there are exceptions there as well. It is unfortunate that a proper estimation of effect sizes has not been possible but there does not seem to be a systematic variation of number of participants between the studies that have found results and those that have not, with participant numbers normally varying between 15-50 per group or condition.

Almost all studies presented here (and for which arousal and valence ratings have been explicitly reported) have used a stimulus material where the emotional items have differed from the neutral ones in both valence and arousal so that the negative and positive stimuli have been more arousing than the neutral ones. Therefore, it is difficult to say exactly which of these dimensions that sleep has affected in those cases where significant effects have been observed. Importantly though, both the studies that have found a specific effect of sleep on emotional memory and those that have not, have had quite similar stimulus material regarding valence and arousal. The only study that have systematically varied both the valence and the arousal of the stimulus material found no interactions of sleep



with either valence or arousal, which suggests that sleep affects these two components equally (Atienza & Cantero, 2008). In this study however, the neutral stimuli still differed in arousal from the negative and the positive stimuli.

Even though several studies have not found an interaction effect, a main effect of sleep on memory, regardless of emotion, has been reported in most, but not all, of the studies discussed here. The main effects of sleep are quite equally distributed between the studies revealing interaction effects and the ones that do not. A main effect of sleep still indicates that an emotional event will be better remembered after sleep compared to after a similar amount of time spent awake, even if they are not strengthened more than neutral events.

Beyond simply studying the potential strengthening of the emotional memory, the memory transformation associated with the trade-off paradigm is also interesting and must be taken into account when evaluating what impact sleep would have after an emotional experience. Further, the role of sleep in increasing or decreasing intrusive memories must also be considered. These studies have also shown contrasting findings with results in opposite directions (Kleim et al., 2016; Porcheret et al., 2015; Porcheret et al., 2016).

In conclusion, sleep has in several studies been found to result in a specific benefit for emotional memories compared to neutral ones. This effect does however not seem to be so reliable that it is repeatedly replicated every time and a majority of the studies have not found such an interaction, or only partial support for it. Studies examining qualitative changes in memory have also found contrasting results which have not always been replicated.

## Mechanisms during sleep involved in emotional memory consolidation

Whereas the last section discussed differences between sleep and wake groups, this section will discuss differences within the sleep groups. Most of it will concern the contributions of different sleep stages but also various other factors, such as sleep duration and the effect of cortisol will be discussed.

### **The contributions of specific sleep stages**

REM sleep has often been suggested to be an optimal state for emotional memory consolidation. The first studies to examine the role of REM sleep on the consolidation of emotional memories had a clear psychodynamic perspective in

which REM sleep was viewed as synonymous with dreaming. The role of REM sleep/dreaming was suggested to integrate novel stressful experiences with similar experiences from the past. Without REM sleep however, it was hypothesized that people would not be able to deal with threatening experiences, and would therefore need to repress them, which would make them less accessible for retrieval in a memory test. Grieser, Greenberg and Harrison (1972) had participants complete anagrams. This was followed by a night of sleep where the participants were either specifically deprived of REM sleep, or subjected to an equal number of awakenings from NREM-sleep. In a free recall re-test, participants were asked to write down as many of the anagrams as they could remember. In the data analysis, the anagrams were divided for each participant, into the ones that they had successfully come up with a correct solution to and the ones to which they had not. The rationale for this was that the anagrams that they had failed to solve would be experienced as threatening, whereas the solved ones would be experienced as non-threatening. The results revealed that the group subjected to NREM awakenings remembered a higher ratio of the anagrams that they had failed to find a solution to, compared to the REM deprived group, whereas there was no difference in memory performance for the completed items. This was interpreted as that the group allowed to have undisturbed REM sleep had less of a need to repress the threatening unsolved anagrams and were therefore more successful in recalling them.

Adopting a similar perspective, Cartwright and et al. (1975) first had participants rate a list of adjectives based on how well they thought they described them. Then, participants were asked to rate the adjectives based on how much they would like the adjectives to describe them. A “tension score” was created for each word by calculating the distance between how much an adjective described a participant and how much they would like it to describe them. After an immediate re-test followed a delay interval consisting of five different conditions; a full night of undisturbed sleep, a night of total REM deprivation, a night of partial REM deprivation, a night spent awake or a day spent awake which was followed by a second memory test. Results showed that, when comparing words that were not recalled at the immediate re-test with words that were recalled on the second test, the groups with higher amounts of REM sleep specifically showed gains in words with high “tension scores”, making the authors conclude that words associated with a high degree of discomfort become more accessible during REM sleep.

Studies are rarely carried out in this fashion anymore, and it is difficult to say that better memory for anagrams one have failed to solve or for words with high “tension scores”, really is synonymous with less need to repress these items. However, several theories about the role of REM sleep today would predict similar results, albeit for other reasons. The idea that REM sleep is involved in the consolidation of emotional memories is still very often suggested today. As we

will see in the next chapter, the hypothesized role of REM sleep in processing negative experiences has been found in several studies. Further, REM sleep has also been suggested to be involved in “repairing” memories for items that for various reasons could be expected to be forgotten, which will be discussed in chapter four.

During REM sleep, the amygdala and hippocampus are highly active (Hennevin, Hars, Maho, & Bloch, 1995; Maquet et al., 1996). Activity in the hippocampus has been suggested to allow for replay of events that has taken place before sleep, and due to the high activity in the amygdala, these events are suggested to be of a mainly emotional character. Other suggested reasons for the beneficial role of REM sleep in emotional memory consolidation are its elevated levels of acetylcholine (Vazquez & Baghdoyan, 2001), which has been found to be involved in amygdala dependent learning (see Walker & van der Helm, 2009), combined with a low adrenergic tone, and the elevated levels of cortisol during this sleep stage (see Bennion, Payne, & Kensinger, 2015).

## **Correlational studies**

Here, results will be presented from studies examining correlations between different sleep variables and memory consolidation in participants who have had undisturbed sleep that has not been manipulated in any way. Studies that have manipulated sleep in any way (such as for example selective REM deprivation or split night designs) will be presented in the following sections. Once again, this presentation will get quite detailed because of the large variation in findings between studies.

Once again, it would have been preferred to be able to present the weighted average correlations of all studies combined, but unfortunately the exact correlation statistics are not always reported. As we shall further see, there is a large variation of which sleep variables that have been found to co-vary with different memory aspects between the different studies. Only few effects, if any, have been reliably replicated. In order not to have to repeat all the effects that are *not* reported in each study, I urge the reader to read between the lines and also note which correlations that are *not* reported.

Some studies have examined the correlation between memory performance and time spent in a sleep stage during only a half or even a quartile of the night. For the reason of clarity, such correlations will not be mentioned here. The reason for this is that very little is known about how different sleep stages would have different functions depending on when during the night that they occur. Until we have some kind of indication of that, I find the meaning of those results difficult to interpret, and I believe that they greatly increase the risks of false positives.

All the findings reported here are specific to emotional memories. If a sleep variable has also been found to correlate with neutral memory performance, this will be explicitly stated.

I will start by discussing the largest study on the effect of different sleep stages on the consolidation of emotional memory that has been performed so far. Ackermann et al. (2015) tested 929 participants, which is more than twice the number of participants as in all other studies on the topic combined. The study used positive, negative and neutral images in an overnight design with memory performance measured with free recall. Nothing in the PSG; percentage of time spent in either sleep stage, spindle density, theta activity during REM, spindle density, REM density, or REM latency correlated with memory for either neutral or emotional images. Neither did the amount of time spent in any sleep stage (Ackermann, personal communication). When correcting for performance on the immediate re-test performed directly after encoding, there was a significant negative correlation between overnight memory retention (for all items combined regardless of emotionality) and percentage of time spent in REM sleep. This study design is slightly different from most other designs mentioned here. For example, it tested memory through free recall whereas most other studies have tested recognition. Further, the participants did not sleep right after encoding, but instead first spent the afternoon awake. Still, despite these differences, this is the largest study ever carried out on the topic and because it found no significant correlations between any sleep variables and the specific consolidation of emotional memories, the results of the studies presented hereafter should be taken with an enormous grain of salt.

One study showed that the difference in memory for negative items learned before sleep compared to negative items learned after sleep to be correlated with both time and percentage of time spent in REM as well as REM latency (participants remembered more negative items the quicker they entered REM sleep during the nap) and right prefrontal theta activity during REM (Nishida et al., 2009). Other studies have shown a positive correlation between time spent in REM and memory for negative objects (Payne et al., 2012), shorter REM latency to be correlated with memory for positive objects (Chambers & Payne, 2014b), and theta power during REM to be correlated with superior memory performance for negative compared to neutral material (emotional memory bias) in a study pooling children and adults (Prehn-Kristensen et al., 2013). One study found effects in the opposite direction, with time spent in REM sleep being negatively correlated with memory for positive items (Cairney, Durrant, Power, & Lewis, 2015).

Other studies have instead found effects of NREM sleep. Time spent in all NREM stages combined has been found to be positively correlated with memory for happy and angry faces (Wagner et al., 2007). The results reported above by

Nishida et al. (2009) were not replicated by Cellini et al. (2016) who used a similar design, but instead found a positive correlation between TST and memory performance for negative images learned before sleep. The Cairney et al. (2015) study mentioned above also reported a positive correlation between time spent in SWS and memory performance for negative items. Cairney et al. (2014) found time spent in Stage 2 sleep to be correlated with correctly associating negative backgrounds with the objects that they had previously been shown on, as well as a negative correlation between right frontal spindle activity and performance on associating neutral backgrounds with their respective objects. Payne et al. (2015) found that delta power during sleep, as well as time and percentage of time spent in SWS, was positively correlated with memory performance for negative objects. The study by Prehn-Kristensen et al. (2013) mentioned above additionally found slow wave oscillation power during SWS to be positively correlated with emotional memory bias.

Several studies have not reported any significant correlations between any sleep variables and emotional memory performance (Baran et al., 2012; Göder et al., 2015; Jones et al., 2016; Tessier, Lambert, Scherzer, Jemel, & Godbout., 2015).

Regarding intrusive memories, Kleim et al. (2016) found that time spent in stage 2 sleep and parietal fast spindle density was negatively correlated with the amount of intrusive memories during the week after having watched the traumatic movie. REM density, wake after sleep onset (WASO) and time spent in in Stage 1 sleep predicted a higher number of intrusions.

## **Split night designs**

It could of course be possible that a certain sleep architecture and a certain emotional memory bias are co-occurring without there being a causal relation between them. It could for example be so that a certain sleep feature is not the causal mechanism in itself, but instead some form of trait marker of enhanced emotional memory processing. In order to be able to say something about the causality of different sleep stages, sleep has to be manipulated in some manner. Comparing the effect of early and late sleep allows for comparisons of two sleep periods with different sleep architecture (as the early night is dominated by SWS and the late night by REM). Wagner et al. (2001) found that only late, and not early, sleep resulted in improved memory for a negative text compared to a neutral one. No correlations between any sleep variable from the PSG and any memory variable were reported. Groch, Wilhelm, Diekelmann and Born (2013) found a significant interaction of sleep time and emotion, with memory for the emotional items being higher than for the neutral ones only after late sleep. The amount of

REM sleep in the late sleep condition was positively correlated with memory performance for the emotional items.

Groch, Zinke, Wilhelm and Born (2015) had participants view either neutral or negative images. Each image was preceded by a frame, varying in different colors. During the recognition re-test, participants were also asked which color frame that each image had been preceded by during encoding. Results showed a tendency toward an interaction between sleep time and emotion, with negative images being better remembered than neutral ones only after late, but not after early, sleep. There was also a tendency towards better memory for the associated colored frames after early sleep compared to after late sleep. After analyzing the images separately by emotion however, it was revealed that this early sleep effect on memory for color frames was only evident for the neutral pictures, and not for the negative ones. In a second experiment, another early sleep group was tested and information about a reward for correct remembering was added for half of the images during encoding. This revealed that rewarded color frames were better remembered than non-rewarded color frames, and better remembered for neutral items compared to negative ones but that there was no longer an interaction effect of sleep time and emotion. These results were interpreted as that SWS normally enhances only neutral material but with the presence of a reward, this salience cue can “override” the cue of emotionality, making SWS benefit emotional and neutral items equally (studies combining emotion with other cues that predict enhanced memory performance will be further discussed in chapter 4). Interestingly though, this was the case only for the color frames and not for the images themselves. No correlations between REM sleep or SWS and any of the memory measurements were found.

Another split night design did not find any difference in late or early sleep in making memory performance less dependent on being tested in the same mood as had been induced under encoding (Deliens, Neu, & Peigneux, 2013).

## **REM deprivation designs**

Morgenthaler et al. (2014) reported no impairing effect of selective REM deprivation on memory performance compared to a night of normal sleep. Neither was there any interaction with emotion, or any correlation between any sleep and memory variables reported. Wiesner et al. (2015) found selective REM deprivation to lead to impaired memory performance for negative images compared to selective SWS deprivation. There was no difference between the REM deprived group and a wake control group. Time spent in REM sleep was positively correlated with emotional memory bias (memory for negative items

minus memory for neutral items) in the SWS deprived group, whereas this was only a trend in the REM deprived group.

## **Other manipulations of sleep**

### *Sleep duration*

Gilson et al. (2015) tested the effect of a short and a long nap on memory for a sad and a neutral story respectively, in a within-subject design. The long nap had more REM and Stage 2 sleep as well as more REMs, slow spindles and higher REM density compared to the short nap. There was no difference in memory performance between the groups. There was a negative correlation between wake duration as well as WASO and memory performance for the neutral text. In the long nap group, memory performance for the sad story was correlated with REM density. No other sleep related correlations were reported.

### *Pharmacological manipulations of sleep*

Kaestner, Wixted and Mednick (2013) tested the effects of two different sleeping medications compared to placebo on images that systematically varied on both the valence and arousal dimensions in a nap design. Results showed that the medication that increased spindle density (Zolpiderm) also increased memory performance for negative images and for images with high arousal. Compared to placebo however, Zolpiderm also decreased time spent in SWS and there was a tendency towards it also decreasing time spent in REM. The other medication also changed sleep in comparison to placebo, even though it did not alter memory performance. No sleep variables were significantly correlated with memory performance in either the Zolpiderm or in the placebo group. Therefore, it is difficult to draw any exact conclusions about the causal mechanisms in this study.

Three studies have measured the effect of cortisol on sleep-dependent memory consolidation, with quite varying results. Wagner, Degirmenci, Drosopoulos, Perras and Born (2005) found decreased cortisol to result in impaired memory for neutral, but not for negative texts, when tested with free recall. Wilhelm, Wagner and Born (2011) found that pharmacologically increasing cortisol during the delay interval increased memory performance of temporal order for a neutral, but not for a negative, text in the wake group but decreased it in the sleep group. Cortisol did not interact with sleep or emotion when testing memory with free recall. Van Marle, Hermans, Qin, Overeem and Fernandez (2013) found that enhancing cortisol during sleep resulted in better memory for emotional images compared to neutral ones, whereas there was no such difference in the placebo group

The only study so far to examine the effect of reduced norepinephrine on emotional memory consolidation during sleep found no effect on either free recall

or recognition memory for negative compared to neutral texts. Memory for temporal order was however better for negative texts compared to neutral texts after placebo, but not after norepinephrine reduction (Groch et al., 2011).

## Summary

As we have seen, no sleep variable has been found to correlate with emotional memory performance more often than such a correlation has not been found. There are several different findings regarding a role for various REM related variables. Which variables (duration, latency, density or theta power) have however varied between studies, and it has also varied exactly which outcome measure that they have been correlated with. Findings of correlations with NREM sleep variables (Duration of SWS and Stage 2, delta power, spindle activity) has further been almost equally commonly reported. In light of the Ackermann et al. (2015) study, which found no correlations between emotional memory and any of the different sleep variables in a study with more than twice the participants of all other studies combined, we can at this point not say with any certainty that any sleep variable is specifically associated with emotional memory consolidation.

All of the split night designs studies conducted have found an interaction of sleep time and emotion. Only one of them has however found a correlation between time spent in REM and emotional memory. Thus, late sleep seems to be especially beneficial for emotional memories, to a higher degree than early sleep. Still, we do not know what the active mechanism of this is, and it could very well be some other factor unrelated to the increase of REM sleep during the second half of the night. Selective REM deprivation has only been found to be specifically detrimental for emotional memory consolidation in one of two studies.

Only three studies have found a clear correlation between REM sleep duration and emotional memory performance (Nishida et al., 2009; Payne et al., 2012; Wiesner et al., 2015). The Wiesner et al. (2015) study only found this correlation in the SWS-deprived group whereas this was only a trend in the REM-deprived group. Further, Groch et al. (2013) also found such a correlation but only in the late sleep group. It is unclear why these kinds of correlations are often presented group-wise and I believe that it would make more sense to present these correlations for all participants combined. Of course there might be a floor effect in a group that has been REM deprived, but if we believe that REM is the causal mechanism in emotional memory consolidation, then these correlations should hold up anyway. Presenting the correlations separately somehow implies an expectation that REM sleep has a different role in early sleep compared to in late sleep. I am not claiming that this is not possible, late REM sleep could perhaps be more beneficial for emotional memory consolidation than early REM sleep. There could for example



be some kind of interaction with some physiological event driven by circadian rhythms, such as cortisol, that takes place late during the night, but there are at this moment no studies showing such an interaction. Presenting separate correlations for the different sleep groups becomes especially problematic if one thinks that the effect is dose dependent and that every minute spent in REM improves emotional memory consolidation further. It could of course also be the case that after a certain amount of time spent in REM sleep, a certain ceiling effect is reached, where additional REM does not benefit emotional memory consolidation any further. Further, it is possible that below a certain amount of REM, the exact number of minutes is not interesting because it is still not enough to increase memory performance.

To complicate matters further, Morgenthaler et al. (2014) suggested that even if visual signs of REM sleep (that determines how we score the PSG data) are decreased through REM deprivation, other factors believed to be involved in emotional memory consolidation, such as high levels of acetylcholine and theta synchronization between the amygdala and prefrontal cortex, might still persist even though the epochs will not be scored as REM based on visual criteria.

Regarding the role of pharmacologically manipulating sleep, or which sleep stages that are involved in a suggested role for sleep in unbinding memories from the mood they were encoded in, studies have so far been too few or too mixed to draw any certain conclusions.

This chapter has only discussed studies that have examined memory for material that is intrinsically emotional. In the following chapters, we will also discuss memories for material of which the emotionality has been experimentally manipulated (for example by associating it with a reward for successful remembering of it, or pairing it with an electric shock in order to give it a negative association). The next chapter will discuss how sleep and wake are differently involved in altering reactivity to emotional material.

# 3. Sleep and emotional reactivity

This chapter will discuss the experimental literature that has aimed to answer the question if sleeping after an emotional experience will alter emotional reactivity when one is re-exposed to the emotional stimuli again, or to a reminder of it. The focus will be on studies that have exposed participants to some kind of emotional stimulus or situation on two different occasions and manipulated the delay interval between those two exposures so that it has contained either sleep or wake. Studies manipulating sleep in some way will also be discussed. The first section of this chapter will be a review of studies that have examined changes in emotional reactivity to stimuli that are intrinsically emotional, and then go on to discuss changes in affective responses to stimuli that has become emotional through experimental manipulations such as fear conditioning. Another important research question discussed in this chapter, central to the two first studies of this thesis, is how sleep and wake differently affect the generalization of emotional reactivity to other stimuli that have not themselves been associated with an emotional experience.

## Sleep related changes in reactivity to intrinsically emotional stimuli

What will be discussed here are studies that have exposed participants to emotional material before and after a delay interval that has either contained sleep or wake. Some of the studies mentioned here have not used a wake control group but have instead compared two different sleep groups. Most studies have used images as the stimulus material. The studies will be divided into different sections based on which type of outcome measures that have been used. The first section concerns studies using subjective ratings of stimuli, the second section will be about changes in physiological reactivity, and the last section will discuss studies with neural measurements, mostly fMRI. For studies that have used several kinds of measurements, the results of each measurement will be discussed separately in each section. The exception to this is studies that have looked specifically at the generalization of emotional learning. These will be discussed in their entirety in the end of this section.

Walker and van der Helm (2009) suggested that during sleep, and especially during REM sleep, emotional experiences are re-activated in a state devoid of the adrenergic tone that they have come to be associated with during wake. This allows for the processing of these experiences in a state with less physiological arousal, which results in a reduction of the affective tone associated with these memories. The re-activation during sleep would simply make us get used to these memories, and thus react less the next time we encounter the same negative stimuli or a reminder of them. Walker and van der Helm (2009) stated that this makes REM sleep “an optimal biological theatre within which a form of ‘affective therapy’ can be achieved”. As we shall see below though, the empirical support for sleep in general and REM sleep in particular to have this function is quite mixed, with significant findings of sleep both decreasing and increasing emotional reactivity to stimuli during a delay interval.

Before we begin the review of the literature, it is important to note that a change in emotional reactivity to a stimulus from pre- to post-sleep is not necessarily caused by that specific stimulus having been processed during sleep. As mentioned in the introduction, if we find altered reactivity after sleep, this could also be caused by sleep having influenced emotional reactivity in general. Therefore, in order to be able to say that sleep has processed a specific experience, the re-test must include a control for this. This can be done either by presenting novel emotional stimuli to both groups and show that there is no group difference in reactivity to those stimuli, or at least that the differences for the previously shown stimuli remain even when controlling for changes in reactivity to the novel stimuli. Another way of doing this is to control for sleep-dependent changes in mood.

## **Studies using subjective ratings**

Results of the role of sleep in altering emotional reactivity are highly mixed. One study found that negativity ratings of images had decreased more after wake compared to after sleep (Baran et al., 2012). There was a strong tendency towards a significant interaction between group and valence so that negative images were rated as less negative after the delay interval in a DW/NS design, and that this decrease was significantly larger in the wake group than in the sleep group. There was no group difference for valence ratings of neutral images. For arousal ratings, there was no main effect of group and no interaction of group and valence. When subtracting ratings of new images from the ratings of the old images in order to control for general emotional reactivity, no group differences occurred for either valence or arousal. This indicates that the larger decrease in negativity in the wake group was perhaps not specific to the stimuli shown during encoding but could instead be attributed to a general larger decrease in reactivity in the wake group. No sleep variables based on the whole night were correlated with changes in

valence or arousal. Using the same paradigm in older adults, Jones et al. (2016) found no effect of sleep on either valence or arousal ratings. In another study replacing the negative images with positive ones, it was found that arousal ratings of positive images increased after wake but decreased after sleep in young adults. In older adults, the decrease in positivity ratings of positive images was larger after wake compared to after sleep.

Using a similar method in a nap design, with negative and neutral stimuli, Pace-Schott et al. (2011) revealed no significant interaction effect of group and session (before and after the delay interval). However, a close to significant trend showed that the wake group rated all images as less positive when viewing them the second time, whereas there was no such effect in the sleep group. There were no differences in arousal ratings and no differences in ratings of novel images. No correlations were found between changes in subjective ratings and time spent in either REM or SWS. Chambers and Payne (2014a) found that humorous cartoons were rated as more humorous after wake but as less humorous after sleep. There were no novel images being shown during the re-test even though results from two additional control groups revealed no effects of circadian rhythms on ratings of the cartoons.

Another study first found no differences in overnight changes of ratings of either positive, negative or neutral images for either valence or arousal in a TSD design (Tempesta et al., 2015). In an additional analysis however, the participants in the sleep group were post hoc divided into poor or good sleepers depending on their sleep quality. This analysis revealed that the TSD group had stronger decreases in positivity ratings of positive and neutral images compared to the good sleepers. There was also a significantly stronger reduction in ratings of positivity for neutral items in the poor sleepers compared to the good sleepers. However, it is important to remember that sleep quality was not experimentally manipulated, and therefore it is difficult to say if this overnight difference in changes in valence ratings was caused by the difference in sleep quality or by something else, such as general negative affect, which is known to affect both emotional regulation and sleep quality. There were no effects of sleep quality on changes in arousal ratings.

Two studies have measured changes in emotional reactivity using split night designs. Wagner, Fischer and Born (2002) had participants view negative images before and after early or late sleep. Results revealed that after early sleep, old images were rated as more positive than new ones, whereas this effect was the reverse after late sleep, where old images were rated as more negative than new ones. Late sleep also resulted in higher negativity ratings compared to late wakefulness. The difference in arousal ratings between old and new images was higher after sleep than after wake, even though there was no interaction with sleep timing. PSG was performed but no correlations between sleep stages and changes

in emotional reactivity were reported. An additional control group that slept all night showed similar results as the late sleep group, with increased negativity ratings. Also using a split night design, Groch et al. (2013) only measured emotional ratings post-sleep but included images not seen before as a comparison. No differences were found between the two sleep conditions in differences in ratings of old and novel images.

Using selective REM deprivation, Lara-Carrasco, Nielsen, Solomonova, Levrier and Popova (2009) found that the between-session decrease in arousal ratings was larger in the group in which the amount of REM sleep had been reduced. There were no group differences in valence. There were no correlations between percentage of REM sleep and overnight changes in arousal or valence ratings. The morning re-test did not include any novel images, and therefore it cannot be concluded if this increased arousal in the group with less REM sleep was specific for the images seen before or represents a general decrease in reactivity. Contrary to this, Rosales-Lagarde et al. (2012) asked participants to classify images as threatening or non-threatening and then calculated the percentage of images that had been classified as threatening. Selective REM deprivation after the first rating session led to a larger increase in the percentage of images that were rated as threatening during the second rating session. No images not seen before were used during the re-test.

Also using a REM deprivation design, Wiesner et al. (2015) found no group differences in overnight changes of either valence or arousal ratings. When analyzing valence ratings to the novel images however, results revealed that the REM deprived group rated new negative images as less negative than the SWS deprived group and the wake group. This could suggest that REM sleep, beyond its potential role in processing emotional experiences during the night, is also involved in configuring baseline reactivity and perhaps making mood more changeable during the next day. Another study with a finding implicating such a function for REM sleep is Gilson et al. (2015), who found that after a long nap (which among other differences also contained more REM sleep than the short nap comparison), participants' mood became more negative by hearing a sad story a second time, even though there were no group differences in any other measures of reactivity, or in the change in emotional reactivity from hearing the stories from pre- to post-nap. The authors argued that this could indicate that REM sleep increases general emotional reactivity. Another study did not find any sleep variable to be involved in the overnight altering of reactivity to a negative movie, except for a trend showing that the amount of REM sleep during the fourth quarter of the night was associated with a smaller decrease of self-reported arousal (Werner et al., 2015). Two studies have however revealed somewhat contrary findings to this. Greenberg, Pillard and Pearlman (1972) found REM deprivation, compared to a night of NREM awakenings or normal sleep, to result in a larger

increase of anxious mood after watching a distressing film clip again for a second time after sleep. Groch et al. (2013) found the percentage of time spent in REM sleep to be correlated with rating negative images as less negative.

Another study indicating that REM sleep is involved in re-setting baseline emotional reactivity is Gujar, McDonald, Nishida and Walker (2011) who had participants view pictures of faces that were either sad, angry, happy or fearful while rating how strongly each face was expressing the respective emotion. Results revealed that participants in the wake group significantly increased their ratings of anger between sessions whereas no change was observed in the nap group. The wake group also significantly increased their ratings of fear whereas the nap group significantly lowered theirs. The nap group further significantly increased the ratings of happiness and there was a trend towards significance for this difference being higher in the nap group than in the wake group. There were no group differences for ratings of sad faces. The nap group was then additionally divided into those who had entered REM sleep during the nap and those who had not. Comparing the two different nap groups revealed that the increase in ratings of happiness and the decrease of ratings of fear were only significant in the group who had entered REM sleep. Time spent in REM within the REM group did not correlate with changes in ratings for any of the emotions. No novel images were included during the re-test.

Van der Helm, Yao et al. (2011) found that the percentage of images in a stimulus set that was rated as highly emotionally intensive decreased after sleep, but not after wake, whereas there were no group differences for novel images. The decrease in the percentage of stimuli classified as the most emotionally intense was negatively correlated with frontal gamma activity during REM sleep, which was used as a marker of adrenergic activity. This is a very interesting finding because it might help explain the contrasting findings of the role of REM sleep presented above. Perhaps REM sleep in itself cannot be said to be a state that decreases emotional reactivity. If reactivity will decrease or increase could instead depend on other factors present during this stage. If emotional memories are activated more during REM than during other sleep stages or wake (which we do not know with certainty yet, this is just hypothesized because of various indicators of this), the change in reactivity to them is perhaps dependent on the quality of REM, such as for example how much adrenergic tone that is present during these re-activations. This is especially relevant considering a study that showed that higher sympathetic activity during REM after a traumatic experience predicted the later development of PTSD (Mellman, Knorr, Pigeon, Leiter, & Akay, 2004). This heightened activity might also be an indicator of a failure to adaptively process the experience during REM.

Kleim et al. (2014) examined if a nap would increase the effects of exposure therapy in individuals suffering from spider phobia. Results revealed that a nap decreased subjective distress when approaching a caged tarantula spider as well as the severity of catastrophic spider-related cognitions. These reductions in self-reported fear and catastrophic cognition severity were correlated with percentage of time spent in Stage 2 sleep. There were no such correlations with REM or SWS. One reason for the lack of a correlation with REM could have been that the average time spent in this stage was very short, just 1.5 minutes.

In another study examining the effect of a nap on the consolidation of exposure therapy to spiders, Rihm, Sollberger, Soravia and Rasch (2016) first had participants undergo an exposure session. Then, participants were asked to verbalize their subjectively experienced therapy success. Half of the participants did this in the presence of a certain odor. During the nap, half of the participants in the sleep group had this odor presented to them again during sleep stages 2 and 3. Neither sleep nor odor presence influenced the ability to approach a living spider or arousal ratings of images of spiders. Neither did it affect subjective ratings of spider phobia. Cuing the odor during sleep did however result in increased spindle activity.

In the previously mentioned study on the effect of sleep deprivation on intrusions, Porcheret et al. (2015) found that sleep deprivation after watching a traumatic film resulted in less (subclinical) PTSD symptoms the day after, compared to the group that slept as normal. As mentioned in the previous chapter, the TSD group had a lower number of intrusions during the first two days, but there was no difference in the degree of distress related to these intrusions. Kleim et al. (2016) however, reported that participants who slept after watching the traumatic film clip rated their memories of it to be less distressing.

Another study that should be mentioned although it was not experimental examined the role of REM sleep in the overnight resolution of emotional distress (Wassing et al., 2016). The hypothesis was that if sleep is involved in decreasing emotional distress, then disturbed sleep would hinder this overnight decrease. The aim of this study was to examine if habitually disturbed REM sleep was associated with reports of feelings of shame taking longer time to dissipate, which would indicate a role for REM sleep in decreasing this kind of feelings. To be able to test this in a large sample, they first validated a proxy measurement of disturbed REM sleep (measured by arousals from REM and REM density) in a smaller sample, using PSG. They found that disturbed REM sleep was correlated with the degree of self-reported thought-like mentation during the night. Thought-like mentation during the night was then used as a proxy variable in a larger sample with 1199 participants for testing if reports of slower resolution of feelings of shame was related to disturbed REM sleep. The results revealed that thought-like mentation

was correlated with more reports of shame lasting for a long time, but not with reports of shame lasting for a short time (shorter than a day, which the authors reasoned means that it is emotional distress of a kind that does not need sleep to be resolved, and thus, disturbed sleep would have no impact on it). A further analysis revealed that the link between insomnia severity and hyperarousal could be explained by reports of long lasting distress (which in turn was associated with thought-like mentation during the night). These results suggest that the link between insomnia and negative affect is caused by difficulties in overnight resolution of emotional distress, which is caused by (or at least co-occurs with) disturbed REM sleep. Before drawing too grand conclusions from this study, it should be noted that the proxy variables for disturbed REM - REM fragmentation and REM density, was only correlated with thought-like mentation during the night (the proxy variable in the larger sample) to .57 and .46 respectively, meaning there is plenty of variance in thought-like mentation that cannot be explained by this variable. Further, it is of course also possible that the affect during the day preceding day influences the degree of subsequent REM fragmentation. Still, the concept of disturbed REM being involved in the inability to resolve emotional issues during the night is an interesting approach that merit future research.

#### *Summary – subjective ratings*

Studies using subjective ratings have found highly contrasting results with findings showing sleep to both increase and to decrease between-session emotional reactivity. Neither have any conclusive results been found regarding the specific role of REM sleep. REM deprivation designs have been shown to both increase and decrease emotional reactivity and no study has found a clear correlation with REM duration when measured throughout the entire sleep interval. Regarding the results of the van der Helm, Yao et al. (2011) study, it might also be the case that the duration of REM sleep in itself is not the relevant variable to study. Instead the important issue may be the quality of the REM sleep (in that case, the level of adrenergic activity). In summary, we simply do not know yet if sleep will increase or decrease subjective emotional reactivity.

#### **Studies using physiological outcome measurements**

In the previously mentioned study by Pace-Schott et al. (2011), skin conductance responses (SCRs) to negative images decreased after sleep, but not after wake. There was no group difference for the novel images used as control stimuli. Similar results were found for corrugator EMG (a measurement of facial muscle activity related to frowning, which is associated with subjective ratings of valence) for both neutral and negative stimuli. For this measurement, there was also a trend towards an increase in responsivity to the novel neutral images in the wake group



which was not present in the sleep group. However, results also revealed a larger between-session decrease in reactivity in the wake group when measured by heart rate deceleration (HRD). For the wake group, there was also a trend towards higher reactivity to novel neutral images. The between-session decrease in cEMG responses was only present for the group that entered SWS during the nap. Decreases in SCRs were larger in participants who did not enter REM sleep. There were however no significant correlations between any between-session changes and time spent in any sleep stage. This makes it more probable that achieving SWS and REM is markers of some other traits independently associated with altered between-session habituation, rather than being the causal mechanisms.

Cunningham, Crowell et al. (2014) found a significant interaction between sleep and session where HRD and SCRs to both neutral and negative objects in the emotional trade-off paradigm was reduced after sleep whereas there was no such effect after wake. There were also some novel objects during re-exposure, but the article contains no reports of physiological arousal related to those images, once again making it difficult to say if this decrease in reactivity was specific to the images having been processed during sleep, or the result of a general decrease. No correlations with any sleep stages were reported.

A long, compared to a short nap, has been found to result in higher skin conductance levels (SCLs) while listening to a sad story again for a second time after sleep, whereas there was no difference for the neutral story (Gilson et al., 2015). There were no correlations between time spent in REM or SWS and changes in physiological reactivity.

Werner et al. (2015) found an overnight increase in SCLs when watching short neutral and negative clips from a distressing movie seen the night before. The increase was stronger for the neutral movies. There was no wake control group so it is not possible to say if this increase was specific to sleep. Correlations with REM sleep were unfortunately reported only for the third and fourth quarter of the night separately and revealed that more time in REM during the fourth quartile of the night correlated with a stronger SCL increase, whereas more time in REM in the third quarter of the night was negatively correlated with cEMG responses to the negative scenes of the aversive film. Once again it must be stressed that there was no correlation with total REM duration or any other REM measurements. There were similar effects for the neutral clips from the aversive film but not for neutral clips from the neutral film.

One study examined if altered levels of norepinephrine contributed to sleep dependent changes of emotional reactivity. Groch et al. (2011) measured participants' heart rate responses while they viewed negative and neutral pictures before and after three hours of early sleep with either medication that blocked norepinephrine or placebo. The results revealed no difference in changes of heart

rate responses between the norepinephrine and the placebo groups, thus finding no support for that changed levels norepinephrine would be the active component determining the degree of altered emotional reactivity during sleep, at least not during early sleep.

### *Summary – physiological measurements*

Only one study has found clear decreases in physiological reactivity after sleep compared to after wake. Considering the lack of reports of reactivity to the novel stimuli however, it is not possible to say if this was the result of a general decrease in reactivity, or if it was specific to the stimuli seen before. Another study found larger decreases of SCRs and cEMG, but smaller decreases in HRD in response to negative stimuli in the sleep group, as compared to the wake group. No sleep stages have been clearly found to be involved in the overnight altering of physiological reactivity (but see the section below about the role of sleep in processing of fear conditioning for more findings on this topic).

## **Generalization of emotional learning**

This section is about studies examining if sleep has a role in generalizing emotional reactivity from a stimulus to other stimuli that are somehow related to it. Because this is the body of studies that has the strongest relevance for the first two studies in this thesis, they will be described together here in quite a detailed manner. Studies that have examined generalization of emotional responses elicited by fear conditioning will however be discussed in the next section, even though they are highly relevant for this topic as well.

In a study aiming to examine if sleep could be a more beneficial state than wake in generalizing the beneficial effects of exposure therapy for treating spider phobia, Pace-Schott, Verga, Bennett and Spencer (2012) had participants view different video clips of the same spider and rate how disgusting, fearful and unpleasant they found the spider to be. These scores were then summed together into a composite negative rating score. Then, after sleep or wake in a DW/NS design, participants viewed six videos of the same spider as well as six videos of a novel spider, not seen before. This allowed for examination of both if fear had decreased to the particular spider that was used during the first exposure session, as well as if this potential decrease had been generalized also to the novel spider. At the re-test, both groups initially showed more negative ratings of the novel spider compared to the old one, but in the wake group, the novel spider was rated more negatively than the old spider had been the first time it was seen during session one. The wake group also rated the old spider more negatively during session two than at the end of the first session. In the sleep group there has however a retention of the

decreased negativity ratings to the spider that been used during the exposure therapy. There was also a decrease in negativity ratings of the novel spider, as compared to the wake group. This can be interpreted as that sleep to a greater degree both transfers the negativity ratings of the old spider to the novel spider, as well as consolidates the decreased negativity achieved during the first session. Results for the SCRs showed less retention of the decreased responses to the old spider in the wake group. This was the case for both the reactions to the videos in themselves, as well as for reactions to a sudden burst of sound played during the videos. The wake group further showed higher responses to the novel spider than they did to the old spider the first time they saw it during session one, indicating a sensitization. The sleep group showed lower heart rate acceleration to the novel spider than they did to the old spider the first time they saw it during session one, indicating decreased sensitivity. No such decrease was evident in the wake group. This kind of generalization is very important because exposure therapy is of quite little use if fear only decreases to one particular spider. Instead, for therapy to be successful, the decrease in reactivity must be generalized to other spiders. Abstraction of the emotional gist during sleep, as suggested by Payne et al. (2008) can become very useful if it helps emotional learning to be extended to other situations than the one where it was initially learned.

Sleep has also been found to be involved in generalizing negative emotional experiences. Kuriyama et al. (2010) first had participants view film clips of motor vehicle accidents as well as of normal traffic situations. During the re-test, participants viewed images from these clips and were asked to rate the degree of fear they associated with these images. The TSD group and the sleep group did not show any differences for the images during a re-test the first day after encoding. However, on a re-test that took place three days after encoding, the TSD group showed significantly lower subjective fear responses while viewing images from the film clips that contained normal traffic situations. The sleep group did however not generalize their responses to novel images that had not been present during encoding, arguing for the specificity of this effect to stimuli that were present during encoding. In the TSD group, there were also larger SCRs to images incorrectly identified as stemming from the aversive films, compared to stimuli correctly identified as coming from the aversive film. No such differences were found in the normal sleep group. This group difference was however only found three days, and not at another re-test nine days, after initial encoding. Contrary to this, Porcheret et al. (2016) found that TSD, compared to normal sleep, resulted in increased generalization of subjective fear ratings to images that did not originate from the traumatic films but that had been present during encoding.

Another study used a similar design but also asked participants to either try to remember or to suppress what they saw in the videos during encoding (Kuriyama et al., 2013). The results showed lower SCRs to all kinds of images in the sleep

deprived group that had received remember instructions. For participants that had tried to suppress the information during encoding, there was a tendency towards a significant effect in the opposite direction, with the TSD group, as compared to the sleep group, showing increased SCRs to all kind of images. There was no interaction effect of sleep and image type, showing no differences in the generalization of physiological responses.

No group differences were found in a by Lehmann et al. (2016). In this study, participants first rated neutral words for arousal. Each word was then paired with an image that was either negative, positive or neutral. Later, after sleep or wake, words were rated for arousal once again which showed that the word that had been associated with either a positive or a negative image were now rated as more arousing than the words that had been associated with a neutral image. However, these differences did not vary depending on sleep or wake, which indicates that sleep did not increase the degree to which the emotion of the image was “transferred” to the neutral words associated with them.

Examining if targeted reactivation during sleep could enhance generalization, Groch et al. (2016) first let participants view images that were each combined with a word that created either a positive or a negative interpretation of the image. During sleep, half of these words were acoustically presented to the participants. The next morning, participants watched novel images that were similar to the ones seen the day before. Each image was presented twice, once together with a positive word, and once together with a negative word. Participants were asked to rate how well the word corresponded with the image. For images that were similar to images that had been presented together with a positive word during encoding, the positive words were rated as having a better fit to it for cued, but not for uncued, words. Similarly, for images that were similar to images that had been presented together with a negative word during encoding, the positive words were rated as having a worse correspondence to it for cued, but not for un-cued, words. Correspondence ratings of negative words were not affected by cuing. These effects were present both in adults and adolescents and show that the generalization of interpretations of certain situations can be enhanced by cuing during sleep. There was no wake control group which does not allow us to say if this generalization can be enhanced in an equivalent manner during wake or if these effects are specific to sleep.

## **Brain imaging studies**

This section will present studies that have used brain imaging in order to examine what happens with an emotional memory during sleep. The studies presented here vary considerably in what task participants have been performing during the re-test

and in which contrasts that have been used. Therefore, the results can be quite difficult to compare to each other and the large variation of results could perhaps be explained by these differences. In some of the studies, the second viewing of the images have been a memory test, whereas some just asked participants to passively view the images or to rate them for emotionality. Studies on the effect of sleep on fear conditioning and extinction will be presented in the next section, even if they contained neural measurements. The focus will be on differences in activity of the amygdala, because it is an area established to be involved in emotional processing and it is also one of the regions that is mentioned in most studies, making findings involving this the most fruitful to compare with each other.

### *Studies examining emotional reactivity only*

Van der Helm, Yao et al. (2011) found a decrease in activity in the amygdala after sleep, but an increase in activity after wake when watching negative images. This decrease in the sleep group was also associated with an increase in functional connectivity between the amygdala and the vmPFC, whereas the wake group instead showed reduced functional connectivity between these two regions. In the sleep group, the decrease in amygdala reactivity was negatively correlated with gamma activity during REM. There were no differences in amygdala reactivity to the novel images, indicating that these effects were specific to the stimuli that had been viewed before. Further, as described in a previous section, this decrease in amygdala reactivity was also accompanied by a decrease in subjective ratings, even though no correlations between these two measurements were reported.

Rosales-Lagarde et al. (2012) found that in a REM deprived group, there was very little difference between when viewing threatening and non-threatening images for the first and for the second time, whereas for a group subjected to NREM awakenings, there was decreased activation in the right inferior and the middle frontal gyri, the right fusiform gyrus, left superior frontal gyrus, inferior parietal lobule, posterior middle temporal gyrus and the parahippocampal gyrus. Contrasting threatening and non-threatening images revealed increased activity for threatening images in the left middle occipital gyrus after REM deprivation. REM duration was negatively correlated with activity in the left middle temporal gyrus and positively correlated activity in with the right putamen. For the contrast between threatening and non-threatening images, there was a negative correlation between REM sleep and activity in the cingulate gyrus, the right precuneus, left inferior frontal gyrus and left cerebellum. The authors interpreted the lack of a decrease in activity in the cingulate gyrus in the REM deprived group as representing a higher need for top down control. This study thus revealed several differences in the changes of reactivity depending on which kind of sleep

participants had been deprived of, but it is unclear exactly how these changes are involved in emotional reactivity.

### *Studies including memory tasks*

Sterpenich et al. (2007) found larger responses in the amygdala in a group that had been sleep deprived the night after encoding when viewing the negative pictures again at a re-test taking place three days later. The left hippocampus was more connected to the middle frontal gyrus, the right hippocampus and the amygdala in the sleep group, and more so for positive items compared to neutral ones. For the sleep deprived group, the amygdala was more connected to the orbitofrontal cortex, the striate and extrastriate cortices, the superior temporal gyrus and the posterior insula. This reduced amygdala activity in the sleep group have been cited as to support that sleep right after encoding decreases the affective tone associated with an emotional memory. Remarkably, different neural responses were observed between these two groups still 6 months later as reported by Sterpenich et al. (2009). At this time point, for correctly remembered negative images, the sleep group had higher activity in the vmPFC and in the amygdala, among other regions. Similar contrasts for functional connectivity showed larger connectivity between the amygdala and the vmPFC, and between the amygdala and the fusiform gyrus in the sleep group. The results for positive images were similar but weaker. The larger amygdala activity would argue against that sleep after learning results in decreased affective tone of the images. However, subjective ratings of the images were not collected and because of that it is difficult to say what the change in amygdala reactivity actually represents.

Payne and Kensinger (2011) contrasted hits for negative objects compared to misses for negative objects, in order to examine which regions of the brain that correspond with successful recall of emotional memory, in a DW/NS design. The results revealed that after sleep, successful recall was related to activity in the amygdala, hippocampus and the vmPFC whereas after wake, successful recall recruited a much larger and widespread network. Analyses of functional connectivity revealed that there were larger influences of the amygdala on the hippocampus, of the amygdala on the vmPFC, of the hippocampus on the fusiform gyrus and of the fusiform gyrus on the amygdala in the sleep group. None of these differences were significant for neutral items, suggesting a specific effect of sleep on negative items.

Lewis et al. (2011) found that when participants correctly identified a neutral object as previously having been placed on a negative background, there was larger activity in the amygdala and the vmPFC in the sleep group compared to in the wake group.

In an event-related potentials (ERP) study, Groch et al. (2013) found no differences in late positive potentials between 500 – 800 ms after stimulus onset, a

measurement that has previously been associated with arousal ratings, to negative images after early sleep compared to after late sleep.

Bennion, Mickley Steinmetz et al. (2015) examined the interaction of cortisol levels and viewing time during encoding on sleep dependent consolidation of negative items. Results revealed that in the sleep group, there was a correlation between looking time at negative objects during encoding and activity in the vmPFC and the amygdala during the re-test, whereas no such relation was found in the wake group. In the wake group, there were instead correlations between looking time during encoding and activity in the hippocampus, inferior frontal gyrus and middle frontal gyrus. Another study found that medically elevated cortisol levels during sleep resulted in a decrease of activity in the amygdala and anterior hippocampus compared to placebo (van Marle et al., 2013).

### *Summary – brain imaging studies*

As we see here, the results of sleep compared to wake regarding the neural responses to emotional memories are inconclusive. Sleep has been shown to result in both lower and higher activity in the amygdala, as well as in various differences in functional connectivity. Sleep does however seem to change the neural trace of emotional memories, which suggests that some form of transformation of these memories take place during sleep, even though the exact effects seem to vary considerably depending on which paradigms and contrasts that have been used. As evident by the studies of Sterpenich et al. (2007, 2009), future activity in the amygdala when encoding is followed by sleep could also vary depending on the length of time between encoding and the re-test.

## Fear conditioning paradigms

Fear conditioning is a paradigm that has frequently been applied in sleep studies. In these paradigms, a neutral stimulus of some kind (e.g. an image, a smell or a sound) is paired with an aversive unconditioned stimulus (UCS), most often an electric shock. After repeated exposure of this pairing, the previously neutral image will be so associated with the aversive UCS that it will start to elicit a fear response all by itself, that is, even in the absence of the UCS (making it a CS+). Fear conditioning paradigms often also include another neutral stimulus that is never paired with the UCS (a CS-). The degree of fear learning is defined as the difference in responding to the CS+ compared to the CS-.

Fear responses to the CS+ can be diminished by repeatedly showing it in the absence of the UCS. This eventually creates a new safety memory where the CS+ is no longer associated with danger. This process is called fear extinction.

Fear conditioning paradigms are useful because they can be used in both human and animal experiments, which makes results between the two research areas more easily comparable. Furthermore, it is more similar to the traumatic experiences that researchers often wish to be able say something about when studying how sleep affects emotional memories. While it is obviously not as aversive as a real traumatic experience, it allows us, at least to some degree, to create a laboratory model of a traumatic experience where we can study what happens when one is exposed to “trauma relevant” stimuli again after a delay interval spent either asleep or awake. This type of studies often feature three different kinds of stimuli; one that undergoes fear conditioning but not fear extinction (the CS+), one that undergoes fear conditioning but also fear extinction (the CS+E) and one that is not fear conditioned (the CS-). Some studies have also used an additional CS- that is included during the extinction session as well, in order to make sure that there is a non-reinforced stimulus that has been viewed as many times as the CS+E. This will be referred to as a CS-E. By including these different stimuli, it is possible to examine how sleep affects both the learning and the extinction of fear.

In this section I will first review the literature on the effect of sleep on fear conditioning and extinction in humans, and then go on to discuss studies in animals. For a review on the effect of sleep on fear learning and extinction, in both humans and animals, and its underlying neural circuitry, see Pace-Schott et al., (2015a).

## The effect of sleep on fear conditioning and fear extinction in humans

In a TSD design with the re-test taking place after an additional recovery night, Menz et al. (2013) found that the sleep group showed a larger difference between the CS+ and the CS- as measured by SCRs and amygdala activity. This was driven by higher responses to the CS- in the wake group, which indicates that sleep in this study reduced fear to the stimulus not worth fearing, but retained it for the stimulus that merited a fear response. This difference was also correlated with the REM duration for the SCRs, but not for the amygdala activation. This paradigm also included a CS+E and a CS+U. There were no group differences in responses to these two stimuli when they were presented during the re-test, indicating that sleep did not lead to increased retention of extinction compared to sleep deprivation. In another study using the same stimuli but instead comparing early and late sleep with late and early wake respectively (the early wake group being the same as in the previous study and thus spent the whole night awake), Menz, Rihm and Büchel (2016) found no differences for the retention of either fear



learning or extinction when comparing early wake to early sleep. The late sleep group however showed larger differentiation between the CS+ and the CS- compared to the late wake group for both subjective shock expectancy and SCRs. This was driven both by a decrease of fear for the CS+ and an increase for the CS- compared to the last trials during conditioning in the late wake group. No such changes were found in the late sleep group. Late sleep compared to late wake also resulted in better extinction recall where the difference between the CS+E and the CS-E was higher in the late wake group for both SCRs and shock expectancy ratings. The late wake group also showed larger differences in responses in the amygdala and in the vmPFC between the CS+E and the CS-E compared to the late sleep group. There were no correlations between any differences in fear or extinction retention and duration of time spent in any sleep stage (Menz, personal communication).

In a study without a wake control group, REM duration during the night between fear learning and the re-test was found to be correlated with the difference in EMG startle responses between the CS+ and the CS-, so that more REM sleep increased this difference (Marshall, Acheson, Risbrough, Straus, & Drummond, 2014). REM sleep did not affect the degree of retention of responses to either the CS+ or the CS- in themselves, so it is not possible to infer that this differentiation was driven by changes in either fear or safety memory separately.

Pace-Schott et al. (2009), using a DW/NS design, found that the wake group had higher responses to the CS+U compared to the CS+E, which was not the case in the sleep group. The authors interpreted this result as sleep generalizing the decrease in fear responses to the CS+E to the CS+U, even though the latter stimulus had not undergone extinction. A subsequent study however found that these results were perhaps caused by differences in the time of testing rather than by sleep (Pace-Schott et al., 2013). Another study however showed that the percentage of time spent in REM sleep was significantly negatively correlated with responses to the CS+E during the re-test, indicating REM sleep to be involved in extinction retention (Pace-Schott et al., 2014). However, Ai et al. (2015) found no group differences in retention of extinction learning in a nap design.

Spoormaker et al. (2010) used a design with fear conditioning followed by extinction with a nap group that was later divided into two groups depending on if they had entered REM sleep during the nap or not. At the re-test, the Non-REM group showed higher SCRs to the CS+E than to the CS-, compared to the REM group, during the last block of trials. This could indicate a role for REM sleep in extinction retention, even if it was just present during the end of the re-test and could thus also indicate REM to be involved in adjusting subsequent changeability in reactivity. The Non-REM group also showed higher SCRs to the CS+U

compared to the CS- than the REM group in the second of the five trial blocks during the re-test, which is opposite to the Menz et al. (2013) study, which found REM to increase the difference between these two stimuli. The fMRI results revealed that the REM group showed higher activation in the vmPFC to the CS+E compared to the CS-, whereas no such difference was evident in the Non-REM group. This indicates a role for REM in downregulating responses to stimuli that should no longer merit a fear response. Another interesting aspect of this study was that during the fear conditioning, SCRs to just the electric shock itself was measured. The results revealed that those who would later have REM sleep had lower reactions to the shocks already at this stage. There were no differences in fear acquisition or extinction learning in either SCRs or neural activation, but this still means that perhaps the presence of REM sleep during the nap was a marker of emotional reactivity before the nap.

Using a similar design but instead using REM deprivation in order to experimentally manipulate the presence of REM sleep between the groups, Spormaker et al. (2012) had participants undergo fear learning on day 1, extinction learning on day 2 and the re-test on day 3. The REM deprivation took place during the night between extinction and the re-test. Fear responses were measured both when the stimuli appeared on the screen (stimulus onset), in order to measure responses to the CS in itself, but also when it disappeared from the screen (stimulus offset), which is when the electric shock was delivered during conditioning, in order to measure the degree to which participants expected a shock at that moment. Results revealed that during the re-test, there was a tendency towards higher responses to the CS+E at onset in the REM deprived group, indicating impaired extinction retention. There was also a tendency towards increased responses to the CS- at offset in the REM deprived group, but only during the last trial block. The fMRI results revealed group differences at stimulus offset, compared to onset, which indicated that REM deprivation leads to difficulties in reducing shock expectancy to stimuli that have undergone fear extinction and thus should no longer merit a fear response.

A subsequent article (Spormaker, Gvozdanovic, Sämann, & Czisch, 2014) reported the results of the fMRI during fear learning and fear extinction, as well as PSG data from the night between learning and extinction training. The analysis of the PSG data revealed several interesting results that further argue that sleep might be a trait marker of the ability to successfully learn that something is no longer dangerous, or that REM prepares us for subsequent learning the next day. REM duration the night after fear learning was positively correlated with activity in the left and the right vmPFC to the CS+E during fear extinction. There was also a trend towards a significant correlation between Stage 3 sleep duration and activity in the right vmPFC. Activity in the left vmPFC was negatively correlated with the time it took to fall asleep. There was also negative correlation between REM

duration with SCRs to the CS+E. The latter was also correlated with REM latency. The correlation between activity in the left vmPFC during fear conditioning and SCRs during extinction was no longer significant when controlling REM duration during the night between those two sessions. The correlation between left vmPFC activity and REM sleep amount was however still significant when controlling for SCRs during extinction. This suggests a role for REM sleep in increasing the ability to acquire subsequent safety learning, and to activate the vmPFC during extinction. Similar correlations between vmPFC activity during conditioning and less SCRs during extinction was found for the CS+U as well, even though no sleep correlations were reported for this stimulus. Correlations between vmPFC activity and SCRs were not significant for the CS-. There was a trend towards a correlation between REM duration and the decrease in SCRs to CS+E, but not to the CS+U or the CS-.

Similar results, arguing for a role of sleep before fear extinction, were reported by Straus, Acheson, Risbrough and Drummond (2016). Participants underwent fear learning on day one, extinction learning 24 hours later and then a re-test additionally 24 hours later. Fear responses were measured with EMG startle responses. There were three different groups, one that slept as normal on both nights, one that was subjected to TSD the night after fear learning and slept as normal after extinction and a third group that slept as normal after fear learning and were then subjected to total sleep deprivation after extinction. The group that was sleep deprived after conditioning did not show impaired extinction learning. However, during the re-test, they showed increased fear responses during the first half of the session compared to the normal sleep group. The normal sleep group did not differ from the group that was sleep deprived the night after extinction. REM sleep consolidation (a composite variable consisting of REM percentage, REM sleep latency and REM sleep efficiency), the night after extinction learning, was negatively correlated with responses to the CS+ during the first half of the re-test. There was also a tendency towards REM duration being positively correlated with extinction recall (Drummond, personal communication).

### *Summary*

To summarize, the results from studies on fear conditioning and extinction are quite varied with different effects found in different studies. This is partly because the methods and contrasts that have been used in the data analysis have been quite varied. This makes it difficult to compare the results of the different studies with each other. In the three studies that investigated fear conditioning only, with none of the stimuli present during fear learning being repeated during extinction, the results have indicated that sleep increases the difference between the CS+ and the CS-. In two of these studies, this effect has co-varied with the duration of REM sleep.

Studies also including extinction have in general found REM to be involved in strengthening extinction retention. It might also be that REM, or sleep in general, before extinction learning, could be predictive of the degree to which one is able to learn that something is no longer dangerous, and specially in retaining that learning to a future re-test. There are also findings indicating that sleep after fear conditioning and before extinction is equally, and in one case (Straus et al., 2016), even more important for long lasting extinction than sleep after extinction learning. Just as described in the previous section, REM sleep seems to have a role in both processing and changing reactivity of the emotional memory, as well as in preparing for novel learning. Disentangling these two effects is an important task for future research. It has been suggested that impaired ability to retain extinction learning due to disturbed sleep is one of the active mechanism in maintaining PTSD (Pace-Schott, Germain, & Milad, 2015b).

## Fear extinction during sleep

A very recent line of studies have examined if it is possible to conduct extinction training during sleep. This has been attempted by repeating sounds or odors that were present during conditioning or extinction during subsequent sleep. One study found replay of extinction cues to be more efficient during SWS than during wake (Hauner, Howard, Zelano, & Gottfried, 2013), one found no group difference between a sleep and a wake group (He et al., 2015) and one has found the opposite, with decreased extinction during sleep compared to during wake (Ai et al., 2015). A difference between the studies is that the two that have found that extinction is possible during sleep (even if it was not more efficient than during wake in one of them), there was no extinction phase before but instead, all extinction took place during sleep. Even though re-exposure during sleep did not result in increased extinction compared to reactivation during wake in the He et al. (2015) study, the authors still argued that this is an important finding. Being exposed to trauma reminders during wake could be very stressful, and if extinction is equally effective during sleep, where participants are not aware of it, this could be the preferred method of performing extinction learning.

## Animal studies on fear learning and extinction

Studies of sleep and fear learning and extinction in animals have exclusively been conducted in rodents. Two different conditioning paradigms are normally used: cued and contextual. Cued fear learning is similar to what has been described

above, where the aversive event (once again, most often an electric shock) is preceded by a cue (in these rodent studies, almost always a sound or a flashing light). In contextual fear learning, there is no explicit cue but the electric shock could instead appear at any time when the rodent is placed in a certain context (such as a cage with certain features). Thus, the rodent will show a fear response just from being placed in that context. Fear responses in rodents are often measured by freezing behavior, where the animal simply stops moving. In cued conditioning designs, fear is measured as freezing as a response to the CS+ whereas in contextual designs, fear responses are defined as the percentage of time in the context that is spent freezing. These two can also be measured in the same study where freezing is measured both to the response to the cue, as well as to being placed in the shock context again. Fear extinction in contextual conditioning paradigms is obtained by letting the animal spend time in the conditioned context without receiving any electrical shocks. Studies on animals are different from studies in humans in that there is often no equivalence to the CS-, making results somewhat difficult to translate given that can often not know how specific the fear reactions are to the CS+, or if they just symbolize a general increase in reactivity. Another issue with animal studies is that it is more difficult to disentangle the effect of alterations of emotional reactivity from the effects of memory of the association between the CS+ and the UCS. We cannot ask rodents for subjective ratings but instead, memory has to be inferred from behavior.

## **Effects of sleep on fear conditioning**

### *General Sleep Deprivation*

Sleep deprivation after contextual fear learning has been found to result in less freezing during the re-test, indicating less retention of fear learning (Cohen et al., 2012; Graves, Heller, Pack, & Abel, 2003; Hagewoud, Bultsma, Barf, Koolhaas, & Meerlo, 2011; Hagewoud et al., 2010; Vecsey et al., 2009). One study has further found sleep deprivation to result in decreased freezing at re-test after cued conditioning (Kumar & Jha, 2012) whereas one study did not find such an effect (Graves et al., 2003). An additional interesting aspect of the Kumar and Jha (2012) study is that they included an additional control group that were not sleep deprived but that were instead kept under intense light during the delay interval, which was supposed to function as equally stressing. By doing this, the effect of sleep could be disentangled from the effect of stress caused by sleep disruption. The sleep deprived rats showed less freezing during the re-test compared to both the non-sleep deprived, and the stressed control rats.

### *Specific REM deprivation*

Silvestri (2005) found selective REM deprivation after cued conditioning to increase freezing to the CS+. This effect was however not present during the first three exposures but instead only during the end of the re-test session, indicating that REM deprivation did not impair the memory of the fear conditioning, but rather the ability to acquire extinction learning. A second experiment used contextual fear learning and found a tendency towards less freezing after REM deprivation, but only during the beginning of the re-test, indicating impaired fear memory. Silvestri and Root (2008) found similar results, with no effect of REM deprivation after cued fear conditioning during the first half of trials during the re-test but instead during the second half, indicating impaired extinction learning during the re-test session. A second experiment reported in the same article however revealed more freezing during the early trials after REM deprivation. An additional test of retention of extinction learning 48 hours later in both revealed no group differences at this point in either study.

Ravassard et al. (2016) found that REM deprivation after contextual fear learning resulted in less freezing during the re-test, and that there was a correlation between freezing and time spent in REM sleep. Another group of rats were REM deprived before fear conditioning which then resulted in a REM rebound when they were allowed to sleep again after conditioning. This REM rebound resulted in increased freezing during the re-test. There was no correlation between REM duration and freezing, but there was one between the increase in REM sleep after deprivation compared to the baseline night and freezing. In an additional experiment, rats were REM deprived at a previous stage so that they had a REM rebound before conditioning, which increased both the acquisition of fear learning, and increased freezing during the re-test. REM deprivation before conditioning did however not affect the degree of acquisition of fear learning compared to rats that had slept as normal before conditioning.

### **Effects of sleep deprivation on extinction**

Total sleep deprivation after extinction learning has in one study been found to result in less extinction retention in a cued conditioning paradigm (Melo & Ehrlich, 2016). Most studies have focused specifically on the effect of selective REM deprivation. One study found decreased extinction retention after REM deprivation in a cued, but not in a contextual, fear learning paradigm (Fu et al., 2007). Hunter (2014) found that rats who were subjected to REM deprivation after cued fear conditioning showed impaired safety learning ability during subsequent fear extinction learning. At a later re-test, testing the retention of extinction learning, results revealed a trend towards reduced extinction to the

context in the REM deprived group compared to the controls. Hunter (2015) found that REM deprivation after contextual fear conditioning resulted in increased freezing at re-test. These effects were still present additionally 48 hours, but not 96 hours later. These two studies also showed that the effect of sleep on fear learning was moderated by the rats housing situation and living environment.

### *Summary*

Generally, sleep deprivation seems to impair the memory of both fear learning and extinction. Selective REM deprivation has revealed similar results as general sleep deprivation. This could mean that REM is the active component in strengthening memory consolidation during sleep, but we still do not know that, considering that REM deprivation often means less sleep in general, and therefore we do not yet know if the effect of REM is different than that of other sleep stages.

There are contrasting findings here as well, with REM sleep deprivation resulting in both increased (Silvestri, 2005; Silvestri & Root, 2008) and decreased (Ravassard et al., 2016) freezing during re-test. A difference between these studies however is that the former used cued, and the latter used contextual fear conditioning. The results from Ravassard et al. (2016) however indicated that REM sleep might be the active component in the consolidation of fear learning, considering the correlation between REM duration and freezing. Just as in humans, it is however still unclear to what degree REM is involved in processing the fear and safety memories, and to which degree REM affects the ability to acquire novel fear and safety learning. Thus, sleep, and perhaps specifically REM sleep, could be involved in strengthening the memory of emotional learning, but the lack of REM could also perhaps make it more difficult to acquire novel learning during the next day.

## **The causal mechanisms during sleep**

All sleep is not alike, and therefore, it is important to determine which mechanisms during sleep that are involved in altering fear responses. Three studies have examined which mechanisms, beyond sleep stages, that affect the learning and extinction of fear. Popa, Duvarci, Popescu, Lena and Paré (2010) subjected rats to cued fear conditioning and measured their brain activity during both their pre- and post-learning sleep. The next day, some rats showed more freezing than others during the re-test. Analyzing brain activity during sleep revealed that fear memory consolidation was significantly correlated with changes from pre- to post learning, in theta coherence between the basolateral amygdala and the mPFC, as well as between basolateral amygdala and the hippocampus. There was also a trend towards significance for a correlation between REM duration and fear

memory. Changes in theta coherence were not correlated with baseline anxious behavior.

Boyce et al. (2016) first had mice undergo cued fear conditioning. During post-training sleep, hippocampal theta activity was optogenetically blocked in a subgroup of the mice. When placed in the same context the next day, the mice with blocked hippocampal theta activity during sleep showed less freezing behavior. When the mice were exposed to the conditioned cue again in another context, there was no difference in freezing behavior between the groups.

Datta and O'Malley (2013) subjected rats to contextual fear learning and extinction. Brain activity was measured during post learning sleep and comparisons were made between the rats who showed retention of fear extinction during the re-test and those who did not. Results revealed a higher degree of pontine waves during REM sleep in the group that showed fear extinction retention as well as a negative correlation between pontine wave density and freezing behavior during the re-test. The rats without extinction retention did not differ from the rats with extinction retention during extinction learning, making these findings even more interesting because it indicates that pontine waves are a causal mechanism and not a marker of previous learning.

## **Fear extinction during sleep in animals**

Two studies have examined if it is possible to perform extinction learning in animals during sleep, and found quite the opposite. Both Rolls et al. (2013) and Barnes and Wilson (2014) subjected mice and rats respectively to fear learning where an odor was paired with an electric shock. Rolls et al. (2013) found increased fear responses the next day in the mice that had been exposed to the odor during sleep compared to mice that been exposed to a control odor. Barnes and Wilson (2014) found increased fear responses in the group that had been exposed to the odor during sleep compared to the controls that had not been exposed to it. Furthermore, rats that had been exposed to the odor during wake showed reduced freezing during the re-test. Exposing rats to a novel odor during sleep did not increase freezing to the CS+ during subsequent wake, but it did reduce the difference in freezing between the CS+ and the CS-, indicating a more generalized freezing response.





## 4. Other factors that determine which memories are consolidated during sleep

One of the central research questions for the third study in this thesis was which factors that determine if a memory becomes strengthened during sleep or not. The study combined manipulations of the emotionality of the material with different instructions during encoding. Studies on the effects of emotion on sleep dependent memory consolidation were discussed in chapter 2. The focus of this chapter will be studies that have looked at other factors than emotions that could be expected to influence which memories that get a beneficial effect of sleep and which that do not. The reason that emotional memories have been suggested to be especially consolidated during sleep is that they are often more important for our survival than neutral material. Sleep would then work in such a way that memories that are believed to be relevant for the future get a preferential strengthening compared to memories that are not. If such an effect for some reason is less present during wake, this suggests that sleep sorts memories in a more adaptive way than is done during wake, or at least that sleep and wake have different “algorithms” for determining which memories that are strengthened.

This chapter will focus on two different kinds of studies. First, there are studies that have tested the effect of sleep compared to wake depending on the encoded material’s perceived future relevance. This has for example been manipulated by telling one group that there will be a subsequent memory test, and compare their results with a group that have not expected a memory test. Relevance has also been manipulated by telling participants that the different stimuli will be associated with different levels of reward if successfully remembered. A second line of studies have examined how sleep affects memory for items that for various reasons can be expected to be forgotten. These two categories can of course sometimes be highly similar and difficult to separate from each other. Still, there are theories saying that sleep is involved in actively weakening unwanted memories, beyond simply not having a strengthening effect on them, which is why these two categories of studies will still be discussed separately.

The first section will be about basic comparisons between sleep and wake groups, whereas the second section will discuss the contributions of specific sleep variables within the sleep groups. Once again, because of the large variations both in experimental designs and in findings, the descriptions will be quite detailed.

## Factors that determine which items that are selectively consolidated during sleep compared to wake

### **Re-test expectancy**

A DW/NS study by Wilhelm, Diekelmann et al. (2011) found that sleep only had a beneficial effect on memory if participants after encoding were told that there would be a subsequent memory test after the delay interval. The sleep group that was expecting a memory test performed better than the sleep group that did not expect a test, as well as both the wake groups, regardless of test expectancy. None of the other groups differed from each other in memory performance. This effect was found in two different studies, one using word-pair locations and one using both word-pair locations and a finger sequence tapping task. Van Dongen, Thielen, Takashima, Barth and Fernandez (2012) had participants in a DW/NS design encode object-location associations. The objects were divided into two different categories and after encoding, participants were told that they would later be tested on only one of these categories. At the re-test, participants were tested on both categories and the results revealed a significant three-way interaction. In the sleep group, memory for items from the relevant category was significantly better than items from the irrelevant category. This effect was the opposite in the wake group, who showed better memory for the irrelevant category compared to the relevant one. The sleep group performed significantly better than the wake group on the relevant items whereas there was no group difference for the irrelevant items. This study also reported a correlation between TST and memory for relevant, but not for irrelevant, items. However, Wamsley, Hamilton, Graveline, Manceor and Parr (2016) found test expectancy to strengthen memory performance for a finger tapping task as well as for navigation in a virtual maze equally, regardless of sleep and wake in a within-subject DW/NS design.

### **Reward**

One study that found sleep to be especially beneficial for items associated with a reward for successful remembering is Fischer and Born (2009) who had

participants in a DW/NS design learn two different finger sequence tapping tasks. After encoding, participants were told that there would be a reward based on the performance on one of the tasks after the delay interval. Two additional groups received no reward information. The results revealed that the increase in performance for the sequence for which a reward was expected, compared to the one where it was not, was larger in the sleep group compared to the wake group. In another study, Igloi, Gaggioni, Sterpenich and Schwartz (2015), using a nap design, found that in the sleep group, performance was better for the high reward items than for the low reward items, whereas no such difference was observed in the wake group, even though the interaction effect between reward and group was not significant. At a re-test three months later, there was an interaction between group and reward, showing better memory for high reward compared to low reward items in the sleep group, but not in the wake group. On the other hand, there are also several studies that have not found interactions between sleep and reward. Tucker, Tang, Uzoh, Morgan and Stickgold (2011) found main effects of both sleep and reward, but no interaction between them in a DW/NS design measuring memory of face-object associations, where half of the participants were informed about receiving a reward during the re-test, before encoding. Similarly, Baran, Daniels and Spencer (2013) found main effects of sleep as well as for reward, but no interaction effect between them in a DW/NS design using words as the stimulus material and testing memory with both recognition and free recall. Testing adolescents, Lo, Bennion and Chee (2016) had participants read prose passages where certain sentences were highlighted, which meant that participants would receive an additional reward for remembering them. Then, participants either slept as normal or were limited to only five hours of sleep per night during the following week. At the re-test, there was no interaction effect between sleep and reward value, even though a selective benefit for the highlighted, compared to non-highlighted, sentences was only present in the group that had slept normally, and not in the sleep deprived group. At a subsequent memory test 6 weeks later, no group differences were found.

One study varied the reward value in a task where participants encoded object-location associations (Oudiette, Antony, Creery, & Paller, 2013). Each object location was further paired with a sound. There were four different conditions, two wake and two sleep conditions. Half of the sounds associated with the low reward items were replayed during the subsequent delay interval in one of the sleep and in one of the wake groups. For the groups where no sounds were played during the delay intervals, there was no difference in memory performance between high and low reward items between the sleep and the wake group. High reward items were better remembered than low reward items, regardless of group. When playing sounds associated with the low reward items during the delay interval, the items related to those sounds were strengthened in the wake group, whereas in the sleep

group, memory was enhanced also for the low reward items that had not been cued during sleep. This indicates that re-activation some of the low reward items during sleep perhaps re-activated the other low reward items as well. The hypothesis that re-activation during sleep is more widespread and associative than during wake will be further discussed in the next chapter.

Another study examining the relation between sleep and reward information is Stamm et al. (2014). In this study, participants navigated through a virtual maze with the goal to reach the exit as quickly as possible. One group had a meter ticking down on the screen, indicating the monetary reward that they would receive when finding the exit. A quicker navigation through the maze would result in a higher reward. Another group received no such information. The re-test was performed the next morning. Contrary to expectations, reward information had a negative effect on overnight improvement on navigating in the maze. This was interpreted as perhaps the ticking meter should not be viewed as reward information but instead as negative reinforcement. This could further have resulted in a stress response that impaired overnight memory consolidation by decreasing sleep quality, even though stress induced by the task was not measured.

## **Intrinsic relevance**

Regarding intrinsic relevance, Abel and Bäuml (2013a) had participants rate words for either their pleasantness or for their survival value. This is known as survival processing and it has previously been shown that rating something for its survival value will lead to improved memory performance compared to other kind of ratings that contain the same depth of processing during encoding (Nairne, Thompson, & Pandeirada, 2007). This was a DW/NS design where the re-test was a combination of a cued and a free recall task. The results revealed positive main effects of both sleep and survival processing on memory performance, but no interaction. These effects were replicated in a second experiment using a recognition task as the re-test.

Another study tested the effect of sleep on a procedural skill with low relevance for the participants (Hoedlmoser et al., 2015). In this study, participants first learned to ride a bicycle that had its steering device reversed so that turning the steering device to the right resulted in the bicycle turning to the left. After training, participants either took a nap or remained awake. When tested again after the delay interval, results showed that slalom riding performance was significantly worse after sleep compared to after wake. The authors interpreted this finding as that acquiring this skill requires inhibiting the skill of riding a normal bicycle, and that perhaps sleep had a role in removing this unwanted learning.

In the first study to actually measure how relevant the participants themselves considered the encoded material to be, Van Rijn, Lucignoli, Izura and Blagrove (2016) had native English speakers who had recently moved to Wales rate how much they valued the Welsh and the Breton languages respectively. Participants then learned the English translation of Welsh and Breton words, and then either slept or spent the day awake in a DW/NS design. During the subsequent memory test, there was a correlation between how much the participants valued the Welsh language and memory performance for the Welsh words. This was not the case in the wake group, indicating that subjective value of encoded material is a stronger predictor of it being strengthened during sleep compared to during wake. There were no correlations with memory performance and valuing the Breton language for either group (according to the authors, because of a ceiling effect in valuing this language).

### **Studies inducing forgetting**

As mentioned above, it is of course difficult to draw a precise line between studies using material that can be expected to be remembered in different degrees and studies that have actively tried to induce forgetting. Items associated with a low reward can for example be expected to be forgotten compared to items associated with a high reward. Here however, I will discuss studies that have either explicitly told participants to forget something, or that have tried to induce forgetting through either repeated retrieval suppression or inhibition.

In a DW/NS design by Abel and Bäuml (2013b), half of the participants first studied a word list and then another one after which they were instructed to try to remember both lists. The other half of participants were after encoding the first list told that there had been a technical error so that they had studied the wrong list, and were then given the “correct” list that they were instructed to try to remember while forgetting the list that they had studied initially. At the re-test, participants were tested on the first list using a cued recall task. The results revealed impaired memory performance after ‘forget’ instructions compared to after ‘remember’ instructions among participants who had spent the delay interval awake. No such decrease was found in the sleep group, indicating a role of sleep in “repairing” memories for items cued to be forgotten. These results were replicated in a second experiment using different words as the stimulus material.

A directed forgetting paradigm was used by Saletin, Goldstein and Walker (2011). In a nap design, participants first viewed different words and after each word, they were instructed to either remember or forget the word that they had just seen. Memory was tested with free recall where participants were asked to remember all words, also those that had been subjected to forgetting instructions during

encoding. Results revealed that the sleep group remembered more words cued to be remembered than the wake group. There was no group difference between the groups in performance for words cued to be forgotten, showing that sleep had a stronger effect than wake only for memories which participants had been instructed to remember. In a similar directed forgetting paradigm using TSD as the sleep manipulation and a recognition task taking place after two additional recovery nights as the re-test, Rauchs et al. (2011) found similar recognition accuracy in both groups for both 'remember' and 'forget' items. For 'forget' items however, the sleep group showed an increase in both hits and false alarm responses, indicating a more lenient response criterion. Analysis of the fMRI results showed that the sleep group showed higher activity in the hippocampus during encoding for 'remember' hits compared to 'forget' hits (during the re-test), whereas no such effect was observed in the TSD group. This indicates that hippocampal activity during encoding is more predictive of subsequent memory performance when encoding is followed by wake compared to when it is followed by sleep.

#### *Retrieval-induced forgetting*

Another method to induce forgetting in a more implicit manner is the retrieval-induced forgetting (RIF) paradigm (Anderson, Bjork, & Bjork, 1994). In this paradigm, participants are not explicitly asked to try to forget anything. Instead they first encode items (most often words) associated with different categories. Then, participants get additional retrieval practice on some of the items belonging to this category (Rp+ items) whereas some of the items from this category do not receive additional practice (Rp-). At the re-test, participants are tested on memory for Rp+ and Rp- items, as well as for items belonging to another category, which have been encoded but that are not present during the practice phase (Nrp items). This memory test often reveals improved memory performance for the Rp+ items compared to the Nrp items, and impaired memory for Rp- items compared to the Nrp items. The suggested explanation for this is that in order to retrieve the Rp+ items during the practice phase, one must also inhibit the interfering Rp- items from the same category, which causes the impaired below baseline memory performance for the latter (the baseline being the Nrp items that have not been additionally practiced but neither subjected to any inhibition, given that because they belong to another category, they do not need to be inhibited in order to retrieve the Rp+ item).

Three studies have tested if this effect is differently affected by sleep or wake during the delay interval between retrieval practice and the re-test. In a DW/NS design, Racsmány, Conway and Demeter (2010) found that impaired performance for Rp- items compared to Nrp items was only significant in the sleep, and not in the wake group, whereas there was no group difference for the difference between

Rp+ and Nrp items. A second experiment also added a control group that studied the words in the morning and then did the re-test one hour later. Results from this experiment showed that the difference between Rp- and Nrp items was reliable only in the sleep group and not in any of the two other groups. There were no differences between the groups in the difference between Rp+ and Nrp items. Abel and Bäuml (2012) used four different groups, a sleep and a wake group in a DW/NS design, as well as two different short-delay groups who did the re-test after 20 minutes in either the morning or in the evening. Results revealed a significant decrease in memory performance for Rp- items compared to the Nrp items in the short delay groups as well as in the sleep group, but not in the wake group. This was driven by a decrease in memory performance for the Nrp items in the wake group. The increase in memory performance for the Rp+ items compared to the Nrp items was similar in all groups.

In contrast, Baran, Wilson and Spencer (2010) found that the difference between Rp- and Nrp items was larger after wake compared to after sleep, in both a nap and in a DW/NS design. This difference was driven by memory for Rp- items being higher in the sleep compared to the wake group, whereas no such group difference was found for the Nrp items. In an additional subsequent nap design, this was only significant at a trend level.

#### *The Think/No-Think paradigm*

The third study of this thesis utilized the Think/No-Think (T/NT) paradigm (Anderson & Green, 2001). In this paradigm, participants first learn associations between a cue and an associate. Most frequently, both of these are words (but there are also studies that have used for example word-image pairs, as for example in this thesis). Then, during the Think/No-Think phase, participants are presented with only the cue, written in either green or red font color. If the word is presented in green, the participant is instructed to think about the associate that it was previously presented together with (Think items), whereas if it is shown in red, they are asked to try avoid all thoughts of the associate (No-Think items). This is repeated several times for each cue and at a subsequent unexpected memory test, all cues are shown again and participants are asked to say which items they were previously associated with. There are also baseline items that are only present during the initial encoding, but not during the T/NT phase. At the memory test, which normally takes place right after the conclusion of the T/NT-phase, it is usually found that Think items are better remembered than the Baseline items and that the No-Think items are more poorly remembered than the Baseline items, indicating that the repeated suppression of these items during the T/NT phase has actually resulted in worse memory performance than if the items would not have been seen after encoding at all.



The only previous study that has combined sleep with the T/NT paradigm is Fischer, Diekelmann and Born (2011). This was a DW/NS design where the T/NT phase took place before the delay interval and the memory test after it. Results revealed a main effect of group, with improved memory performance after sleep regardless of item type (Think, Baseline, No-Think), although the effect was the strongest for the Baseline items. The difference in memory performance for Baseline and No-Think items did not differ between the sleep and the wake group.

### **Studies manipulating multiple variables that differently predict subsequent remembering in the same study**

The studies discussed so far have only included one variable in the stimulus material that predicts subsequent remembering, such as reward value or test expectancy. Here, I will discuss studies with several such variables in the same design, such as for example using a stimulus material where the items have varied in both emotion and reward value. This literature is highly relevant for the third study in this thesis, in which we manipulated both the emotion of the stimulus material as well as tried to induce forgetting through the T/NT paradigm. In this way, we aimed to measure if the effect of sleep on the memory for items that had undergone retrieval suppression was different for negative compared to for neutral material.

Only four studies have previously examined how sleep affects and interacts with multiple variables that individually predict subsequent remembering in the same study. Three of them will be discussed in this section and the fourth one in the following section because it did not include a wake control group.

In the previously mentioned study by Kuriyama et al. (2013), where participants viewed film clips depicting either motor vehicle accidents or normal traffic, participants were further told to either try to remember, or to try to quickly forget what they were watching. In the subsequent memory test after either TSD or normal sleep, participants were asked to indicate if images were taken from either the accident movie, the movie with normal traffic or if they were new. The results revealed no interactions of group with either emotion or remember/forget instructions.

In a study that combined both emotion and test expectancy, Cunningham, Chambers and Payne (2014) used the emotional trade-off paradigm in a DW/NS design and additionally after encoding told half of the participants that there would be a memory test after the delay interval. In the wake groups, there was a stronger trade-off effect (increased memory for the objects compared to the backgrounds) for the negative items when a re-test was expected compared to when it was not. There was no such trade-off effect for neutral objects or their backgrounds. In the

sleep group, this trade-off effect was similar regardless of if a re-test was expected or not. This shows that test expectancy did not increase the emotional trade-off effect after sleep but that it did so after wake. The authors argued that this was because during sleep, emotion is already such a strong salience cue for further consolidation that it is not additionally enhanced by re-test expectancy. Similar results were found by Bennion et al. (2016). This study combined images that varied in emotion, re-test expectancy and reward for subsequent remembering. The stimulus material came from the emotional trade-off paradigm but the results reported contained only memory performance for the objects, and not for the backgrounds. Results revealed no additional benefit of sleep when two or more variables that predicted remembering were combined. The lack of an additional boost from sleep when combining multiple factors that would each individually predict increased memory performance was interpreted by the authors as that sleep “binarizes” information based on if it is important or not. Information that has been judged as important is then consolidated during sleep regardless of how many different cues of its importance that it was associated with during encoding. This is however somewhat contradictory to the results of Baran et al. (2013), which are discussed above, who found a linear increase in memory performance as a function of a continuous reward value. This effect was present in the wake groups as well and did not show this kind of dichotomized spread as suggested by Bennion et al. (2016), even though a difference between the studies is that Baran et al. (2013) varied the same variable in different intensities instead and did not combine different ones.

## **Summary**

In overview, sleep has in several cases been found to have a stronger effect on memory performance compared to wake when a re-test or a reward based on memory performance is expected. There are however also several studies not finding such an effect, indicating that the effect perhaps is not that strong.

Studies inducing forgetting have reported highly contrasting results, with sleep having been found to have a role in both increasing the difference between ‘remember’ and ‘forget’ items, as well as in “repairing” memory for items subjected to forgetting, without affecting the ‘remember’ items.

With such varied results in the literature, it is still difficult to draw any certain conclusions about if and how sleep selects which memories to strengthen or weaken differently compared to time spent awake.

## The active mechanisms during sleep

Findings on which aspects during sleep that have been shown to be specifically associated with the consolidation of certain types of memories and not with others have been quite varied. There are some very interesting findings, but once again, just as with the case of sleep and emotional memory, there is no effect that is reported more often than not. This of course does not question the validity of those findings within each study, considering the large variation of paradigms used, but it does suggest that perhaps those sleep effects are specific only to the particular designs that they were found in, and it is difficult to know to which degree they could be generalized.

### Slow wave sleep and early night sleep

Wilhelm, Diekelmann et al. (2011) found that the percentage of SWS correlated with memory performance for the word pair task and for the object location task, but only in the group that was expecting the re-test, and not in the one that did not. Interestingly, there were no correlations between any sleep variable and improvement on the procedural memory task, even though it showed a similar improvement during sleep when participants were informed of an upcoming test. Oudiette et al. (2013) found that when there was targeted memory reactivation through a sound during sleep, memory performance for the reactivated items was correlated with SWS duration and delta power. None of these correlations were observed for the group for which no sounds were played during post-learning sleep. Baran et al. (2013) reported a positive correlation between percentage of time spent in SWS and memory for the Rp+ items, but not with any other items.

A study by Groch et al. (2015), which has already been discussed in chapter 2, examined the effect of early sleep on emotion and reward value. During encoding, participants viewed neutral and emotional images. The images were preceded by a color frame and participants were instructed to remember the color. Half of the trials also included information that there would be a reward during the re-test if the color-picture association was correctly remembered. For image recognition, results revealed no main effect of emotion, no main effect of reward and no interaction. For color-picture associations, there were no main effects of either emotion or reward, and no interaction between them. An additional group did not get any information about reward value during encoding. Comparing these two groups revealed decreased memory performance for the associations between color and emotional items compared to neutral ones after early sleep when there was no reward, but that the effect of emotion disappeared when reward information was present. This was interpreted as that early sleep would normally

only strengthen the memory of color frames related to neutral items, but that the inclusion of reward information removed this effect of emotion.

## **Spindles**

Spindles have in several studies been found to be related to affecting memory for certain items specifically based on their reward value or perceived relevance. Igloi et al. (2015) found a positive correlation between slow spindles and memory improvement for high reward items, but not for low reward items. Saletin et al. (2011) reported that fast sleep spindles correlated with the difference in memory performance between items cued to be remembered compared to items cued to be forgotten. This effect was driven by fast spindles correlating positively with memory of 'remember' items and negatively with 'forget' items, even though none of these two latter correlations survived after controlling for multiple comparisons. Studte, Bridger and Mecklinger (2016) found a correlation between spindle density and memory performance for high reward items, even though this was only marginally significant when controlling for pre-nap performance, adding further support to the concept of spindles also being a general marker of learning ability. There was no correlation between spindle density and memory for low reward pairs. Hoedlmoser et al. (2015) found a correlation between spindle activity and the decrease in slalom riding performance with the bicycle with the reverse steering device, which also indicates a role for spindles in removing unwanted learning.

## **REM and late night sleep**

Theoretical accounts have suggested a role of REM sleep in forgetting and in the removal of unwanted learning (Crick & Mitchison, 1983; Norman, Newman, & Perotte, 2005). Oudiette et al. (2013) found that in the group without the targeted memory reactivation sounds during sleep, memory for the low value objects was negatively correlated with the duration of REM sleep, indicating a role in REM sleep in sorting out memories that are not considered relevant. Baran et al. (2010) found a negative correlation between percentage of time spent in REM sleep and the difference between Nrp and Rp- items in the RIF paradigm, so that REM decreased this difference. REM sleep did not correlate with memory performance for either of these two item types by themselves, only with the difference between them.

A second experiment in the T/NT study by Fischer et al. (2011) also used a split night design comparing early and late sleep. Here, for the No-Think items, there was an interaction effect between sleep timing and the number of No-Think trials

during the T/NT phase. In the late sleep group, items subjected to 8 and 16 No-Think trials during the T/NT phase were actually better remembered than the Baseline items, whereas no such effect was observed in the early sleep group, in which there was no difference between Baseline and No-Think items, regardless of the number of No-Think trials. This indicates that REM sleep is involved in “repairing” memory for items subjected to retrieval suppression.

Hoedlmoser et al. (2015) also found a correlation between the decrease in straight line riding performance of the inverse bicycle and REM duration, which could be interpreted as REM being involved in removing unwanted learning. Another study from the same lab however found a negative correlation also between REM duration and the retention of acquired juggling skills (Hoedlmoser, Bothe, Gruber, & Schabus, 2016). It is more difficult to say which other skill that would need inhibition in order to maintain a good juggling performance, or why juggling would be determined to be “unwanted”, and thus we still do not know if this “removing of inhibition” account is the correct way to interpret these findings, even though it is an exciting concept for future research. In the juggling study, there was also a positive correlation between performance and fast spindle activity, indicating a more specific role for REM sleep compared to the bicycle study in which both REM sleep and spindles decreased learning performance.

## **The role of dopamine**

One study examined if dopamine could be the active mechanism in sleep dependent consolidation of stimuli associated with a reward. Feld, Besedovsky, Kaida, Münte and Born (2014) had participants encode images with either high or low reward value. Just before going to bed, participants received either placebo or a dopamine receptor agonist in order to increase the brain’s dopamine levels. Results revealed better memory for high reward items compared to for low reward items in the placebo condition only. In the dopamine condition, participants showed equal performance for both reward categories, and this effect was driven by dopamine enhancing memory for the low reward items. However, dopamine also decreased the time spent in both REM and SWS which of course also could have affected memory performance in that condition, even though no correlations between memory performance and sleep stages were reported.

## 5. Sleep and the active processing of information

Two of the studies in this thesis are about the role of sleep in the generalization of fear learning. More specifically, they examined if sleep, compared to wake, increased the degree to which we have fear responses to stimuli that were visually similar to a stimulus that had previously been associated with an aversive sound or an electric shock. Drawing conclusions, for example learning to generalize that something that is relevant for one stimulus is applicable to other similar stimuli as well, is mostly a good and adaptive thing. This kind of generalization could however also be problematic, for example when someone is involved in a motor vehicle accident and then wrongfully draws the conclusion that being in a car is always associated with danger. That kind of generalization is not adaptive at all, and if it could be reduced, for example by sleep deprivation right after the learning situation, that could perhaps be a promising intervention in order to reduce unwanted generalization. Thus, understanding how sleep is involved in drawing conclusions based on previous learning is an important aspect of sleep research, which could have important clinical implications.

As we have seen in previous chapters, sleep has been found to have a role in the generalization of emotional learning (e.g. Kuriyama et al., 2010; Pace-Schott et al., 2012). Those studies have already been discussed in previous chapters and therefore they will not be mentioned further here. This chapter will instead be a summary of the scientific literature examining how sleep actively processes non-emotional material.

It has been suggested that when a newly acquired memory is reactivated during sleep, it is reactivated in concert with other similar memories. The part of the memories that share the most overlap with other memories will get the strongest re-activation. Individual details specific for the novel memory in particular, will be reactivated to a lesser degree. Therefore, the memory for commonalities will be strengthened more than memory for specific details, which would be the reason that sleep has often been found to be superior state than wake for creating schemas and “connecting the dots” (Lewis & Durrant, 2011). Similar functions of sleep have been suggested by Stickgold and Walker (2013) as well as by Inostroza and Born (2013). Another way that sleep is suggested to transform memories is by de-

contextualizing them from the context that they have been encoded in, which has already been discussed in chapters 2 and 3. If sleep abstracts the “gist” of an experience at the expense of veridical details, this could argue for that sleep would result in a larger degree of generalization of fear learning. This would be because fewer details present during the learning experience would have to be present in order to re-trigger a fear response. After sleep, it would be sufficient with only the gist of the learning experience and a stimulus similar to the previous CS+ would elicit a fear response as well, regardless of its exact features or the context it is being presented in. It is however still far from established with any certainty that the role of sleep in gist abstraction is associated with decreased veridical recall, and it should be mentioned that this is just one of many theories regarding the role of sleep in information processing.

This chapter will review the literature that has examined if sleep, beyond just strengthening memories, actually processes information differently compared to wake, and discuss which clues that this can give us about how emotional learning can be generalized during sleep. Compared to previous chapters, this one will be less detailed because of the many paradigms with no direct relevance for the studies included in the thesis. Therefore, several of the paradigms will not be described in detail but only mentioned in order to illustrate the many ways in which sleep has been found to be involved in the active processing of information. However, when a study has found an effect in only one of several outcome measures, that has to be described in a detailed way in order not to overestimate the degree of significant findings. Studies with a more clear relevance for generalization will be discussed in more detail.

A meta-analysis by Chatburn, Lushington and Kohler (2014) divided the literature of active information processing during sleep into three different categories; rule extraction, item integration and false memory formation. The meta-analysis revealed that there was moderate effect for rule extraction and a moderate to a large effect size for item integration. The effect of sleep on false memory formation was found to vary depending on which kind of memory task that was used. This will be discussed in its own section at the end of this chapter.

## Sleep and insight tasks

Sleep has been found to be a more beneficial state than wake for figuring out a hidden rule for solving a number series task (Wagner, Gais, Haider, Verleger, & Born, 2004). Participants worked on a task where they were supposed to figure out the next number in a number sequence, based on the two previous numbers. The goal of the task was to come up with the final number of the series. Unbeknownst

to the participants, there was a simple rule to this so that the second number of the series was always the same as the last one. This meant that participants only had to figure out the second number in order to solve a sequence. Participants worked on the number sequences before the delay interval and then again afterwards. Results revealed that the probability of having gained insight of the hidden rule during the re-test was higher after sleep. Another study used the same task with a split night design (Yordanova et al., 2008). This study showed that participants who had gained implicit knowledge (defined as quicker performance on the sequences that followed this rule compared to sequences not following the rule in the absence of explicit rule awareness) before sleep were more likely to reach explicit knowledge of the rule after early sleep compared to after late sleep. There was no difference for participants who had not gained implicit knowledge before the delay interval. In the late sleep group, those who reached explicit knowledge during the re-test had significantly less REM duration, indicating that REM sleep is not involved in making implicit rule awareness explicit, and may perhaps even hinder this.

Other studies have found sleep to be more beneficial than wake in figuring out the hierarchical or spatial relationships between objects. This has been the case even though no information has been given about the specific relationship between the objects and instead the exact relationship has to be inferred based on the relationships between other objects (Coutanche, Gianessi, Chanales, Willison, & Thompson-Schill, 2013; Ellenbogen, Hu, Payne, Titone, & Walker, 2007). A similar effect was found in another study even though a group difference was only present when participants encoded the initial relationships through reinforced learning and not by simple observational learning (Werchan & Gomez, 2013). Another study showed sleep to lead to larger improvements than wake on figuring out which clues that in combination predicted a certain outcome event. This task requires being able to make inferences of probabilities that have never been explicitly stated but instead just learned implicitly from studying the outcome of several previous trials (Djonlagic et al., 2009). Results further showed that performance during the initial training session was correlated with more REM sleep during the following night, once again implicating that perhaps REM sleep could function as a marker of successful learning.

Sleep has also been found to be superior to wake for increasing the ability to solve a puzzle game which participants were stuck on before the delay interval (Beijamini, Pereira, Cini, & Louzada, 2014). Further, participants in the nap group who reached SWS were more likely to solve the puzzle than those who did not. This study did however only include the puzzle that the participants had been stuck on, and no novel tasks not seen before. This makes it difficult to say if it was the puzzle that they had attempted to solve before sleep that had been processed during the night or if sleep did just increase the general puzzle solving ability. A similar critique can be directed towards another study that found sleep to increase



the ability to transfer the solution to a problem solved before the delay interval to a novel but similar problem that was presented after the delay interval (Monaghan et al., 2015). Given that no new problems were presented, it could be that sleep just increased the participants' general problem solving ability. A subsequent experiment however revealed no circadian rhythm effects on general problem solving ability.

One study showed that sleep, and especially REM sleep, made participants more able to use clues that they had been previously primed with in a prior supposedly unrelated task as the solution on the Remote Associates Task (RAT) (Cai, Mednick, Harrison, Kanady, & Mednick, 2009). This benefit of sleep compared to wake was however present only for the participants that had entered REM sleep during the nap, and not for the ones that had not. There was however no correlation reported between REM duration and improvement on the RAT items, making it unclear if REM sleep was a causal factor in itself or if having REM during a nap is associated with some other variable related to solving the RAT. This study also included another RAT which showed that the benefit was specific for the primed RAT items and was not attributable to sleep increasing general RAT performance. Another study using the RAT without prior priming showed that sleep resulted in increased improvement on a RAT that was completed before and after the delay interval (Sio, Monaghan, & Ormerod, 2013). This effect was however only observed for the difficult and not for the easy, items and no measurement of baseline RAT ability was included. Using a task highly similar to the RAT, Landmann et al., (2016) did not find sleep to improve performance on items that participants had not been able to solve before the delay interval. Neither was there any correlation between any sleep variables and any of the RAT measurements.

## Sleep and relational memory

Relational memory is one step more complicated than simple associative memory which indicates remembering the association between two items. In relational memory tasks, one cue (A) is sometimes presented together with B and sometimes with C. B and C are never presented together but they are still related because they have both been presented together with A. A relational memory test measures the ability to associate B and C. Sleep has been found to increase relational memory compared to wake in two different studies (Alger & Payne, 2016; Lau, Tucker, & Fishbein, 2010). Alger & Payne (2016) found a negative correlation between REM sleep and associative memory but a positive correlation between REM and relational memory. Lau et al. (2010) instead found effects of SWS, which was

related to an increase in relational, but not in associative memory. However, there was also a correlation between the amount of post learning SWS and performance on an immediate associative memory test before the delay interval, which could have been driving this effect. Further, in the sleep group, there was no correlation between associative and relational memory performance. In the wake group however, there was a tendency towards such a correlation, suggesting that perhaps after sleep, the connection between B and C was less dependent on correctly remembering the cue that they had in common, but instead they had formed an association of their own.

## The effect of sleep on learning of rules and patterns

Several studies have examined the effect of sleep on detecting patterns as well as on learning to generalize rules in made-up languages to novel stimuli that follow the same rules. One study found sleep to increase participants' explicit, but not their implicit, knowledge of a pattern of in which location on a screen that a target would appear depending on where previous targets had appeared (Fischer, Drosopoulos, Tsen, & Born, 2006). There were no correlations between any sleep variables and either implicit or explicit knowledge of this pattern. Using a similar design, Fischer, Wilhelm and Born (2007) found that implicit knowledge increased after sleep compared to after wake in adults, but the opposite effect in 7-11 year old children, where sleep led to a decrease of implicit knowledge whereas performance was unchanged after wake.

Other studies have found similar effects of sleep on understanding rules and predictabilities in either sequences of sounds as well as for figuring out grammatical rules in made-up languages in both adults (Nieuwenhuis, Folia, Forkstam, Jensen, & Petersson, 2013) and in children (Gomez, Bootzin, & Nadel, 2006; Hupbach, Gomez, Bootzin, & Nadel, 2009). But see also Mirkovic and Gaskell (2016). Two studies without wake control groups found that the combination of SWS and REM sleep during the night predicted having understood a grammatical rule (Batterink, Oudiette, Reber, & Paller, 2014) and that cuing sounds that had been present during encoding increased the grammatical rule understanding during the re-test in a similar task (Batterink & Paller, 2015).

## Lexical integration

Several studies have found a role of sleep in the lexical integration of recently learned words. Lexical integration means that for example having integrated the pseudo word “Cathedruke” would make it take longer to make judgements about the previously known word “Cathedral” (compared to making judgements about a word to which no competitor has been introduced). This is because these two words would now be lexical competitors, whereas no such competitor to “Cathedral” would exist before having integrated “Cathedruke” into one’s vocabulary. Such a role for sleep in lexical integration has been found in several studies (Dumay & Gaskell, 2007; Henderson, Weighall, Brown, & Gaskell, 2012; Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010; Wang et al., 2016). Tamminen et al. (2010) further showed that the degree of lexical integration was correlated with the amount of spindles during the night after learning. In these studies, it has also been found that the sleep and the wake group did not differ at an additional re-test taking place after 24 hours or more after encoding when both groups had slept. This indicates that unlike for memory, the timing of sleep in relation to learning is perhaps not as important for lexical integration. Another study found lexical integration to be a mere effect of the passage of time, regardless of if that time had contained sleep or wake (Szmalec, Page, & Duyck, 2012).

## Gist abstraction

One study found sleep to be beneficial compared to wake for making participants able to understand the meaning of novel Chinese signs, based on similarity to signs that they had seen before (Lau, Alger, & Fishbein, 2011). Participants first learned the English translations of Chinese signs which were divided into blocks of three signs each. The signs in each block were all conceptually related and shared a similar “conceptual radical”. For example, the signs for “sister”, “mother” and “maid” all share a similar feature meaning “woman”. After sleep or wake, the participants were tested on the memory for the meanings of the signs that they had previously learned, as well some novel signs that they had not previously seen but which included the same conceptual radicals as the signs seen before. Then, participants viewed the different conceptual radicals by themselves and were asked to type their meaning. Sleep resulted in better performance both for guessing the meaning of the novel signs as well as for the meaning of the conceptual radicals. Another study examined the role of sleep in identifying commonalities with 9-15 months-old children (Friedrich, Wilhelm, Born, & Friederici, 2015). The

children first viewed images of made up objects combined with their pseudo-word names. Each name had several similar looking objects associated with it, so that they would make up a category. At the re-test, the children viewed both the same objects again as well as some novel ones that looked similar to those seen before. The objects were presented together with either the correct or the incorrect category name. ERP results revealed better generalization learning after sleep compared to after wake, as evident by larger ERP differences between correct versus incorrect word-object pairings in the sleep group. In the sleep group, generalization of word meaning was correlated with spindle amplitude during the naps. Even if none of these two studies involved emotional material they are still relevant when discussing the effect of sleep on the generalization of fear learning. If sleep is superior compared to wake for identifying commonalities and in grouping objects into categories based on their similarities, it could suggest that after sleep, less similarity to something previously associated with danger would be needed for the triggering of a fear response. This would be because after sleep, a person would be more likely to think that they are associated with the dangerous stimulus. Neither of these two studies showed impaired memory for the studied objects however, arguing that generalization was not dependent on forgetting of the veridical details.

A contrasting result was found in a study which showed that sleep led to less generalization of word learning compared to time spent awake (Werchan & Gomez, 2014). Participants were 2.5 year old children who first viewed different versions of made up objects presented on differently colored backgrounds, and then learned the name of these object, which were pseudo words. At re-test, the children were presented with four different objects, of which one was a different version of the object that they had previously learned the name of, and were asked to point at the object with that name. Results revealed significantly worse performance in the children who had slept between learning and re-test, compared to the children who had not. Only the wake group performed significantly better than chance. The authors suggested that this could be related to sleep preserving the memory of the individual features which made generalization more difficult.

Takeuchi et al. (2014) measured the effect of sleep on memory organization. During encoding, participants first viewed 16 different words that were divided into five different categories (animals, countries, musical instruments and vegetables). Memory organization was defined as the degree to which words belonging to the same category were presented together (semantic clustering ratio) in a free recall task. There was no difference between the sleep and the wake group in semantic clustering ratio. This could argue that sleep is not involved in categorizing stimuli to a higher degree than wake, even though it is unclear to which degree clustering items together when writing them down is representative for to which degree one thinks about them as a category.

## False memory formation during sleep

A highly suitable paradigm for measuring if sleep enhances gist abstraction at the cost of veridical recall is the Deese-Roediger-McDermott paradigm (Roediger & McDermott, 1995). In this paradigm, participants are presented with several different word lists. Each list contains words that are all categorically related to a target word (critical lures) which is not presented in the list itself. At a subsequent re-test however, participants often claim that the critical lures have been presented in the lists (to a higher degree than non-related lures are claimed to have been present in the lists). This is believed to be caused by the fact that when these words are processed, the target word is activated as well, which creates a false memory of having seen it. If newly acquired memories are reactivated during sleep in concert with previous memories that are related to them, it would be expected that sleep, compared to wake, after encoding, would increase the presence of false memories. If sleep creates more false memories, it would suggest that it could also be involved in the generalization of fear learning. This would be because it would create fear responses also to stimuli that has not been directly associated with an aversive stimulus, based on them being conceptually associated with stimuli that has.

Studies on sleep and false memory formation have revealed quite mixed results. According to the meta-analysis by Chatburn et al. (2014), the main factor predicting whether there is an effect or not has been if memory has been tested with free recall or through recognition. For free recall, there has been a large effect size of sleep increasing the degree of false memory formation whereas with recognition tests, there has been a very small effect size.

### **Free recall tests**

Several studies using free recall have found more false memories after sleep compared to after wake (Diekelmann, Born, & Wagner, 2010; McKeon et al., 2012; Payne et al., 2009). The study by Diekelmann et al. (2010) however also included a TSD group that did the re-test at the same time as the sleep group and found no difference, which indicates that perhaps the effects in this study were rather caused by circadian rhythms. The McKeon et al. (2012) study used both negative and neutral word lists but found no difference in the degree of false memory formation depending on emotion.

## **Recognition tests**

One study found less false memories after nighttime sleep compared to after TSD, but not compared to after daytime wake (Diekelmann, Landolt, Lahl, Born, & Wagner, 2008). Additional experiments showed that the increased degree of false memories after TSD was more related to the effects of being sleep deprived during the re-test, rather than by the lack of sleep after encoding. Another study consisting of several different experiments found sleep to reduce the degree of false memories (Fenn, Gallo, Margoliash, Roediger, & Nusbaum, 2009). A study with older adults (Lo, Sim, & Chee, 2014) found less false memories in the sleep group for ‘Remember’ responses but not for ‘Know’ responses, as well as a negative correlation between time spent in SWS and false memories, but only for ‘remember’ responses. Darsaud et al. (2010) found an increased degree of false memories after sleep, but only for ‘Remember’ responses. However, the sleep group also claimed that they remembered more of the unrelated lures, indicating that the difference was based on a more lenient response criterion after sleep rather than on any actual difference in false memory formation. There was no difference in false memory formation for ‘Know’ responses.

## **Other paradigms examining the role of sleep in false memory formation**

Two studies have examined the role of sleep in false memory formation with paradigms not based on semantic relationships between the encoded items and the expected false memories. In one study (Calvillo, Parong, Peralta, Ocampo, & van Gundy, 2016), participants first viewed photographs depicting two different events and then read statements about these events. Some of these statements were inaccurate, in that they did not correspond to the content of the photos. At the re-test, participants read statements about the photos and were asked to say if they were true or false. Some of these statements included information from the misleading statements read after watching the photos. Results revealed that sleep, to a larger degree than wake, made it more difficult to differentiate information seen in photos from information read in texts that inaccurately described these photos. Another study found quite opposite results with restricted sleep leading to more incorporation of misinformation (Frenda, Patihis, Loftus, Lewis, & Fenn, 2014). This study however had all participants sleep after learning and divided participants into groups post-hoc based on their sleep duration the night after learning with those reporting less than 5 hours of sleep being counted as a “restricted sleep” group whose results were compared with those with a sleep duration of more than 5 hours. Because of the division into sleep different groups being done post hoc in this way, it is possible that poor sleepers differ in the

degree of false memory formation to begin with, and that the found differences were not causally related to the amount of sleep after encoding.

## 6. Summary of the empirical studies

Here follows a summary of the studies included in this thesis. The first two studies were about the effect of sleep on the retention and the generalization of fear learning whereas study 3 examined the role of sleep in the consolidation of emotional memories subjected to retrieval suppression.

### Study 1 and 2 - The effect of sleep on the retention and generalization of fear learning

Sleep has previously been found to be involved in consolidating emotional memories, altering emotional reactivity as well as in making generalizations based on previous learning. Based on this, we examined if sleep was involved in the generalization of fear learning. Because sleep has been found both to increase the discrimination between a CS+ and a CS-, as well as to be involved in the generalization of learning, we had an open-ended hypothesis where there were reasons to expect results in both directions. This is a highly relevant research question when it comes to determining if it is adaptive to sleep in the aftermath of a traumatic experience or not, because it is important that a fear response is constrained only to the stimulus that is actually worth fearing, and is not generalized to other stimuli that should not merit a fear response. The important novel contribution of the design used in these studies was that visual similarity to the original CS+ varied gradually, which allowed for the examination of exactly how many “steps” of visual similarity that the fear learning had been generalized after sleep compared to after wake.

In order to examine fear generalization, we used a paradigm developed by Lissek et al. (2008). In this paradigm, participants first undergo fear conditioning where a small and a large circle function as the CS+ and the CS- respectively (counterbalanced across participants). Then, during the re-test, participants are once again exposed to these two circles, but also to eight novel circles that gradually vary in size between the CS+ and the CS-. With this design, it is possible to examine to which degree fear responses are generalized also to stimuli similar to the CS+, even though participants have not had any negative



experiences with those stimuli in particular. With the suggested role of sleep in the generalization of learning, it could be expected that fear responses would be generalized to a higher degree after sleep compared to after wake. Previous studies on fear conditioning have however also found sleep to increase the difference in responses between the CS+ and the CS- (Menz et al., 2013, 2016) and thus, the exact role of sleep in this process remains uncertain.

## **Study 1**

In the first study, we recruited 53 participants, of which 43 remained (20 in the wake group and 23 in the sleep group) after excluding participants for various reasons (most commonly because they did not have any fear responses at all during the re-test). Participants arrived to the lab in the morning and then underwent a fear conditioning session where the UCS was an aversive sound. Fear responses were measured by SCRs. After conditioning, participants were randomized into either a wake group, who spent two hours quietly resting, or a sleep group, who had a two hour sleep opportunity. The re-test was performed approximately 3.5 hours after the end of the conditioning session. No sounds were played during the re-test, in order to avoid novel fear learning that could perhaps vary between the groups depending on if they had spent the delay interval asleep or awake. After the re-test, participants viewed the stimuli again and rated the degree of unpleasantness they associated with each circle.

Results revealed that conditioning was successful, with significantly larger responses to the CS+ compared to the CS-, and that there were no differences between the groups. Analyzing the retention of fear learning, through comparing responses the CS+ to the CS- during the re-test, revealed a tendency towards larger responses to the CS+ compared to the CS-, but no interaction with group, indicating similar retention of fear learning in both groups. Including also the novel stimuli in order to test the generalization of fear learning revealed that for all participants combined, there was an increase in fear responses depending on visual similarity to the CS+. There was however no interaction effect between group and CS, indicating an equal degree of generalization in both groups. This was also the case for the subjective ratings. No sleep variables were correlated with differences in SCRs between the CS+ and the CS-.

This study thus found no support for that sleep compared to wake in the delay interval between conditioning and the re-test would differently affect either the retention or the generalization of fear learning.

## Study 2

In the second study, the same research question was examined again but with some important methodological differences. First, we used electric shocks instead of the aversive sound as the UCS, in order to create larger fear responses. Additionally, we added a novel stimulus not seen before (a blue triangle) during the re-test, in order to control that the groups did not differ in their baseline physiological reactivity due to having spent the delay interval asleep or awake. All other procedures followed those of Study 1.

We initially recruited 58 participants of which 49 remained after excluding non-responders. We analyzed the data in two different ways: 1. Including all participants; and 2. Including only those who acquired a differentiated fear response (responses to CS+ > CS-) during conditioning ( $n=33$ ). In a questionnaire on various mood scales completed before participation, we found a tendency towards participants in the sleep group having higher scores on the Penn State Worry Questionnaire (PSWQ) (Meyer, Miller, Metzger, & Borkovec, 1990). Therefore, PSWQ scores was added as a covariate in all analysis, because it has previously been shown to correlate with higher responses to the CS+ compared to the CS- (Otto et al., 2007).

Results from the conditioning, when including all participants in the analysis, revealed larger responses to the CS+ compared to the CS-, but also that there was an interaction effect between CS and group, showing that this difference was significantly larger in the participants who would subsequently be randomized into the sleep group, compared to those who would be randomized into the wake group. When analyzing only the participants who had higher responses to the CS+ compared to the CS-, this group difference was no longer present. Thus, we went on to only analyze the participants who had acquired a differentiated fear response during conditioning.

Examining the retention of fear learning revealed a significant interaction between group and CS which was driven by larger responses to the CS+ compared to the CS- in the wake group, whereas no such difference was present in the sleep group. Responses in general were similar in both groups, the only difference was in how the responses were distributed between the stimuli.

For the generalization of fear learning, there was a tendency towards a significant interaction between group and CS. Post hoc tests revealed that in the wake group, there was an increase in responses to the stimuli depending on their similarity to the CS+ whereas such an effect was not observed in the sleep group. In the sleep group, responses to the CS+ did not differ from any of the other circles, regardless of their fear relevance.

There were no group differences in the subjective ratings of unpleasantness. Neither were there any group differences in fear responses to the novel blue triangle (which surprisingly elicited larger responses than most other stimuli in both groups), indicating no group differences in general physiological reactivity. No sleep variables were correlated with the difference between the CS+ and the CS-.

### Study 3 – The effect of sleep on unwanted emotional memories

In the third study, we examined the role of sleep in consolidating memories for items that had been subjected to retrieval suppression. An additional research question was, if sleep has an effect on the forgetting of unwanted memories – will this effect be larger for emotional compared to neutral material, considering the suggested role of sleep in emotional memory consolidation. Because previous studies have reported contrasting findings on the role of sleep in forgetting, we did not have a directed hypothesis for this research question either. Based on previous studies, sleep could be expected to increase the difference in memory performance for items expected to be remembered compared to items expected to be forgotten, but sleep could also be expected to “repair” memory for items subjected to suppression or inhibition.

In order to induce suppression, we used the Think/No-Think (T/NT) paradigm (Anderson & Green, 2001). In our version of this paradigm, participants first arrived at the lab in the morning and learned associations between neutral words and images that were either neutral or negative. Learning of these associations was tested by only showing the words on the screen, to which the participants were asked to tell which image it had previously been associated with. When participants showed sufficient learning of these associations they proceeded to the T/NT phase. In this phase, a subset of the words were repeatedly shown on the screen again, in either green or red font color. When a word was presented in green, participants were asked to think about the image it had previously been associated with (Think items). When a word was shown in red, they were asked to try to keep all thoughts of the previously associated images out of mind (No-Think items). A subset of words were not shown at all during this phase (Baseline items). Suppression-induced forgetting is defined as the decrease in memory performance for the No-Think items compared to the Baseline items. This is referred to as the No-Think effect.

After the T/NT phase, participants were randomly divided into either a sleep ( $n=17$ ) or a wake ( $n=16$ ) group. Participants in the sleep group had a two hour

sleep opportunity, whereas participants in the wake group spent two hours quietly resting. An additional group, the No Delay group ( $n=17$ ), performed the re-test 5 minutes after the conclusion of the T/NT phase.

The re-test (taking place approximately 3.5 hours after the T/NT phase for the sleep group and the wake group) was a cued recall memory test where all the words were shown again, all in white font color, and participants were asked to say which image they had previously been associated with, regardless of which color they had been presented in during the T/NT phase.

Results revealed that in the No Delay group, there was a significant below baseline decrease in memory performance of the No-Think items (85.3 % for No-Think items compared to 95.1 % for Baseline items). Analyzing the items divided by emotion of the images showed that this forgetting effect was only significant for the negative (a No-Think effect of 15.4 %), and not for the neutral images (a No-Think effect of 4.4 %). No significant No-Think effect was however present in either the sleep or in the wake group, regardless of emotion. Thus, this study showed no support that sleep has a different role in affecting memory for items subjected to forgetting compared to wake. Neither did sleep have a different effect on the material depending on its emotionality, regardless of item type.

The only sleep variable that was associated with memory performance was a negative correlation between SWS duration and negative Baseline items. This was a surprising finding and we are not aware of any theoretical account that would explain why SWS would be involved in decreasing memory performance for only this item type in particular.

Another interesting finding of this study, however not related to sleep, was that there were more intrusions (subjective reports of failing to suppress thoughts of the images associated with the No-Think words during the T/NT phase) for negative, compared to neutral material.



# 7. General Discussion

## Study 1 and 2

In study 1, we found no support for that a daytime nap would affect either the retention or the generalization of fear learning in a different manner than time spent awake. In study 2 however, where we used electric shocks as the UCS instead of the aversive sound in order to elicit a stronger fear response, the results showed a significant difference in the retention of fear learning. Responses to the CS+ were significantly larger than to the CS- after wake whereas after sleep, there was no such difference.

This was surprising considering that previous studies have found sleep to increase the difference between the CS+ and the CS- (Menz et al., 2013; Menz et al., 2016). The results of those these previous studies could be interpreted as that sleeps preserved fear responses to stimuli worth fearing, while decreasing them for stimuli that should be considered safe. In our study, it is difficult to interpret exactly what drove the decreased discrimination of fear responses observed after sleep. In the sleep group, fear responses to the CS+ were significantly lower during the re-test compared to during the last trials of the conditioning. Responses to the CS- changed in the opposite direction, with significantly larger responses during the re-test compared to during the last trials of the conditioning. In the wake group, responses to both stimuli were equivalent before and after the delay interval. One can thus not say that the lack of differentiation between the CS+ and the CS- in the sleep group was driven by the fear responses of the CS+ having been generalized to the CS-, or vice versa. Instead, the degree of fear responses were the same but whereas the wake group showed large responses to the CS+ and low responses to the CS-, the sleep group can be said to have showed “average” responses to both stimuli.

One reason for these contrasting results could be that we used a daytime nap which contained very limited spent time in REM sleep, on average about 10 minutes. Previous studies have found REM sleep to be associated with a differentiation of fear responses (Marshall et al., 2014; Menz et al., 2013). Menz et al. (2016) did not find such a correlation but still only found a group difference for late sleep compared to late wake, and not between early sleep and early wake.

Because late sleep is rich in REM sleep, this could have perhaps been a contributing factor, even though there was no significant correlation between REM sleep and the differentiation of fear responses. The amounts of REM sleep in our Study 1 and 2 were more equivalent to the amount of REM in the early sleep condition of Menz et al. (2016). The small amount of REM sleep could perhaps explain the null finding of Study 1, where the fear responses were unaltered. In our Study 2 however, there was not just a lack of a change, there was one in the complete opposite direction compared to the previous findings. This cannot be explained solely by the low amounts of REM sleep. Further, one previous study has found that a nap is sufficient to detect REM related differences in the retention of fear extinction (Spoormaker et al., 2010).

Whereas the result in our study differed from previous studies in humans, they are in a way more similar to the results often found in rodent studies. Here, there are several findings revealing sleep deprivation after fear learning to impair the memory of this learning (Cohen et al., 2012; Graves et al., 2003; Hagewoud et al., 2010; Hagewoud et al., 2011; Kumar & Jha, 2012; Vecsey et al., 2009). Most of these studies have however used contextual fear learning which is different from the cued fear paradigm that has been used in human studies. For cued fear learning, results have been slightly more contrasting. Kumar and Jha (2012) found that sleep deprivation after learning reduced fear responses when re-exposed to the CS+, whereas this was not found by Graves et al. (2003). Another difference with rodent studies is that there is more rarely a CS-, and that we cannot ask for any subjective ratings of fear. This means that it is more difficult to disentangle how much of the reduction in freezing that is caused by impaired memory of the CS+ meriting a fear response, and how much that is caused by general forgetting of having been in a stressful situation. Thus, it can be difficult to determine how specific the decrease of the fear response is to only the CS+ in particular. Considering that general reactivity was not lower in the sleep group in our Study 2, the results cannot be explained by that these participants had forgotten about the conditioning session, which is a possible explanation in some of the animal literature.

The test of generalization in Study 2 revealed a tendency towards an interaction between group and CS. In the wake group, fear responses increased linearly as a function of similarity to the CS+. In the sleep group however, responses were similar to all the circles, regardless of CS+ similarity. There was no main effect of group which once again indicates that the only group difference was that the responses were differently distributed. This means that one cannot simply say that it was the fear response to the CS+, or the safety learning of the CS-, that had been generalized to the other stimuli. Instead, the sleep group just showed a more “blunted” response, where unlike in the wake group, CS+ similarity was not a predictor of the size of the fear response.

As described in chapter five, sleep has in several previous studies been found to be involved in the active processing of recently learned information. Normally in this kind of studies, several different exemplars of following a certain rule are presented, which participants then after sleep, in a higher degree than after wake, are able to apply to a novel exemplar not seen before that also follows this rule. These studies often show many exemplars following this rule (which of course is necessary in order to understand that it is a rule or a general pattern). The fear conditioning design we used is different from this in that we only repeatedly showed one exemplar of each circle and then expected participants to generalize their experience of these to several different novel stimuli. Still, based on the gist and rule extraction seen in previous studies, we expected that sleep and wake could differ in the degree to which conclusions were drawn based on this learning experience.

### **Different kinds of generalization**

Generalization of fear learning in the Lissek et al. (2008) paradigm that we used is based on the concept of perceptual similarity. Generalization to the novel stimuli is believed to be caused by these being visually similar to the original CS+. One reason for generalization to occur after sleep could thus be decreased veridical recall. If the exact details of the circle that was associated with the electric shock are forgotten, this would make it more difficult to predict exactly which circle size one should be afraid of. It has previously been suggested that sleep abstracts the gist of an experience at the expense of veridical recall. This has been evident in for example the emotional trade-off paradigm where sleep strengthens the memory for an emotional central object without strengthening the memory for the neutral background it has been presented in (Payne et al., 2008). It can also be seen in studies of false memory formation, where words that are categorically similar to words that are presented in a list are falsely remembered as having been presented in the list as well. This effect has usually been found to be larger after sleep compared to after wake (e.g. McKeon et al., 2012; Payne et al., 2009) (these sleep effects however only seem to be present when testing memory with free recall and not with recognition, as discussed in chapter 5). This abstraction of the gist, at the expense of veridical recall, would make the memory more applicable to novel situations that are similar, but not exactly the same, as the original learning situation. This is because less similarity to the original learning situation would be needed in order to understand that the same rule or pattern still applies. If sleep in our study decreased the memory for which circle that functioned as the CS+ and the CS- respectively during conditioning, then this could explain that the sleep group had similar responses to both of them. With maintained veridical recall, one might for example associate large circles with danger and small circles with safety,



but with decreased recall of this contingency, all circles could instead have potential fear relevance. The results of subjective ratings of unpleasantness did however not support such an interpretation, considering that both groups rated the CS+ as more unpleasant compared to the CS- and that this difference was similar in both groups, even though it should be noted that this was not a memory test per se. That sleep dependent generalization of emotional responses is not driven by veridical recall is further supported by the findings of Kuriyama et al. (2010), who also found generalization of physiological responses but no differences in explicit memory. Menz et al. (2013) did also not measure memory of which stimulus that had been associated with the shock itself but found that the difference in shock expectancy ratings during the re-test between the CS+ and the CS- was smaller in the wake group, indicating less explicit awareness of which stimuli that was worth fearing after wake. Menz et al. (2016) further found a larger difference in shock expectancy to the CS+ compared to the CS- after late sleep compared to after late wake, but not after early sleep compared to after late wake. Regarding the Pace-Schott et al. (2012) study, where it was found that the sleep helped to generalize the decreased fear responses from one spider to another, it is of course possible that this was aided by a sleep dependent forgetting of the exact details regarding the first spider, making it easier to generalize learning based on the first to a novel spider, but this was not measured.

Generalization can of course also be perceptually driven without a decrease in veridical recall. Several studies using non-emotional material have found increased gist abstraction after sleep compared to after wake without this being coupled with any impairment of veridical recall (e.g. Ellenbogen, et al., 2007; Lau et al., 2011). Even though one is fully aware of the exact features of the dangerous circle, one could still generalize the fear response to other stimuli that are visually similar, perhaps more based on a categorical generalization. Such an interpretation is perhaps more in line with the findings of Pace-Schott et al. (2012) where the category “spiders” after exposure therapy could be considered as safe, which would allow for the generalization of decreased responding also to novel exemplars belonging to this category, regardless of visual similarity. If sleep allows for a more flexible use of previous memories and for making looser associations, this could be the active mechanism in sleep-dependent transferring of learning based on one exemplar to other exemplars belonging to that same category.

Kuriyama et al. (2010) found sleep to generalize physiological responses to images from the video clips of motor vehicle accidents to images from video clip of normal traffic situations that were also viewed during encoding, but not to novel images. This would suggest that sleep did not create the belief that all images of cars merited a physiological reaction, only the ones that been present during encoding. This argues that sleep related generalization is not mainly perceptual or

categorical, but that sleep generalizes responses based on session. This would for our study mean that sleep could have resulted in equal responses to the CS+ and the CS- because they had both been present during the conditioning session. Because electric shocks were delivered during this session, all stimuli presented during this session could thus be associated with negative affect, regardless of whether they had been directly paired with the shock or not. This would be consistent with theories saying that overlapping memories get activated together during sleep, which would allow for the CS+ to “taint” the emotional responses also to the CS-, and thus give them equal fear relevance. Such an interpretation would be congruent with the findings of Kuriyama et al. (2010) but not with Menz et al. (2013, 2016), where the opposite of such sleep dependent “session based” generalization was found, as evident by the larger differentiation between the CS+ and CS- after sleep. Another contrasting finding is Porcheret et al. (2016) who found sleep, compared to TSD, to decrease the generalizations of fear ratings from images from a non-traumatic film to images from a video clip stemming from a non-traumatic film.

Our Study 1 and 2 was, to the best of our knowledge, the first studies on the effect of sleep on generalization of emotional responses, to add novel stimuli during the re-test that gradually varied in similarity to the CS+. The novel contribution of this was that we hoped that it would allow us to isolate only one continuum along which fear relevance varied (in this case, circle size). Previous studies that have added novel stimuli during the re-test have not been able to do this because similarity (either perceptual or categorical) have not had this gradual variation. However, considering that there were no differences between any circles in the sleep group, we could not draw any conclusions regarding if the generalized responses in the sleep group was caused by perceptual, categorical or “session based” generalization. This is especially difficult given the highly contrasting findings of previous studies. It should also be stressed that these different kinds of generalization in no way are mutual exclusive.

Our study did not include any neural measurements but it could still be of interest to speculate what would have happened if we did. One account of the neural basis of the generalization of fear learning is Lissek (2012). This account suggests a perceptual model, where for each encountered generalization stimulus during the re-test, the hippocampus determines the degree of similarity to the original CS+. If sufficient similarity is detected, the hippocampus initiates a ‘pattern completion’ process which then leads to activation of the same brain regions that would be activated when encountering the CS+. If there is not sufficient visual overlap with the CS+, ‘pattern separation’ is initiated in the hippocampus, and brain areas related to inhibiting the fear response are activated. Thus, with increased visual similarity to the CS+, there would be a linear increase of regions associated with fear expression and a linear decrease of regions associated with inhibiting the fear

response. Support for this account was found in an fMRI study using a paradigm similar to ours (Lissek et al., 2014). In another study using a similar paradigm, but with faces instead of geometrical shapes, Onat and Büchel (2015) suggested that all generalization of fear learning is not perceptually driven. Whereas the activity of several brain regions, as well as behavioral and autonomic responses in a linear way depended on visual similarity to the CS+, other brain areas responded to the stimuli based on other factors than this. Further, different regions had different “fear tuning profiles”, meaning that the slope of increase or decrease depending on CS+ similarity varied considerably between regions. Responses in certain object-sensitive visual areas were for example larger for the CS+ and the CS- compared to all other stimuli, indicating that these were perhaps more involved in determining stimulus ambiguity. Similarly, activity in the anterior insula responded strongly to the CS+ but then had a more rapid decrease, indicating that this area is more involved in detecting the actual threat than in detecting similarity to it in other stimuli. Because no study so far has used brain imaging in order to examine the effect of sleep on the generalization of fear learning using stimuli that have gradually varied in similarity to the CS+, we do not know which of these aspects that were affected by sleep in our study. It is possible that sleep decreased veridical recall, making it more difficult for the hippocampus to know if it should initiate a pattern completion or a pattern separation process. Further, we do not know if perhaps visual areas were affected making it more difficult to determine which stimuli that had an ambiguous meaning, or if less discriminative activity in the insula made it more difficult to determine which stimulus that was the original CS+. This could be compared with Goldstein et al. (2013) who showed that after normal sleep, the anterior insula showed larger responses to cues for which it was uncertain if they would predict a negative or a neutral stimulus. After sleep deprivation however, participants had increased insula activity to all cues, both certain and uncertain.

As always with sleep research, it is difficult to know to which degree the observed group differences in our study were actually caused by the stimuli having been differently processed during sleep and wake. Any group differences could instead have been “created” during the re-test due to different learning ability between the groups. If sleep prepares an organism for novel learning to a different degree than wake, that could be what caused the observed group differences during the re-test. We did not include any aversive stimuli during the re-test because we did not want any novel fear learning during this stage. It is still possible however that the group differences had been influenced by different degrees of extinction learning. Our design was not optimized to measure extinction to any stimulus in particular. In Study 1, there was a tendency towards a more rapid decrease of physiological responsivity in general in the wake group. No such effect was found in Study 2. Previous studies have however found that sleep before learning can influence the

degree of learning acquisition. Sleep deprivation before extinction learning has for example been found to impair the ability to achieve lasting extinction learning (Straus et al., 2016) and REM sleep the night between conditioning and extinction has been found to be correlated with lower fear responses to the CS+E (Spoomaker et al., 2014). Similarly, animal studies have showed that REM deprivation after conditioning has made it more difficult to extinguish fear responses during the subsequent day (Silvestri, 2005; Silvestri & Root, 2008). It has further been showed that inducing REM rebound before conditioning increased the degree of fear acquisition, whereas REM deprivation before conditioning did not affect the degree of acquisition (Ravassard et al., 2016). Translating this to our second study, it could mean that the results were caused by the groups to a different degree acquired novel learning during the re-test. Because no electric shocks were actually delivered, all stimuli had the same “actual” fear relevance during this session. Thus, that the sleep group responded similarly to all stimuli could be interpreted as that they were more able to realize this. This should however have been accompanied by a general decrease in responses if the sleep group was somehow more able to learn that the stimuli were no longer dangerous, which was not the case. Still, it is of course possible that the sleep group to a higher degree than the wake group could have expected that other stimuli would be paired with the shock during the re-test. This is however not consistent with the studies of Menz et al. (2013, 2016), where there were larger differences in shock expectancy between the CS+ and the CS- after sleep compared to after wake, indicating no such increased tendency to expect a contingency reversal during the re-test after sleep.

### Study 3

The third study was a null-finding regarding the comparison between sleep and wake. The Think/No-Think paradigm that we used created below baseline forgetting of the No-Think items when the re-test was performed right after the conclusion of the No-Think phase. Such an effect was however not present in the groups performing the re-test after a delay interval of 3.5 hours containing either sleep or wake. This was interpreted as that that the delay interval increased the memory of the No-Think items, considering that there was actually an increase in memory of these items in both the sleep and the wake groups compared to the No Delay group, whereas the groups did not differ in memory performance for any other item type. The major research question was however if sleep and wake would differently reduce the No-Think effect, which was not supported. Previous studies have found sleep to both increase and decrease memory performance for items that for various reasons can be expected to be forgotten. Findings on the

effect of sleep on forgetting have varied both between studies using different paradigms, as well as between studies using the same paradigm (as in the studies on the effects of sleep on retrieval-induced forgetting that were discussed in chapter 4). Given this discrepancy of the previous studies, the null finding is perhaps not so surprising.

The results are similar to those of Fischer et al. (2011), who also found no below baseline forgetting after a delay interval of either sleep or wake. However, they did not have a No Delay group, and therefore it is difficult to know what the degree of forgetting would have been at an immediate re-test (this is of course also the case for our study, even though it maybe be assumed that the sleep and the wake group would have performed similar as the No Delay group at an immediate test). In a second experiment however, they found a rebound effect, with better memory for No-Think items compared to Baseline items after late, but not after early sleep. This could perhaps be related to REM having a role in strengthening the memory of the No-Think items, even though no correlation with REM duration was reported. Our study found no effect of REM duration on memory performance for either kind of item type. This was perhaps caused by the low amount of REM, on average only 9 minutes, even though there are studies that have found REM to be correlated with forgetting also in nap designs (Hoedlmoser et al., 2015; Oudiette et al., 2013).

Most other studies have also found the forgetting effect created in the Think/No-Think paradigm to dissipate with time (Meier, König, Parak, & Henke, 2011; Nørby, Lange, & Larsen, 2010; Noreen & MacLeod, 2014). But see Hotta and Kawaguchi (2009). Our study provided no support for that this would be different if the T/NT phase was immediately followed by sleep. Most previous studies that have tested the duration of this effect have had the re-test after a longer delay interval than we had here, and this is the first study to show that below baseline forgetting had disappeared after already 3.5 hours of wake.

No support was found for that sleep would be especially beneficial for emotional memory, regardless of item type. This was also, to our knowledge, the first study to compare emotional memory performance between a sleep and a wake group where the negative and neutral material varied only in valence and not in arousal. Thus, one explanation could be that sleep mainly strengthens memories based on their arousal and not on their valence. However, as discussed in chapter 2, the effect that sleep is more beneficial for negative, compared to for neutral, memories is replicated in far from every study. None of the previous studies examining this using cued recall have found such an effect. One study found no effect of emotion (McKeon et al., 2012), and one actually found an effect in the opposite direction (Alger & Payne, 2016). Further, we did not find any correlations between REM sleep and emotional memory of either type. This is perhaps not that surprising

considering that quite few studies have found such a correlation. Effects indicating a role of REM sleep in the consolidation of emotional memories are more frequently found in split night or selective REM deprivation designs.

Study 3 was the first study to explicitly examine the role of sleep on forgetting where the material has varied in emotionality. A very interesting previous finding on this topic however is Kuriyama et al. (2013), who found that after sleep, participants' physiological reactivity increased compared to wake after having received 'forget' instructions during encoding, whereas emotional reactivity decreased compared to wake after 'remember' instructions.

The role of sleep in the consolidation of unwanted memories is an especially important research question in regards to affective disorders, where, as will be discussed in the next section, both sleep disturbances and the inability to keep unwanted negative thoughts and memories out of mind are common features.

## The bigger picture

### **Sleep after a traumatic experience**

So, is it adaptive or not to sleep in the aftermath of a traumatic experience? As we have seen, we are quite far from reaching a conclusion regarding this question, and there are several different aspects that need to be taken into consideration. Given that sleep has often been found to be beneficial for memory consolidation in general, and sometimes also to be even more beneficial for emotional stimuli, it is likely that negative experiences will be better remembered after sleep. It is however, not necessarily so that poorer recall of an event in any way means that it will be processed in a more adaptive manner. Poorer memory of the event could for example be related to increased generalization. Regarding the role of sleep in generalization, results have varied greatly, with some studies finding sleep to lead to less, and some to more generalization of the emotional experience. Similar contrasting findings have been revealed regarding the role of sleep in altering emotional reactivity. Two studies have found sleep deprivation after watching negative video clips to result in fewer intrusive memories from these videos, and one study has found results in the opposite direction with fewer intrusions after sleep (Kleim et al., 2015; Porcheret et al., 2015, 2016). It should also once again be mentioned that the sleep we would have after a negative experience will not be the same as the sleep we would have after a normal day, that individuals with difficulties adaptively processing emotional events might also have impaired sleep

quality to begin with and that disturbed sleep could also be a marker of having been more negatively affected by the event.

A finding that has been more reliably replicated however, even if there are some variations of these findings as well, is the role of sleep, and especially REM sleep, in the consolidation of extinction learning (e.g. Kleim et al., 2014; Menz et al., 2016; Pace-Schott et al., 2012, 2014; Spormaker et al., 2010, 2012; Straus et al., 2016). This would argue that sleep after learning that something is safe should probably be encouraged, tentatively suggesting that therapy should be placed in closer proximity to sleep. Similarly here, it could also be so that certain sleep events are not causal, but instead only markers of successful extinction learning, even though experimental studies have found a causal role as well.

### **Sleep in affective disorders**

It might, or might not be, adaptive to avoid sleep right in the aftermath of a traumatic experience. It is possible that sleep deprivation right after the experience could serve a protective function against consolidation, intrusions or overgeneralization. Importantly however, there are also several studies saying that sleep deprivation after a negative experience could have negative consequences. No one could however argue that more chronic sleep problems serve any adaptive function. Sleep disturbances are a common factor in almost all psychiatric disorders. In a meta-analysis containing 177 studies, with in total 7151 participants, it was reported that sleep duration and sleep efficiency was reduced in most patient groups, and that REM sleep percentage was increased in affective disorders (Benca, Obermeyer, Thisted, & Gillin, 1992). It should be mentioned however that sleep disturbances are a part of the diagnostic criteria for many disorders, and thus, some degree of overlap between these two factors is per definition unavoidable.

It has been reported that people suffering from insomnia were almost ten times more likely to be clinically depressed, and 17 times more likely to have clinical levels of anxiety compared to people without insomnia in a community based sample of 772 participants (Taylor, Lichstein, Durrence, Reidel, & Bush, 2005).

It is difficult to disentangle the causality regarding negative affect and sleep disturbances. As mentioned in the introduction, negative affect disturbs sleep and disturbed sleep increases our emotional reactivity. One way of examining the causality is to study the temporal course of the occurrence of negative affect and sleep complaints. In a meta-analysis of longitudinal studies, Baglioni et al. (2011) found that insomnia at baseline in individuals with no depression at this point doubled the risk of having developed depression at a follow-up after one year or later. For anxiety disorders, the order of onset seems to be the reversed, with

anxiety most often occurring at either the same time, or before, the onset of sleep disturbances (Ohayon & Roth, 2003).

Bryant, Creamer, O'Donnell, Silove and McFarlane (2010) recruited participants who had recently been hospitalized after an injury and asked them about sleep disturbances during the two weeks prior to the injury. Three months later, their psychiatric problems were assessed. The results revealed that sleep disturbances prior to the injury significantly increased the risk of having developed a psychiatric disorder at follow-up, also when controlling for prior disorders. This could argue that poor sleep makes it more difficult to process negative events. Adult sleep disturbances can however also be caused by emotional distress earlier in life. In a large sample with over 25 000 participants, it was found that childhood adversity predicted lower sleep quality in adult life, even when controlling for several possible confounding factors such as health behaviors and recent life events (Koskenvuo, Hublin, Partinen, Paunio, & Koskenvuo, 2010). This indicates that sleep could perhaps be a marker of previous aversive experiences that makes it harder to cope with novel negative experiences, and not the causal mechanism of this impaired coping. One study found insomnia at baseline to predict depression four years later (Batterham, Glozier, & Christensen, 2012). However, this effect disappeared when controlling for rumination, which indicates that sleep problems could for example be a marker for rumination, which affects both sleep and the ability to cope with negative events without being causally related to each other.

### *Sleep in depression*

Depression has been associated with several alterations of sleep architecture, such as increased time spent in REM, decreased REM latency, increased REM density and decreased SWS (for review, see Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013). Sleep alterations also seem to persist after remission from depressive episodes, and they also seem to be a predictor of novel episodes. It has also been shown that people with depression show a smaller decrease of metabolism in several regions of the brain during NREM sleep which could perhaps explain that their sleep is experienced as less restorative (Germain, Nofzinger, Kupfer, & Buysse, 2004).

Regarding the contribution of different sleep stages, it should also be mentioned that the REM sleep of individuals suffering from depression is different as compared to the REM sleep of individuals who do not. It has for example been shown that the amygdala is more activated during REM sleep in depressed people (Nofzinger et al., 2004). Thus, drawing conclusions about the role of REM sleep in depression based on studies in non-depressed samples is difficult considering that when we are examining the REM sleep of non-depressed participants, we might be studying something else compared to what actually goes on during the REM sleep of a depressed person. This is of course relevant for all sleep studies. For example,



depriving a person with poor sleep quality of sleep is probably less detrimental than sleep depriving a good sleeper. Thus, this is also something to keep in mind also when conducting experimental manipulations of sleep.

Surprisingly in relation to what we know about the aversive effect of poor sleep on mood and emotional reactivity in healthy samples, it has been shown that sleep deprivation could actually improve mood in people suffering from depression (for review, see Wu & Bunney, 1990). These effects however seem to disappear quite rapidly after recovery sleep (for a review on how the effects of sleep deprivation can become more durable in combination with other chronobiological therapies, see Dallaspazia, Suzuki, & Benedetti, 2015). Even though it still has not been examined, one intriguing possibility is that the way in which emotional experiences are processed during sleep in individuals suffering from depression is somehow maladaptive, perhaps because of the increased time in REM or the increased REM density. There might be something that happens during sleep, such as the consolidation of emotional memories, which people suffering from depression actually benefit from having interrupted. As mentioned however, no studies have so far explicitly tested this, and there can of course be several other explanations for this improved mood effect.

#### *Sleep in Post-traumatic stress disorder*

PTSD is a disorder characterized by the inability to cope with a traumatic experience in an adaptive way. Research about the role of sleep in processing emotional experience has thus taken a great interest in the role of disturbed sleep in the inability of adaptive coping in this disorder. Beyond impairing the ability to process an emotional experience during the night, sleep disturbances have also been suggested lead to reduced cognitive resources to handle stress and to a reduced ability to appraise the traumatic event in a functional way during wake. Further the sleep disturbance could also function as an additional stressor in itself (Bryant et al., 2010).

Studies of the specific disturbances of sleep in PTSD have yielded somewhat contrasting results. In a meta-analysis including 20 PSG studies, Kobayashi, Boarts and Delahanty (2007) reported that people with PTSD had more Stage 1 sleep, less SWS and greater REM density. The number of awakenings from REM sleep and WASO have also been found to be positively correlated with PTSD severity (Habukawa, Uchimura, Maeda, Kotorii, & Maeda, 2007). It has further been shown that war veterans with PTSD have higher activity in regions of the brain involved in arousal regulation and fear responses during REM (as well as during wake), compared to war veterans without PTSD (Germain et al., 2013).

Sleep disturbances after a traumatic experience have been found to predict the degree of PTSD symptoms at a later follow-up (Brown, Mellman, Alfanio, &

Weems, 2011; Koren, Arnon, Lavie, & Klein, 2002). In the Koren et al. (2002) study, sleep disturbances were correlated with subjective ratings of the impact of the event, whereas in the Brown et al. (2011) study, sleep disturbances 24 months after hurricane Katrina predicted the degree of PTSD after 30 months, also when controlling for baseline PTSD severity. Klein, Koren, Arnon and Lavie (2003) found that objective sleep quality (as measured by actigraphy) at baseline did no longer predict PTSD at a follow-up after 12 months. Mellman, Pigeon, Nowell and Nolan (2007) found no difference in initial objective TST or subjective reports of insomnia between those who later developed PTSD and those who did not.

In studies using PSG, shorter average duration of REM periods, as well as more REM periods on average 17 days after trauma was shown to be predictive of PTSD development six weeks later (Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002). Mellman, Kobayashi, Lavela, Wilson and Hall Brown (2014) reported that WASO, as well as average REM period length and percentage of REM sleep were correlated with the duration of PTSD in a group of participants that were either currently diagnosed or had recovered from the disorder. Other than that, there were no group differences between the group with PTSD and any of the control groups in any of the sleep variables. The REM variables were related to increased PTSD duration only, and not with PTSD severity. The authors suggested that this was caused by a “rebound effect” where REM sleep is first decreased and fragmented after trauma and then increases. Cowdin, Kobayashi and Mellman (2014) performed PSG on participants who had been exposed to a traumatic situation and found that those who had not developed PTSD had higher prefrontal theta power compared to those who had developed PTSD. The decrease in theta power in the PTSD group was only found during the first and the last REM periods. The authors argued that this would indicate that theta plays a causal role in adaptive processing of emotional experiences.

A growing body of studies has examined if the sleep problems associated with PTSD are present already before the traumatic experience. One suitable group to examine this in is military personnel before deployment to areas where they are likely to have experiences that would qualify as traumatic (i.e. combat). It has been shown that sleep disturbances before deployment is predictive of later developing PTSD (as well as other disorders such as depression and anxiety) (Gehrman et al., 2013; Koffel, Polusny, Arbisi, & Erbes, 2013). Another study found that baseline nightmares, but not insomnia, was associated with a greater risk of having developed PTSD after deployment (van Liempt, van Zuiden, Westenberg, Super, & Vermetten, 2013). In a study on rats, it was found that the number of REM epochs and REM fragmentation during the second half of the inactive period during the night before fear conditioning was associated with increased startle responses one month later to a loud tone in the environment where the conditioning had taken place (Polta et al., 2013). This means that

fragmented REM sleep even before the traumatic experience could result in, or be co-occurring with, increased fear responses to a reminder of the trauma.

In order to see if sleep disturbances are caused by distress earlier in life, Insana, Kolko and Germain (2012) performed PSG on military veterans, measured PTSD severity and asked them about early and late life trauma. Results revealed that early life trauma was associated with REM fragmentation as well as with later life trauma. REM sleep fragmentation was however not associated with PTSD severity.

As we have seen here, sleep, and especially REM sleep, seems to be disturbed in PTSD even though the exact nature of these disturbances seems to vary between studies. Various sleep disturbances right after the traumatic experiences seem to be predictive of later developing PTSD, even though this has not been found in all studies. It is however difficult to say that sleep was not disturbed before the traumatic experience, as evident by studies showing that prior sleep disturbances is predictive of who would later develop PTSD after a traumatic experience. Early life trauma also seems to be related to fragmented REM sleep, and thus we cannot say which occurs first. Even if it is plausible to believe that sleep serves a function in adaptively processing traumatic experiences and that disturbed sleep might make this adaptive processing more difficult, we still do not know if the disturbed sleep is just a marker of impact of the event, early life trauma or negative affect in general. Neither do we know exactly which features of the altered sleep in PTSD that are associated with the impaired ability to adaptively process a traumatic experience. Further studies of exactly which factors during sleep, especially if we can manipulate these, that predict worse overnight processing of emotional experiences, could be of great clinical importance in treating this condition.

Beyond decreased overnight resolution of stress, it is also plausible, given the findings in non-clinical samples, that poor sleep makes it more difficult to consolidate extinction learning. This could be a factor explaining how disturbed sleep is involved in the maintenance of this disorder (for an extended discussion on this, see Pace-Schott et al., 2015b).

## Directions for future research

Considering the variation of the findings so far, my main wish for future research would be studies with more participants. There seems to be large variations of the effect of sleep on emotional memories and some of this variation could most certainly be attributed to random findings caused by small sample sizes. This is further problematic considering the large amounts of different sleep variables that

one can put into a correlation matrix, where one is almost definitely bound to find something to correlate with some type of behavioral or physiological change. Combined with the generally high inter-individual variability in physiological responding, the risk of random effects is additionally increased. Increasing the sample sizes is of course difficult considering that sleep studies are highly time consuming, and in a scientific world where it is important to count the number of publications, there is unfortunately few incentives for collecting the hundreds of participants that might be necessary for finding really robust and replicable results. This critique is of course relevant for the studies in this thesis as well. I would once again like to mention the study by Ackermann et al. (2015), who did not find any correlations between any sleep variable and emotional memory in a sample of 929 participants, as a very positive example.

Studies examining the effect of sleep processing emotional experiences should further always include stimuli not seen before so that we know if the sleep related changes (in either direction) are caused by specific processing of the stimuli seen before sleep in particular, or just by a general change in mood or reactivity.

Concerning disturbed sleep in affective disorders, it would be highly rewarding to examine exactly which symptoms of the disorders that are related to which exact sleep variables, beyond only correlating it with the simple presence or the general severity of the disorders.

Beyond having the possibility of informing clinical practice concerning sleep in the aftermath of traumatic experiences, research about the effect of sleep on emotional memory is important for several other reasons. If different sleep stages are differently beneficial, and some perhaps during certain circumstances, even detrimental, for obtaining optimal mental well-being, this knowledge could be very important. Especially considering technological advances that probably soon, through different methods such as pharmaceutical or through electrical stimulation of the sleeping brain, will allow us to with precision manipulate the occurrence of different sleep stages and other sleep related events during the night. It would be interesting to see if we could experimentally manipulate such factors as for example REM fragmentation, adrenergic tone during REM or the presence of pontine waves in order to see if these are causal factors or just markers of event impact or general affect. There are already several studies that have shown that different sleep features can be manipulated in ways that also causes changes in sleep-dependent memory consolidation (e.g. Kaestner et al., 2013; Marshall et al., 2006; Ngo, Martinetz, Born, & Mölle, 2013). Thus, from further knowledge about the exact contributions of different sleep related events, we might soon be able to manipulate sleep in order to optimize adaptive overnight emotional processing.



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