THE ROLE OF SLEEP IN THE CONSOLIDATION AND PROCESSING OF EMOTIONAL MEMORY

A thesis submitted to the University of Manchester for the Degree of Doctor of Philosophy (PhD) in the Faculty of Biology, Medicine and Health

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MARIA-EFSTRATIA TSIMPANOULI

SCHOOL OF BIOLOGICAL SCIENCES

Division of Neuroscience & Experimental Psychology

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List of Abbreviations

AASM	American Academy of Sleep Medicine
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
APAA	AM → PM → AM → AM
BDI	Beck Depression Inventory
BOLD	Blood-Oxygen Level Dependent
CCR	Correct Classification Rate
DASS	Depression, Anxiety and Stress Scale
DWT	Discrete Wavelet Transform
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ERP	Event-Related Potential
FDR	False Discovery Rate
fMRI	functional Magnetic Resonance Imaging
G-G	Greenehouse-Geisser
H-F	Huynh-Feldt
IADS	International Affective Digitized Sounds battery
IAPS	International Affective Pictures System
IMG	Imagery
KSS	Karolinska Sleepiness Scale
MEQ	Morningness-Eveningness Questionnaire
MRM	Multivariate and Repeated Measures
MTL	Medial Temporal Lobe
NREM	Non-Rapid Eye Movement sleep
N1	Sleep-Stage 1

N2	Sleep-Stage 2
N3	Sleep-Stage 3
N4	Sleep-Stage 4
PANAS	Positive and Negative Affective Scale
PAPP	PM → AM → PM → PM
PhD	Doctor of Philosophy
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement
RGB	Red Green Blue
ROI	Regions Of Interest
RRS	Ruminative Responses Scale
RT	Reaction Time
SAM	Self-Assessment Manikin
SD	Standard Deviation
SEM	Standard Error of the Mean
SRTT	Serial Reaction Time Task
SSS	Stanford Sleepiness Scale
STAI	State-Trait Anxiety Inventory
SWR	Sharp-Wave Ripple
SWS	Slow-Wave Sleep
TMR	Targeted Memory Reactivation
TST	Total Sleep Time
WASO	Wake After Sleep Onset
Δ	Change
η_p^2	partial-eta square

Abstract

The Role of Sleep in the Consolidation and Processing of Emotional Memory
Maria-Efstratia Tsimpanouli, The University of Manchester
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Spontaneous reactivation of memory traces during sleep enables long-term consolidation and integration of memories with prior knowledge. Emotion can enhance the consolidation of memories during sleep and during wakefulness. However, at the same time, emotion may disrupt consolidation of contextual information. Furthermore, sleep not only consolidates emotional memories, but may also influence emotional salience in terms of valence and arousal. The work presented in this thesis utilises behavioural declarative and procedural memory testing; subjective arousal, valence, and likeability testing; targeted memory reactivation (TMR); polysomnography (PSG); electroencephalography (EEG); and functional magnetic resonance imaging (fMRI), to investigate sleep-related processing and memory consolidation of emotional and neutral stimuli.

In Chapter 2, we investigate sleep-dependent object-location memory and processing of valence and arousal. We use negative and neutral pictures paired with matching sounds as the stimuli. During slow-wave-sleep (SWS) or wakefulness, we replay half of the stimuli. TMR during SWS results in memory stabilization of the cued stimuli regardless of stimuli's emotionality. Furthermore, TMR enhances arousal habituation of the negative cued stimuli. TMR during wake has no effects in memory or emotional ratings.

In Chapter 3, we use fMRI to further investigate the effects of TMR during SWS on emotional associative memory and arousal processing. At the behavioural level, our results indicate that the effects of TMR on arousal depend on whether the stimuli are negative or neutral and the duration of SWS. The neuroimaging results suggest that TMR has different effects on the neural correlates of arousal for negative and neutral stimuli. Furthermore, there is an interaction of TMR, emotion, and rapid-eye-movement sleep (REM) duration on the neural correlates of location memory.

In Chapter 4, we investigate whether the neural traces of negative and neutral memories differ when they are reactivated during SWS. We trained an EEG classifier on wake data while participants imagined performing a motor sequence task they had previously practiced. Subsequently, we classified SWS data while auditory cues of the task were replayed. We find that the classification is above chance for both sequences, having either negative or neutral items. The classification rate of the negative sequence is positively correlated with pre-sleep performance and negatively correlated with overnight improvement. The classification rate of the neutral sequence is positively correlated with REM duration.

Lastly, **in Chapter 5**, we investigate how implicit and explicit associative memory and emotional ratings change across periods of sleep or wakefulness. We use happy, peaceful, scary, and sad musical excerpts as stimuli. Our findings suggest that sleep stabilizes valence and arousal ratings and may stabilize explicit memory too. Conversely, wake makes valence more positive, increases arousal ratings and deteriorates explicit memory. Furthermore, emotions influence how ratings of valence and arousal and explicit memory change.

These results shed light on the role of sleep in emotional processing and memory consolidation. We provide evidence that TMR modulates emotional salience and associated memories differently for negative and neutral stimuli, both at the behavioural and at the neural level. Further work needs to be done to elucidate the different networks associated in the processing and consolidation of emotional and neutral stimuli, and the roles of SWS and REM.

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Declaration

Part of the data referred to in Chapter 4 was used in the Final Dissertation of Alessandra Tafuro in support of her Master Degree in Cognitive Neuroscience and Clinical Neuropsychology at the University of Padova in 2015. These data have been very substantially re-analysed and re-interpreted for the current submission.

No other portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

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Rationale for Submitting the Thesis in Journal Format and Contributions

The four experimental chapters (2, 3, 4, and 5) were written in the style of scientific papers, with a view to submitting them to peer-reviewed journals for publication.

Professors Penelope Lewis, Rebecca Elliott and Ian Anderson supervised the development of all experimental designs and subsequent analyses.

In Chapter 2, Maria-Efstratia Tsimpanouli designed the experiment, recruited participants, collected the data, and performed the analysis. Dr Yu Li assisted with the adaptation of the experimental task to E-prime. Polysomnography data were scored by Maria-Efstratia Tsimpanouli and Isabel Hutchison.

In Chapter 3, Maria-Efstratia Tsimpanouli and Isabel Hutchison designed the experiment and recruited participants. Maria-Efstratia Tsimpanouli collected the data together with Isabel Hutchison and Jules Schneider. Dr Yu Li assisted with the adaptation of the experimental task on E-prime. Polysomnography data were scored by Maria-Efstratia Tsimpanouli and Isabel Hutchison. Behavioural data were analysed by Maria-Efstratia Tsimpanouli. Imaging data were analysed by Maria-Efstratia Tsimpanouli with the assistance of Dr Martyn McFarquhar.

In Chapter 4, Maria-Efstratia Tsimpanouli and Dr Suliman Belal designed the experiment. Maria-Efstratia Tsimpanouli and Alessandra Tafuro recruited participants and sleep scored the polysomnography data. Maria-Efstratia Tsimpanouli collected the data together with Alessandra Tafuro and Jules Schneider. Dr Suliman Belal developed the classifier and scripts for the analysis of the data. Maria-Efstratia Tsimpanouli analysed the data.

In Chapter 5, Maria-Efstratia Tsimpanouli designed the experiment, recruited participants, collected the data, and performed the analysis. Dr Yu Li assisted with the adaptation of the experimental task on E-prime.

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First and foremost, I would like to thank my supervisors, Professors Penny Lewis, Rebecca Elliott, and Ian Anderson who taught me how to do research that matters. I have benefited greatly from their guidance, encouragement, scientific expertise and enthusiasm. Extended thanks go to Penny and Rebecca, whose valuable feedback and suggestions greatly improved this thesis.

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This thesis is dedicated to my families

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The Author

Maria-Efstratia Tsimpanouli completed an undergraduate degree in Biology, following the elective program Biomolecular Sciences and Biotechnology, at the University of Crete. During her undergraduate studies, she was awarded an ERASMUS scholarship to study for a semester in the department of Biology at the University of Barcelona. She then obtained an MSc in Life Sciences and Technology with a specialisation in Neurosciences at the École Polytechnique Fédérale de Lausanne. She subsequently commenced a PhD at the University of Manchester funded by the Engineering and Physical Sciences Research Council. Her previous research experience covers depression, pain and addiction using genetic models of *Mus musculus*, and tonotopic mapping, vestibular system and insular function of *Homo sapiens* at ultra-high field.

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1. General Introduction

1.1 Preface

This thesis investigates the role of sleep in the processing and consolidation of emotion-related memories. Memory is a highly plastic function of the brain that enables us to learn and retain skills and information from seconds up to years. Furthermore, memory enables us to learn from our past history, understand the present, and plan for the future. However, there is a limited capacity of how much information can be stored and successfully retrieved. Therefore, some memories become prioritized while others will be discarded. Sleep can both promote and impair the consolidation of memories (Poe, 2017; Sara, 2017). Furthermore, sleep can alter how we feel, and our mood can influence our sleep. Emotions prioritize the consolidation of certain memories during wakefulness and sleep, but this may be in expense of other memories. A famous example is the weapon focus effect; people who witnessed a crime had better memory of the weapon used but worse of the face of the assailant or other details of the scene (Fawcett, Russell, Peace, & Christie, 2013; Loftus, Loftus, & Messo, 1987).

Evidently, the roles of sleep and emotion on memory consolidation are intertwined. The aim of this thesis is to examine some key research questions regarding how sleep processes emotional salience and associated memories. This chapter provides an overview of the existing literature on sleep, emotion, memory and their interactions and introduces the topics investigated in this thesis.

1.2 Sleep

Earth's rotation around its axis and around the sun results in a non-ending oscillation between day and night. This alternation dictates the rhythms of life and behaviours of most, if not all, organisms on Earth. Bacteria, plants, and animals have periods of high activity, usually during daytime, and periods of decreased activity or rest, usually during nighttime. Sleep is a resting behavioural state present in most of the animal species. Intuitively we know that sleep is essential for our survival as much as breathing and eating. Yet, the function of sleep has been a mystery for a long time. Human efforts to understand sleep

can be traced back to the 8th century BCE in the Upanishads, ancient Hindu texts that include descriptions of sleep, dreams, and wakefulness (Müller, 1962). Around the same time ancient Greeks, recognizing its importance and therapeutic value, deified sleep as Hypnos, an almighty god whose control nobody, god or mortal, could escape (Hesiod, 1844; Homer, 1828). In recent human history, an extended review on dreams and memory was published in the late 19th century (Delboeuf, 1880a, 1880b, 1880c) and the first experiment providing evidence that sleep mediates memory consolidation was performed in the early 20th century (Jenkins & Dallenbach, 1924). A mere century later, our knowledge on sleep has expanded along with technological advancements. Nevertheless, the exact mechanisms behind the multiple roles of sleep and its purpose remain uncovered (Joiner, 2016; Krueger, Frank, Wisor, & Roy, 2016).

In humans, sleep is practiced, usually, during nighttime. With the use of polysomnography (PSG), a combination of electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG), we can identify and study the different stages of sleep (Figure 1-1). Human sleep can be either rapid-eye-movement sleep (REM) or non-REM (NREM). NREM, (75-80% of the total sleep time - TST) can be further categorized into four different stages, stage 1 (N1), stage 2 (N2), stage 3 (N3), and stage 4 (N4). REM was the first sleep stage identified (Aserinsky & Kleitman, 1953) and has been called paradoxical sleep because the EEG recordings are quite similar to the recordings during wakefulness. During REM (20-25% of TST), we observe a combination of beta (15-25 Hz) and theta waves (3-7 Hz), low muscle activity, and a burst of eye movements. Vivid dreaming takes place during REM. The transition from wakefulness to sleep happens during N1 (3-8% of sleep time), which is dominated by theta waves and there is a slow rolling of the eyes. In N2 (45-55% of TST), we have the appearance of characteristic K-complexes (a negative wave followed by a positive wave, both lasting more than 0.5 s) and thalamocortical sleep spindles (a 12-14 Hz waveform lasting at least 0.5 s). Finally, N3 and N4 (15-20% of TST) are often clustered together and called slow-wave sleep (SWS) because of the dominating slow waves (< 1 Hz) and delta waves (0-4 Hz) (Steriade, 2003). In SWS, sleep spindles are still present as well as hippocampal sharp-wave ripples (SWRs – transient high-frequency oscillations 100-300 Hz).

Today, sleep recording is digitized but sleep scoring is still performed manually without using an automated algorithm. For this thesis, PSG data of Chapters 2, 3, and 4 were partitioned into 30 s epochs and scored independently by two researchers following the American Academy of Sleep Medicine (AASM) criteria (Berry et al., 2014). Years of analysis of sleep recordings have revealed that sleep patterns among different individuals are not identical, yet they share common characteristics. For adults, the average duration of an overnight sleep is 8 h, with women sleeping approximately 20 min more (Kronholm, Härmä, Hublin, Aro, & Partonen, 2006). This 8-hour period is divided in 90 min cycles; each cycle starts with NREM and progress to REM (Walker, 2009). At the beginning of the sleep period, a cycle has more SWS whereas towards the end there is more REM and N2 (Figure 1-2).

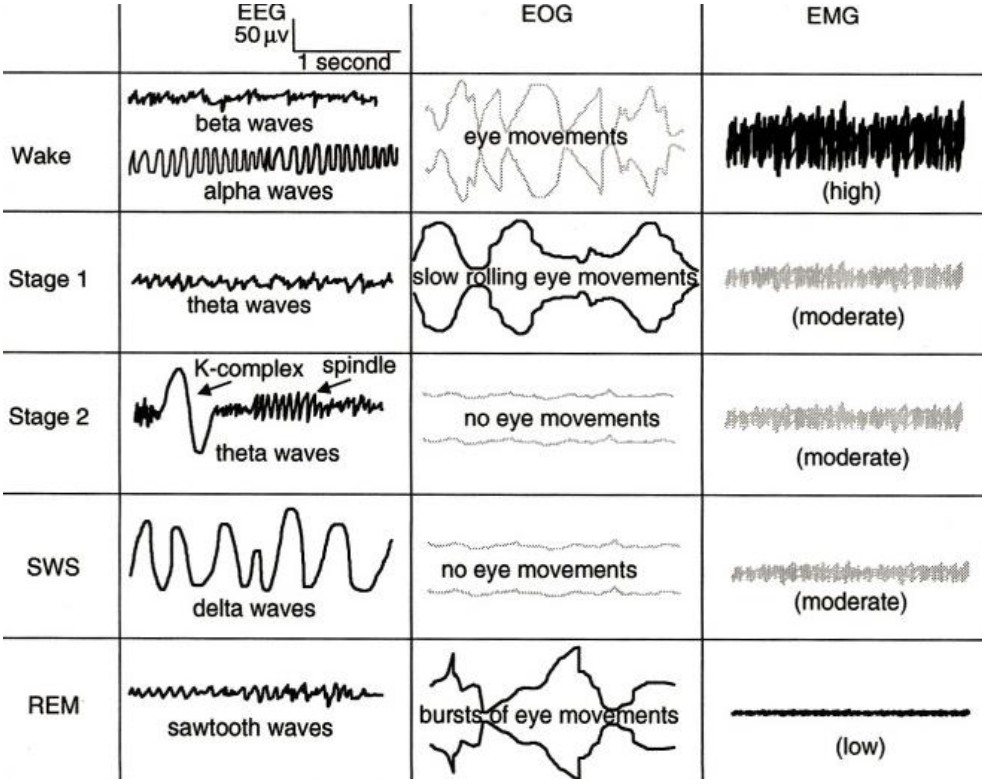

Figure 1-1 Sleep stages and their characteristics. Source:(Moorcroft & Belcher, 2005)

In addition to PSG, other neuroimaging techniques have been used to study in depth the mechanisms of sleep-dependent memory. These techniques include functional magnetic resonance imaging, (fMRI), magnetoencephalography (MEG), and positron emission tomography (PET), for a review see (Peigneux, 2014). Furthermore, sleep has also been studied in a variety of animals. Rodents are a popular experimental model even though they sleep during daytime

and have shorter sleep cycles (Genzel, Kroes, Dresler, & Battaglia, 2014). The sleep of rodents shares similar characteristics with human sleep, such as spindles, SWRs and slow-waves. Their sleep can also be distinguished into REM and NREM, but NREM is usually referred as SWS.

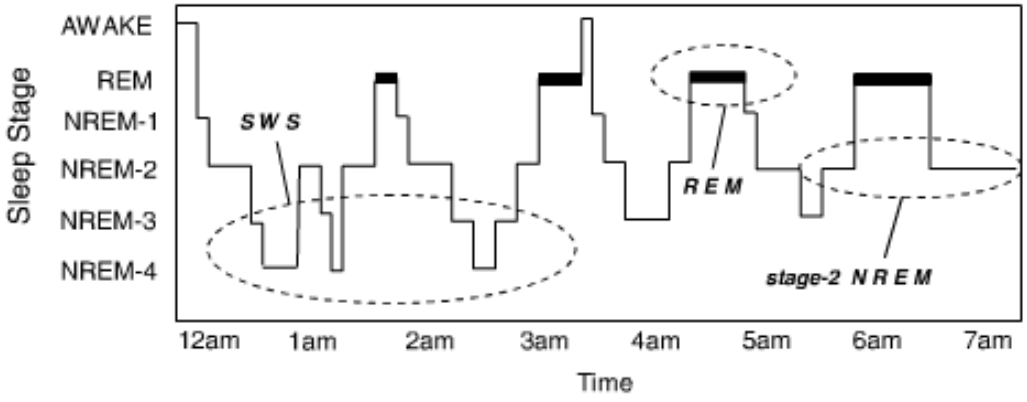

Figure 1-2 The human sleep cycle throughout night. Early hours are rich in SWS and late hours in REM and N2. Source: (Walker, 2009)

1.3 Memory and Sleep

Memory can be divided into two categories, declarative (knowing that) and non-declarative (knowing how) (Squire & Zola, 1996) (Figure 1-3 (a)). Declarative memory refers to the conscious recollection of facts (semantic) and events (episodic). Non-declarative memory refers to a heterogeneous group of unconscious learning abilities, such as procedural skills, conditioning, non-associative and priming effects (Squire, 1992). Declarative memories are considered as hippocampus-dependent and non-declarative memories as hippocampus-independent. However, some procedural memories may also depend on the hippocampus (Albouy et al., 2008; Albouy, Fogel, et al., 2013; Albouy, Sterpenich, et al., 2013; Albouy, King, Maquet, & Doyon, 2013). In this thesis, we used two different experimental tasks having neutral and emotional stimuli, an associative object-location task to study episodic memory (Chapters 2, 3, and 5), and a serial-reaction time task (SRTT) to study procedural memory (Chapter 4).

The formation of a memory starts during the encoding of new information (Figure 1-3 (b)). At this stage, memories are still labile and vulnerable to interference. Then, the process of consolidation takes place either during wakefulness or during sleep. During consolidation, memories are stabilized, strengthened and integrated with previous information. Consolidation can be studied

both at the synaptic level, as the transformation of information at local synaptic and cellular nodes of the neural circuitry, and at the systems level, as the reorganization of long-term representations over distributed brain circuits (Dudai, Karni, & Born, 2015; Kandel, Dudai, & Mayford, 2014). Typically, synaptic consolidation is completed within hours whereas systems consolidation is slower and it may last up to years. Finally, at retrieval, we recall the previously learned information. Retrieval of a memory might be done on demand or it might be triggered by listening to a song, tasting a flavour, or smelling an odour from a long time ago (Belfi, Karlan, & Tranel, 2015; Chu & Downes, 2002).

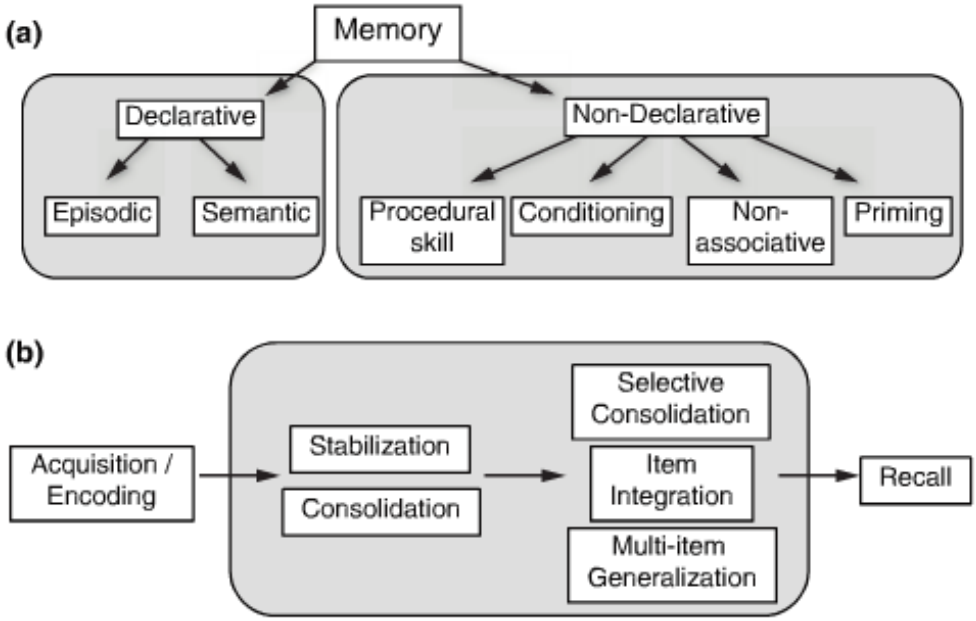

Figure 1-3 (a) Types of memory, (b) Stages of memory processing. Source: (Stickgold, 2013)

According to the standard consolidation model for the declarative memory (Frankland & Bontempi, 2005), the hippocampus and several cortical areas are involved in encoding and temporal consolidation of a memory. The hippocampus is a fast learner with limited capacity, whereas the neocortex is a slow learner with much bigger capacity. The hippocampus is mainly responsible for the encoding of a memory and its initial storage and progressively, the memory is transferred entirely to the cortical areas. The connections between the hippocampus and the cortical areas become weaker until they disappear, whereas the connections among the cortical areas grow stronger. Eventually, the information will be stored only in cortical areas and will be integrated with previously stored information (Dumay & Gaskell, 2007). This model can also be

applied to non-declarative memories that are hippocampus and striatal-dependent.

In order to study the relation between sleep and memory in humans, various experimental approaches have been used. Experimental paradigms include a daytime nap, nocturnal sleep, partial or total sleep deprivation, split-night designs, reactivating memories during sleep by presenting cues, and alternating the brain circuits using auditory, transcranial electrical or magnetic stimulations during wake (e.g. when encoding) or sleep. Research on animals and humans has shown that sleep can have an effect on encoding, consolidation, or integration of memories. Based on the findings of these studies, several models have been developed on how sleep affects the different states of memory, but none has managed to provide a complete explanation.

Regarding the role of sleep on how it benefits memory consolidation, some argue that it is passive, just protecting memories from interference (Rickard, Cai, Rieth, Jones, & Ard, 2008; Vertes, 2004; Vertes & Siegel, 2005). However, the majority of research converged that sleep has a more active role, enhancing the consolidation of certain memories and integrating them with prior knowledge, for an extended review see (Rasch & Born, 2013), while discarding unnecessary information (Feld & Born, 2017; Feld, Weis, & Born, 2016; Hoedlmoser et al., 2015; Poe, 2017). The factors that may bias which memories will get consolidated during sleep include emotion, reward, pre-sleep consolidation levels, future relevance and anticipation of retest (Barner, Seibold, Born, & Diekelmann, 2016; van Rijn, Lucignoli, Izura, & Blagrove, 2016; Wilhelm et al., 2011).

Another "sleep purpose" related question is why are there two different states of sleep, REM and NREM? According to the sequential hypothesis (Ambrosini & Giuditta, 2001; Giuditta, 2014; Giuditta et al., 1995), NREM and REM act synergistically as they are repeated in loops throughout the sleep. SWS strengthens adaptive memories and weakens non-adaptive ones, whereas REM is responsible for integrating the strengthened memories and storing them in long-term memory. However, most of the studies on humans supporting the sequential hypothesis are on procedural memory (Cairney, Durrant, Power, & Lewis, 2014; Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2016; Ficca, Lombardo, Rossi, & Salzarulo, 2000; Gais, Plihal, Wagner, & Born, 2000;

Moroni et al., 2012; Stickgold, James, & Hobson, 2000; Tamminen, Lambon Ralph, & Lewis, 2017; Walker & Stickgold, 2010).

An interesting clue about the nature and need for REM and SWS comes from observing the effects of sleep deprivation or partial sleep deprivation. In young mice, REM deprivation disrupts the healthy development of the hippocampus (Soto-Rodriguez et al., 2016). In adult humans, though, several anti-depressant drugs appear to suppress REM without any memory-related side effects. In case of a withdrawal of these drugs, there is no tendency to compensate for the lost REM in following sleep periods (Feinberg, Hibi, Cavness, & March, 1974). Interestingly, pharmacological suppression of REM in healthy subjects enhanced their skill memory (Rasch, Pommer, Diekelmann, & Born, 2009). Furthermore, some marine mammals do not have REM (Jim Horne, 2013). In contrast, when SWS is disrupted during a part of the sleep period or for the whole sleep period, then there is increased pressure for SWS resulting in a rebound of SWS and a decrease of REM (De Gennaro, Ferrara, & Bertini, 2000; Garside, Arizpe, Lau, Goh, & Walsh, 2015).

1.3.1 Replay of Memories during Sleep

The mechanism supporting sleep-dependent memory consolidation is widely recognized to be the reactivation of memories during sleep. There are several models explaining the underlying physiology and roles of sleep stages, with the active system consolidation hypothesis being one of the most convincing (Born, Rasch, & Gais, 2006; Diekelmann & Born, 2010). According to the active system consolidation hypothesis, which is built on the standard consolidation model, new memories are initially stored in the hippocampus and cortical areas. Then, memories are reactivated during SWS, resulting in the strengthening of the existing cortico-cortical connections and possibly even the creation of new connections. In more details, the slow waves of SWS during SWRs and the thalamocortical spindles are triggering the reactivation of memories that are stored in the hippocampus. As a result, the new memories are redistributed, restored in longer-term memory areas at the cortex, and integrated into older long-term memories (Figure 1-4). The function of REM is to stabilize the synaptic consolidation of the newly transferred memories into the longer-term memory cortical areas.

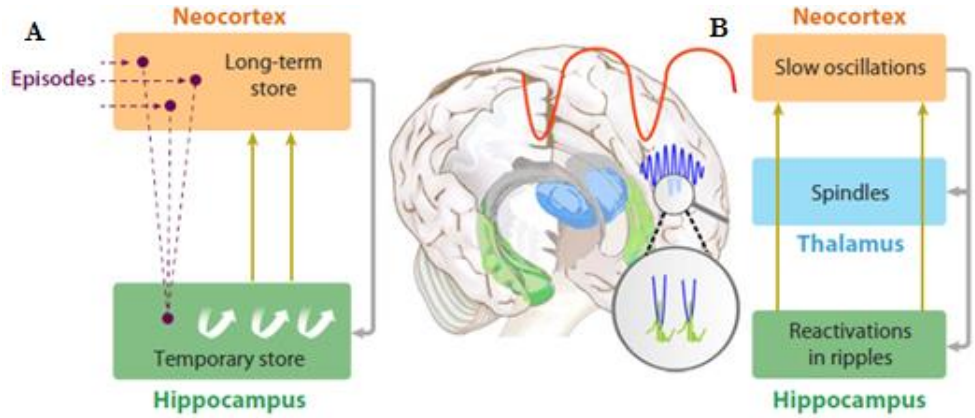

Figure 1-4 Active system consolidation during sleep. A: During wake new memories are encoded into hippocampal and neocortical areas B: During SWS new memories are repeatedly reactivated, leading to their gradual redistribution to the long-term store (the neocortex). During SWS, neocortical slow oscillations control the dialogue between neocortex and hippocampus (red). The depolarizing up-phases of the slow oscillations, hippocampal SWRs (green) and thalamo-cortical spindles (blue) drive the repeated activation of hippocampal memory traces. Source:(Born & Wilhelm, 2012; Inostroza & Born, 2013; Rasch & Born, 2013)

The first evidence of the replay of memories during sleep came from an experiment on rats, where hippocampal place-cell activity was reinstated during subsequent sleep (Pavlides & Winson, 1989). A follow-up study showed that pairs of place cells that had overlapping place-fields and were firing together in wake had an increased tendency to fire during SWS (Wilson & McNaughton, 1994). Further studies have shown that reactivation usually occurs during SWRs in SWS (Kudrimoti, Barnes, & McNaughton, 1999), with reward enhancing hippocampal reactivation during SWRs (Singer & Frank, 2009), whereas disrupting SWRs results in spatial memory impairment (Ego-Stengel & Wilson, 2010). Furthermore, it has been shown that after spatial learning takes place in wake, hippocampal place cells fire repeatedly during SWS in the same, but compressed, temporal order as in prior wake (Lee & Wilson, 2002) (Figure 1-5). Depending on the task, memory traces that can be reactivated during sleep are not only found in the hippocampus but also in cortical areas, such as the visual cortex (Ji & Wilson, 2007) or the entorhinal cortex grid cells (Ólafsdóttir, Carpenter, & Barry, 2016), and their firing patterns are closely coordinated with the hippocampus. A recent study on rats provided evidence confirming that a hippocampo-cortical dialogue occurs during sleep, is mediated by sharp wave ripples, delta waves, and spindles, and is necessary for memory consolidation (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016). Finally, reactivation of the motor cortex during sleep has also been ob-

served in a procedural memory motor task (Ramanathan, Gulati, & Ganguly, 2015).

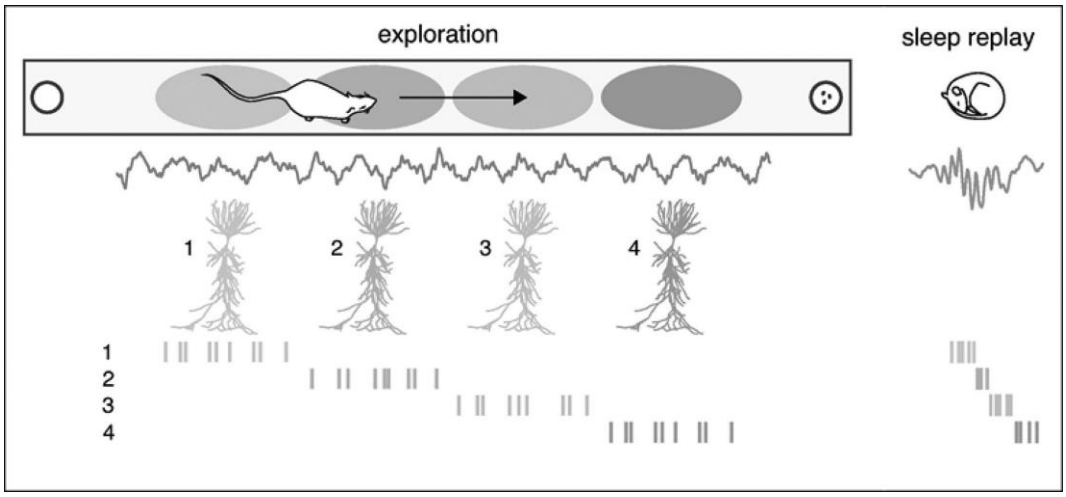

Figure 1-5 Replay of waking neuronal activity during sleep. When a rat runs on a linear track (left), hippocampal place cells are successively firing as the rat passes through their respective place fields (~ 500 ms). In subsequent SWS (right), there is a fast replay of the same firing sequence during a SWR (~ 50 ms). Source: (Girardeau & Zugaro, 2011; Watson & Buzsáki, 2015)

Neuroimaging studies in humans provide additional evidence that memories are spontaneously reactivated during sleep and that the hippocampus has a role in this process. First, (Peigneux et al., 2004) reported that hippocampal areas that were activated during route learning were also activated in subsequent SWS. Similarly, the activation of the trained region of the visual cortex in visual-perceptual learning was enhanced during NREM sleep (Yotsumoto et al., 2009). In both studies, the amount of activation during sleep predicted post-sleep memory performance. Another study used successfully multivariate pattern classification analysis to detect stimulus-specific activation patterns reoccurring spontaneously during post-learning sleep and resting periods (Deuker et al., 2013). Finally, a recent study provided evidence that a hippocampo-cortical dialogue happens during SWS in humans by observing propagation patterns of δ activity and infraslow activity (Mitra et al., 2016).

1.3.2 Declarative Memory and Sleep

Most studies provide evidence that sleep benefits consolidation of declarative memories. Indeed, a number of different tasks have shown that sleep can enhance direct associative and relational memory (Lau, Tucker, & Fishbein, 2010), contextual memory (van der Helm, Gujar, Nishida, & Walker, 2011), spatial associative memory (Talamini, Nieuwenhuis, Takashima, & Jensen,

2008), word learning and grammatical generalisation (Frost & Monaghan, 2017), spatial information (Nguyen, Tucker, Stickgold, & Wamsley, 2013), paired associates learning (Fogel, Smith, & Cote, 2007), gist abstraction (Lutz, Diekelmann, Hinse-Stern, Born, & Rauss, 2017), integration of relative information into an interconnected complex spatial representation (Coutanche, Gianessi, Chanales, Willison, & Thompson-Schill, 2013), and many more. This sleep-dependent declarative memory consolidation is achieved by both active and passive processes (Fenn & Hambrick, 2013; Schreiner & Rasch, 2016). However, if participants have not learned well the tasks during training (Tucker & Fishbein, 2008) or they have to learn too many items (Feld et al., 2016), then sleep doesn't have any effects on memory.

There is as yet no good consensus on which sleep stage is mediating the memory effects. A lot of studies support a main role for SWS, e.g. (Lau et al., 2010; Plihal & Born, 1997, 1999; Ross & Slotnick, 2008). On the other hand, (Fogel et al., 2007) found that REM predicted performance on a declarative task. Similarly, (Rauchs et al., 2004) reported that SWS preserved temporal memory and REM enhanced spatial context. However, as contextual memory and other types of declarative memory are hippocampus dependent (Ross & Slotnick, 2008) NREM is expected to be the sleep stage mediating consolidation effects. Accordingly, sleep spindles and N2 in a nap predicted contextual memory enhancement, but item memory was unaffected by sleep (van der Helm et al., 2011). In another study, sleep enhanced both direct associative and relational memory, although only SWS correlated with relational memory performance (Lau et al., 2010). Further evidence supporting a role of SWS in declarative memory consolidation comes from studies that enhanced slow oscillations and observed a related declarative memory improvement. Manipulation of slow oscillation was achieved either through transcranial application of oscillating potentials (Marshall, Helgadóttir, Mölle, & Born, 2006) or through rhythmic auditory stimulation (Ngo, Claussen, Born, & Mölle, 2013; Ngo, Martinetz, Born, & Mölle, 2013).

1.3.3 Procedural Memory and Sleep

Similar to declarative memory, a wealth of studies indicate that sleep can benefit consolidation of procedural memories. However, which sleep stage will consolidate them depends on the type of task, its novelty, and amount of training. Indeed, either REM (Fischer, Hallschmid, Elsner, & Born, 2002;

Maquet et al., 2000; Plihal & Born, 1997, 1999) or SWS (Gais et al., 2000; Reto Huber, Ghilardi, Massimini, & Tononi, 2004; Landsness et al., 2009; Tamaki et al., 2013) or a combination of sleep stages (Cousins et al., 2016; Fogel, Ray, Binnie, & Owen, 2015) may have a role in the consolidation of procedural memories. Furthermore, spindle activity has also been shown to predict performance improvement (Albouy, Fogel, et al., 2013; Barakat et al., 2013). Interestingly, pharmacological REM suppression improved skill memory (Rasch et al., 2009). Conversely, total sleep deprivation impaired procedural performance even if participants trained more or had an afternoon nap (Kurniawan, Cousins, Chong, & Chee, 2016). However, after a week sleep deprivation effects had disappeared.

Motor sequence memory tasks, such as the serial reaction time task (SRTT), have consistently been found to gain from sleep (Brown & Robertson, 2007; Djonlagic, Saboisky, Carusona, Stickgold, & Malhotra, 2012; Fischer et al., 2002; Korman et al., 2007; Nishida & Walker, 2007; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). However, consolidation of some procedural skills may be independent of sleep. For example, overnight sleep enhanced sequence-specific learning of a complex motor sequence, but transfer of skill to other sequences was independent of sleep (Genzel, Quack, et al., 2012). Similarly, a daytime nap enhanced consolidation of spatial but not motoric representation of a motor sequence (Albouy, Fogel, et al., 2013). A follow up study found that spatial learning is mediated by sleep and hippocampal activity, whereas motor learning is mediated by time and the striatum (Albouy et al., 2015). Thus, there is a functional dissociation in motor sequence memory consolidation processes

1.4 Emotional Memory

Darwin, trying to understand the evolution of emotions, concluded that they motivate behaviours and have value for social communication (Darwin, 1999). Indeed, emotionality is present in every aspect of our lives and the allocation of our attentional resources, how we process information, and how we perceive and interact with our environment can be influenced by our emotional state (Grider & Malmberg, 2008; Levine & Pizarro, 2004). However, the effects of emotion on memory are not uniform but depend on the used information-processing strategy and the type of memory being affected (Knight & Ponzio, 2013).

Although an adult will remember and execute perfectly everyday skills, such as moving, navigating, communicating, recognizing familiar people, surroundings, etc., rarely they will remember how and when these skills were acquired. If such a memory exists, then usually it has strong emotional content. Throughout our lives, emotional memories are of the most persistent memories.

Yet, it is not that easy to describe and assess emotions scientifically. The terms of valence and arousal are often used in an effort to quantify and describe emotion. Therefore, arousal can be defined as the "dimension of emotion that varies from calm to excitement" (LaBar & Cabeza, 2006) and valence as the "dimension of emotion that varies from unpleasant (negative) to pleasant (positive), with neutral often considered an intermediate value" (LaBar & Cabeza, 2006). To measure arousal and valence non-verbally, researchers frequently use the self-assessment manikin (SAM) (Bradley & Lang, 1994), a 9-item Likert-like scale having visual representations of arousal and valence (Figure 1-6).

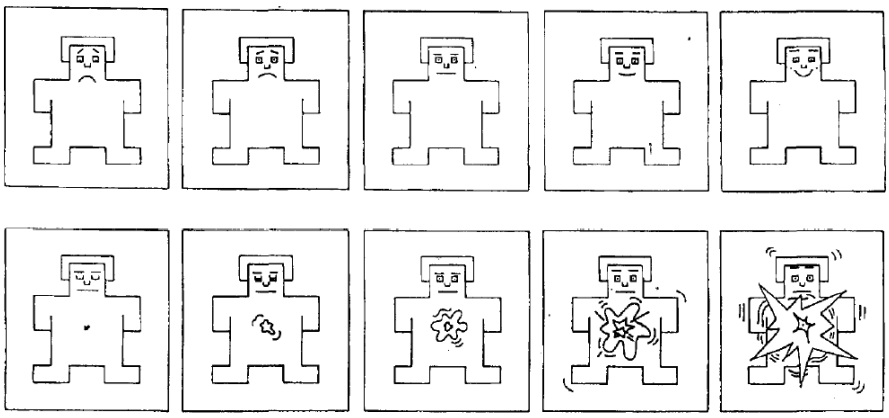

Figure 1-6 Self-assessment manikins for valence (top) and arousal (bottom) Source: (Bradley & Lang, 1994)

According to a hierarchical cluster analysis of 135 emotion names, emotions can be subdivided into further subcategories, positive ones as love, joy and surprise, and negative ones as anger, sadness and fear (Shaver, Schwartz, Kirson, & O'Connor, 1987). Although these categories are distinct in terms of valence, they may vary in terms of arousal. Indeed, each emotion category has unique characteristics both in valence and arousal measurements (Figure 1-7). Thus, the effects of emotions on memory may depend on their valence, arousal, or a combination of both.

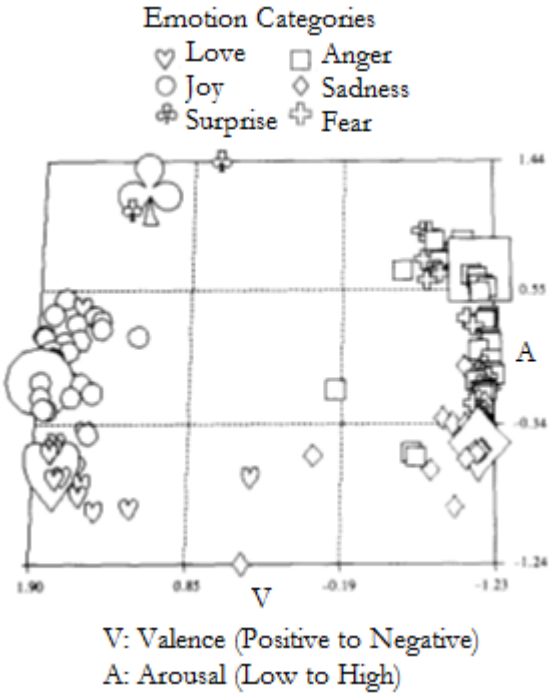

Figure 1-7 Two-dimensional chart depicting valence and arousal characteristics of different emotions. Each of the six symbols represents a different basic-level emotion category. Source: (Shaver et al., 1987)

1.4.1 Emotion and Item Memory

Emotional memory is considered to be a type of declarative memory, yet emotions may affect all different types of memories (Levine & Pizarro, 2004). (Adolphs, Denburg, & Tranel, 2001) identified the amygdala as the structure responsible for the preferential remembering of emotional stimuli over neutral ones. According to the multiple trace theory, the amygdala has strong connections with the hippocampus (Moscovitch & Nadel, 1998). A review by Phelps (Phelps, 2004) presents evidence that expands the standard consolidation hypothesis and supports the idea that the amygdala is interacting with the medial temporal lobe (MTL) memory system (Dolcos, LaBar, & Cabeza, 2004). (Richardson, Strange, & Dolan, 2004) provided evidence that the communication between amygdala and hippocampus could be reciprocal during encoding. Indeed, when emotional stimuli are presented both the amygdala and hippocampus are activated (Strange & Dolan, 2006). In addition, a study by (Ritchey, Dolcos, & Cabeza, 2008) showed that better consolidation for negative pictures, but not for neutral ones, can be predicted by the activation of the amygdala during encoding and the increased connectivity between the amygdala and the MTL.

A meta-analysis by (Murty, Ritchey, Adcock, & LaBar, 2010) on fMRI studies investigating emotional memory encoding, confirmed that emotional stimuli are better remembered than neutral ones. Moreover, they showed that active regions during encoding that predicted subsequent correct recall were found in the bilateral amygdala, anterior hippocampus, anterior and posterior parahippocampal gyrus, the ventral visual stream, left lateral prefrontal cortex (PFC), and right ventral parietal cortex. Based on their results they propose that the interaction of amygdala with these structures favours the retention of emotional stimuli.

Following the notion that the amygdalar activity and the long-term explicit memory of emotional stimuli depend on their arousal and not their valence, (Dolcos et al., 2004) grouped together positive and negative pictures as emotional and compared them to neutral ones. Their findings confirmed that emotional stimuli are better remembered than neutral ones. At the encoding level, the amygdala and the MTL were the two regions with higher activations and stronger correlated for emotional rather than neutral stimuli. In addition, the anterior MTL appeared to predict memory for emotional stimuli whereas the posterior MTL for neutral ones. Following up this study, they re-tested the same participants after one year and found better memory performance for the emotional stimuli (Dolcos, LaBar, & Cabeza, 2005). Implicated regions were the amygdala, hippocampus, and entorhinal cortex. The amygdala had a greater effect on recollection, i.e. vivid remembering, whereas the entorhinal cortex on familiarity, i.e. feeling of knowing.

Although most studies agree that emotional memories are better remembered than neutral ones and that the amygdala plays a crucial role, not everybody agrees on how the beneficial effect of emotion is mediated and about the roles of valence and arousal. Some of the above studies focused only on negative stimuli while others grouped together negative and positive stimuli. Further studies provide evidence that positive and negative emotional memories are processed differently, during encoding and consolidation. At the encoding level, (Lewis, Critchley, Rotshtein, & Dolan, 2007) observed that the orbitofrontal cortex processes only the valence of affective words, the amygdala processes only arousal, and other regions were identified to respond both to valence and arousal. Similarly, (Mickley Steinmetz & Kensinger, 2009) observed different patterns of activity when pictures with various valence and arousal ratings were

presented. In particular, temporal lobe activity was associated with encoding of negative or high arousal, whereas frontal activity corresponded to the encoding of positive or low arousal pictures. At the consolidation level, (Christianson & Fallman, 1990) found that negative stimuli are better remembered compared to positive ones or neutral ones. More evidence comes as well from sleep studies on emotional memory, which will be discussed further below.

1.4.2 Emotion and Associative Memory

The role of emotion in associative memory is less clear. Although it is generally accepted that emotional stimuli are better consolidated than neutral stimuli, research findings on the effect of emotion on contextual information, such as the spatial location of the stimuli, remain inconclusive. Results are conflicting, depending on the type of stimuli, task, instructions, and gender of participants, for reviews see (Chiu, Dolcos, Gonsalves, & Cohen, 2013; Mather, 2007). As we used an object-location task in our studies, we will review other studies that have used similar tasks.

Early studies using words as stimuli mostly support the opinion that emotion is beneficial for the location memory of words. A study found superior location memory for positive and negative words compared to neutral words regardless of the encoding conditions, intentional or incidental (D'Argembeau & Van der Linden, 2004). Similarly, a study using a modified Stroop-colour naming task found enhanced location memory for the taboo words in comparison to the neutral words (MacKay & Ahmetzanov, 2005). However, later studies had contradicting results. A study by (Maddock & Frein, 2009) indicated worse location memory for negative words compared to positive words of equal arousal or to neutral words, both for incidental and intentional learning. Furthermore, location memory was similar for positive and neutral words. Finally, (Wang, 2011) observed the same location memory accuracy for negative, positive, and neutral words. However, gender seemed to modulate the emotional effects since only women had better location memory for positive words in comparison to neutral words. No effect of emotion on spatial memory has also been observed when using positive, negative, and neutral faces on a modified version of the Corsi Blocks Task (Bannerman, Temminck, & Sahraie, 2012).

Research using images as stimuli also gives conflicting results. In one study (Wang & Fu, 2010b) found reduced source memory for negative and positive

pictures in comparison to neutral ones. Similarly, in a study with intentional encoding, location memory was better for the neutral pictures compared to high-arousal negative pictures (Mitchell, Mather, Johnson, Raye, & Greene, 2006). A different location memory task with multiple intentional learning blocks showed that in the first block location memory of high arousing negative pictures was slightly, but not significantly, better compared to neutral pictures (Novak & Mather, 2009). However, negative items had more location recall errors in subsequent blocks and they were less likely to be correctly updated when their corresponding location was changed. These results suggest that item-context binding was stronger for the negative stimuli even if it was wrong (Novak & Mather, 2009). Furthermore, novelty appears to influence location memory of negative stimuli; the location of old negative pictures was remembered worse compared to new negative pictures, but no difference was found between location memory of old and new neutral pictures (Nashiro, Sakaki, Huffman, & Mather, 2013).

Additional studies have investigated the interaction of valence and arousal on location memory. One study reported that higher arousal worsened location memory accuracy and that valence had no effects (Mather et al., 2006). However, a follow-up study using high and medium negative pictures with high and medium arousal and low arousal neutral pictures did not find an overall accuracy difference for arousal (Thoresen et al., 2011). Interestingly, further analysis showed that for the pictures that were presented in the first or last serial position, accuracy was improved as arousal increased. In another study, the memory location of emotional pictures was better compared to neutral pictures, however, the improvement was attributed to valence alone, even though arousal ratings differed between emotional and neutral pictures (Rimmele, Davachi, & Phelps, 2012). Conversely, in a study with incidental encoding, arousal enhanced the location memory of pictures regardless of valence (Mather & Nesmith, 2008). Similarly, another study using an incidental learning task, showed that participants remembered better the spatial and temporal details of the emotional pictures with high arousal irrespective of their valence (Schmidt, Patnaik, & Kensinger, 2011).

In conclusion, it appears that emotion may or may not exert an effect on associative memory depending on the nature of the task. Some studies present arousal to be the effector and others valence. However, not all studies had a

proper setup or did an adequate analysis in order to assess possible differences between valence and/or arousal effects.

1.4.3 Emotional Memory and Sleep

Emotion can enhance memory consolidation across sleep or wake (Corsi-Cabrera & Poe, 2014; Dolcos, Denkova, & Dolcos, 2012; Payne, Stickgold, Swanberg, & Kensinger, 2008).Interestingly, sleep deprivation studies have shown that participants who were sleep deprived had overall worse memory than those who slept (Atienza & Cantero, 2008; Sterpenich et al., 2007, 2009). However, they still remembered better the emotional stimuli relatively to the neutral ones (Atienza & Cantero, 2008; Sterpenich et al., 2007), possibly by recruiting the amygdalo-cortical network in place of the hippocampo-neocortical network (Sterpenich et al., 2007).

Many studies have shown that REM mediates the enhanced consolidation of emotional stimuli (Groch, Wilhelm, Diekelmann, & Born, 2013; Groch, Zinke, Wilhelm, & Born, 2015; Hu, Stylos-Allan, & Walker, 2006; Menz et al., 2013; Menz, Rihm, & Büchel, 2016; Nishida, Pearsall, Buckner, & Walker, 2009; Payne, Chambers, & Kensinger, 2012; Wagner, Gais, & Born, 2001). Modulation of the amygdalar activity is part of the underlying mechanisms (Genzel, Spoormaker, Konrad, & Dresler, 2015; Kocsis, Di Prisco, & Vertes, 2001; Menz et al., 2013; Paré, Collins, & Pelletier, 2002; Payne & Kensinger, 2011; Sterpenich et al., 2009; van Der Helm et al., 2011). Furthermore, results from (Nishida et al., 2009) indicate that emotional memory consolidation is driven by the right-dominant prefrontal theta activity during REM. The beneficial effect of sleep on emotional memories appears to persist for long periods of time (Dolcos et al., 2005; Payne et al., 2012; Ritchey et al., 2008; Sterpenich et al., 2009; Wagner, Hallschmid, Rasch, & Born, 2006).

Other studies contradict the idea that REM, or sleep in general, enhances the consolidation of emotional memories. One such study (Wagner, Kashyap, Diekelmann, & Born, 2007), did not find a valence-dependent enhancement effect of sleep in recognition memory of neutral, angry, and happy faces. Moreover, NREM sleep was correlated with memory accuracy, whereas REM with a faster response to the learned faces. Similarly, (Baran, Pace-Schott, Ericson, & Spencer, 2012) reported that although negative pictures were better remembered than neutral ones, sleep enhanced equally the consolidation of

both sets of pictures. The results of (Cairney, Durrant, Power, et al., 2014) implicated SWS as the sleep stage responsible for enhancing memories with negative emotional content. Furthermore, SWS was correlated with a decreased activation of the right hippocampus during remote retrieval, particularly for the negative stimuli, whereas REM increased the connectivity of the right hippocampus and frontal gyri during retrieval. These findings are in agreement with the opinion that SWS stabilizes the new memories, whereas REM integrates them with older ones.

Focusing on more detailed aspects of emotional stimuli and their sleep-dependent consolidation, sleep unbinds the different components of scenes and consolidates the most emotionally salient parts (Payne et al., 2008). Simultaneously, the unbinding of memories from their emotional context protects them from emotional contextual interference (Deliens, Gilson, Schmitz, & Peigneux, 2013). When the context is neutral and the stimulus is either neutral or negative, sleep enhances the consolidation of the negative stimuli compared to neutral ones (Payne & Kensinger, 2011). However, when the stimulus is neutral and the context is either negative or neutral, sleep reduces forgetting for both contexts (Lewis, Cairney, Manning, & Critchley, 2011). Finally, when neutral faces are paired with two sets of negative or neutral pictures, although there is better memory for negative directly associated pairs overall, a nap preferentially preserved neutral pairs (Alger & Payne, 2016). Furthermore, REM was related with a decline in memory for direct associations and an enhancement for relational associations of neutral pairs, whereas SWS had no effects.

1.4.4 Sleep and Processing of Emotional Salience

Sleep does not only have an effect on emotional memories but on how we (re)experience emotions associated to an event. According to the "sleep to forget and sleep to remember" hypothesis (van der Helm & Walker, 2010; Walker, 2009), while emotional memories get strengthened during REM, in parallel, their emotional component is attenuated until it disappears completely (Figure 1-8). However, few studies on healthy humans have confirmed all aspects of this hypothesis. In support of this hypothesis, (Gujar, Mcdonald, Nishida, & Walker, 2011) found that a nap blocked the emotion of anger, reversed fear and enhanced happy ratings, whereas continuous wake increased emotional reactivity to emotions of anger and fear across the day. Furthermore, the effects on fear and happy ratings were related to presence of REM during the

nap. Similarly, (van Der Helm et al., 2011) found that REM predicted a decrease in subjective arousal ratings and amygdalar activity after sleep. Partially supporting findings come from (Pace-Schott et al., 2011). Although they did not find any subjective differences on the ratings of negative or emotional stimuli after a nap, compared with their equivalent ratings before the nap, it appears that napping increased inter-session somatic habituation, particularly for the negative stimuli.

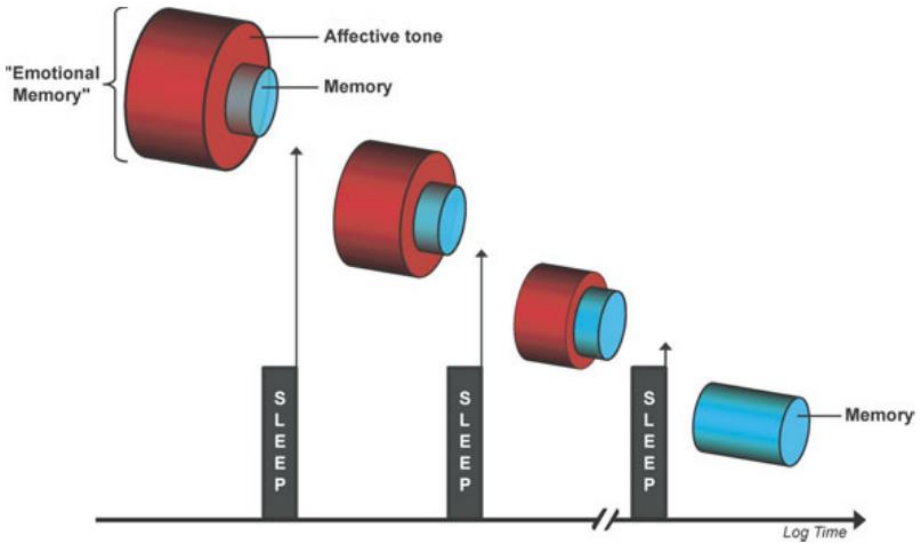

Figure 1-8 Model of sleep-dependent emotional memory processing of the sleep to forget and sleep to remember hypothesis. Source: (Walker, 2009)

Some studies have also investigated the effect of sleep on valence in addition to arousal. According to (Wagner, Fischer, & Born, 2002) sleep rich in SWS made valence ratings of negative pictures more positive whereas sleep rich in REM made them more negative. Both sleep stages enhanced the arousal ratings regardless of valence. Similarly in (Baran et al., 2012), longer REM predicted that valence ratings became more negative. Furthermore, they reported that valence of negative stimuli became more positive after a period of wakefulness relative to sleep. However, they did not observe any significant differences for arousal ratings. In contrast to (Baran et al., 2012) but relatively similar to (Wagner et al., 2002), (Lara-Carrasco, Nielsen, Solomonova, Levrier, & Popova, 2009) found that lack of REM reduced arousal ratings of negative pictures, suggesting thus that REM may enhance reactivity to negative emotional stimuli. Conversely, (Groch et al., 2011) found that after a 3 hours' sleep of early SWS, familiar negative pictures are perceived less arousing and more negative in comparison to novel negative pictures. However, in a later study

(Groch et al., 2013) found that REM and SWS after encoding did not have different effects on valence or arousal ratings. Finally, (Wiesner et al., 2015) did not find any sleep effects on valence or arousal ratings.

In conclusion, it is obvious that more research has to be done to investigate the relation of sleep and emotional memory consolidation in order to clarify which stages of sleep have what kind of effects on emotional memory. Previous findings remain inconclusive, possibly because of the different experimental designs used; nap studies, overnight sleep, split-night sleep sessions, partial or total sleep deprivation, each one using different types of stimuli, informing the participants that their memory will be tested or not. However, the findings of one type of study may not be the same at another type since the brain is plastic and it could be recruiting different mechanisms of action under different conditions.

1.5 Triggering Memory Reactivation in Sleep

A promising tool in investigating sleep-dependent memory consolidation is triggering targeted memory reactivation (TMR) during sleep by presenting associated cues of the task. Initial studies in rats showed that cueing an ear shock during REM enhanced memory consolidation of an avoidance task whereas cueing during SWS impaired learning (Hars & Hennevin, 1987; Bernard Hars, Hennevin, & Pasques, 1985; Hennevin & Hars, 1987). In more recent years, rats trained on an auditory-spatial association task and then auditory cues were replayed during SWS (Bendor & Wilson, 2012). Results indicated that auditory-cueing biased hippocampal replay during SWS. Interestingly, the effect was stronger for early sleep than late sleep. Another study in rats, used a fear-conditioning protocol and olfactory cueing (Barnes & Wilson, 2014). Cueing during wakefulness induced fear extinction whereas cueing during SWS enhanced the strength and precision of the memory. Similarly, auditory cueing during sleep in mice, enhanced conditioned fear memories (Rolls et al., 2013). Use of olfactory TMR has also successfully enhanced memory performance in a non-human model species, honeybees (Zwaka et al., 2015).

The first TMR studies in humans used auditory cues and although promising they did not have enough participants or a proper control. (Tilley, 1979) reported that TMR in N2 but not REM enhanced recall and recognition memory. In another study, TMR in REM enhanced performance in Morse

code task (Guerrien, Dujardin, Mandal, Sockeel, & Leconte, 1989). Similarly, TMR during REM resulted in improved performance at a complex logic task after a week (Smith & Weeden, 1990). Below I will present studies that have used TMR paradigms in humans over the last decade.

1.5.1 TMR of Declarative Memories

A large body of work provides strong evidence that TMR during SWS enhances consolidation of declarative memories and that the hippocampus mediates this effect, for reviews see (Oudiette & Paller, 2013; Schouten et al., 2017). Most studies have used either olfactory or auditory cueing on location memory tasks. A series of studies have also shown that TMR during SWS can enhance language learning (Schreiner, Göldi, & Rasch, 2015; Schreiner, Lehmann, & Rasch, 2015; Schreiner & Rasch, 2015a, 2017; Tamminen et al., 2017). Only one study that re-exposed participants to environmental sounds during SWS did not show any TMR effects (Donohue & Spencer, 2011).

In a seminal study, (Rasch, Büchel, Gais, & Born, 2007) showed that odour cueing during SWS, but during REM or wakefulness, enhanced subsequent memory performance on an object-location task resembling the game "concentration". Furthermore, their results revealed that areas of the left hippocampus were activated during the cueing period. A follow-up study validated that the observed TMR enhancement is odour specific (Rihm, Diekelmann, Born, & Rasch, 2014). Additional studies using the same paradigm confirmed that olfactory TMR during SWS stabilizes memories and renders them resistant to future interference (Diekelmann, Büchel, Born, & Rasch, 2011), whereas TMR during REM does not (Cordi, Diekelmann, Born, & Rasch, 2014). Conversely, cueing during wakefulness destabilized the memories and made them more labile to interference (Diekelmann et al., 2011). Differences were also observed at a neuroanatomical level, with SWS cueing activating left hippocampal and right posterior cortical areas, whereas cueing during wakefulness activated the right lateral prefrontal cortex (Diekelmann et al., 2011). Finally, (Diekelmann, Biggel, Rasch, & Born, 2012) showed that cueing during SWS in a short nap accelerated the formation of stable memories and enhanced them at a similar level as a long nap. However, a short nap without TMR did not enhance memory stabilization (Diekelmann et al., 2012).

Auditory cueing has also successfully triggered TMR during SWS. This was first demonstrated in a nap study by (Rudoy, Voss, Westerberg, & Paller, 2009). Participants were presented neutral pictures paired with semantically related neutral sounds and were instructed to memorize the exact position of each picture on a computer screen while hearing the paired sound. Subsequently, participants trained to a threshold criterion. Once the training was completed, participants had a break during which polysomnography electrodes were placed. After the break and before a nap session, location memory was tested. During the nap, half of the sounds were cued in NREM. After sleep, although memory performance overall decreased, location accuracy was significantly better for the pictures whose sounds were cued during sleep. A follow up study showed that the phase of the slow oscillation is crucial, as administering the auditory cue in the first half of the slow-oscillation downstate corresponded to low forgetting stimuli (Batterink, Creery, & Paller, 2016). Furthermore, auditory TMR during SWS is ineffective if no prior learning has occurred (Creery, Oudiette, Antony, & Paller, 2015; Groch, Schreiner, Rasch, Huber, & Wilhelm, 2017). Similarly to olfactory TMR, the auditory TMR benefit is dependent on the hippocampus (Fuentemilla et al., 2013; van Dongen et al., 2012). Lastly, in another adaptation of Rudoy's experimental task (Rudoy et al., 2009), participants had to learn the location of stimuli with low or high reward (Oudiette, Antony, Creery, & Paller, 2013). Interestingly, memory improvement occurred when TMR was delivered both during sleep and during wakefulness, although the two conditions differed. Cueing half of the low-reward stimuli during SWS enhanced accuracy for all the low-reward stimuli, whereas TMR during wakefulness enhanced only the cued ones (Oudiette et al., 2013).

1.5.2 TMR of Procedural Memories

Studies on TMR and procedural memories are fewer. As discussed earlier procedural memories may also depend on the hippocampus, cueing them therefore during SWS could potentially enhance their consolidation. The first study to investigate TMR of a procedural memory during SWS, REM, or wakefulness used olfactory cueing but did not find any results (Rasch et al., 2007). Next, (Antony, Gobel, O'Hare, Reber, & Paller, 2012) used auditory cueing during SWS with a gamified serial reaction time task. They found improved accuracy for the cued sequence that correlated with the percentage of sleep time spent in SWS and the spindle activity during SWS. This finding was repli-

cated by (Schönauer, Geisler, & Gais, 2014) who found a TMR benefit on accuracy and speed measurements by cueing during NREM. Further studies have shown that cueing an SRTT sequence during SWS enhanced the sequence-specific skill and explicit knowledge of the sequence but not stimulus-response mapping (Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2014; Cousins et al., 2016). Finally, two recent studies reattempted olfactory cueing. One study reported that olfactory TMR during SWS did not have any effects on procedural skills but enhanced explicit knowledge of the sequence only in men (Diekelmann, Born, & Rasch, 2016). The findings of the other study suggest that olfactory TMR during late N2, but not during REM or wakefulness, enhanced consolidation of motor sequence performance, with increased sleep spindles predicting the improvement (Laventure et al., 2016).

Direct evidence that auditory TMR influences brain activation and evokes similar patterns of activity as in wakefulness comes from a study using an EEG classifier (Belal et al., submitted). The classifier was trained on wake EEG data while participants imagined practicing an adapted SRTT sequence and then tested on sleep data from N2 or SWS when the auditory tones of the sequence were cued. Correct classification rate was above chance for TMR in SWS but not in N2. Furthermore, SWS classification accuracy correlated positively with pre-sleep performance and negatively with overnight improvement, possibly indicating ceiling effects on performance.

1.5.3 TMR of Emotional Memories

Studies cueing emotional stimuli during sleep using fear-conditioning protocols have produced conflicting results. TMR during SWS promoted fear extinction in a study using olfactory contextual fear conditioning (Hauner, Howard, Zelano, & Gottfried, 2013) and in a study using auditory fear conditioning (He et al., 2015). The results of another study though showed that TMR in SWS reinstated fear responses whereas TMR in wakefulness consolidated fear conditioning (Ai et al., 2015). However, in that study they used a fear conditioning/extinction paradigm and cued the contextual tone of the extinction phase during SWS. Finally, another study that applied TMR in late REM or N2 did not find an impact of TMR on fear extinction, but a decrease in subjective arousal ratings for both conditioned and non-conditioned stimuli (Rihm & Rasch, 2015). Similar results were found in another study that used TMR during SWS, REM, or wakefulness to assess subjective arousal ratings and auto-

nomic responses to negative and neutral stimuli (Hutchison et al., under review). In that study, only TMR during REM decreased subjective arousal but had no effect on autonomic regulation.

Results from studies that cued emotional declarative memories are relatively more homogeneous suggesting that TMR during NREM benefits negative memories. A nap study by (Cairney, Durrant, Hulleman, & Lewis, 2014) used a location memory paradigm, stimuli being negative and neutral pictures paired with matching sounds, and cued half of the stimuli during SWS. Cueing did not have any effects on memory accuracy but reduced response time for the cued negative items. However, use of a different task indicated that memory cueing during SWS can stabilize and generalize newly acquired memories resulting in biasing interpretation of ambiguous scenes either positively or negatively (Groch et al., 2016). A memory improvement for the cued negative stimuli was also found in a study using neutral words paired with negative or neutral pictures, only when TMR took place during NREM (Lehmann, Schreiner, Seifritz, & Rasch, 2016). Furthermore, successful TMR increased theta and spindle oscillations, especially for the negative stimuli. Interestingly, TMR during REM did not have any behavioural effects but increased theta activity only for neutral stimuli. In a follow-up study on patients with social anxiety disorder and healthy controls, using positive and negative pictures, cueing facilitated equally the retention of all the cued stimuli for both groups (Groch, Preiss, et al., 2017). However, pleasantness ratings decreased after a week for the negative cued stimuli in the patient group. Finally, a study using TMR during REM found enhanced post-sleep accurate recollection and false recognition of faces regardless of their valence, suggesting that TMR in REM facilitates generalisation of memories (Sterpenich et al., 2014)

Summing up, cueing of stimuli during sleep appears to be a promising method towards manipulating the consolidating and emotional processes of the sleeping brain. However, the results so far on emotional memories and emotional salience appear to be sensitive to the experimental paradigm and study design.

1.6 Research Objectives

The aim of this PhD was to investigate the effects of sleep on the consolidation of emotional memories and their salience. In Chapter 2, we aimed to assess the effects of TMR during SWS or wakefulness on the associative memory

consolidation and subjective valence and arousal ratings of negative and neutral stimuli. In Chapter 3, we explored further the effects of TMR by studying the neural correlates of subjective arousal and associative memory after a night with TMR during SWS. Therefore, participants did the post-sleep tasks inside an MRI scanner. Furthermore, we examined whether TMR effects on behaviour would still be significant after a week. In Chapter 4, we studied whether the neural correlates of negative compared to neutral stimuli differ during SWS while they are cued. Thus, an EEG classifier was trained on the wake data, while participants trained on a serial reaction time task (SRTT) with a negative and a neutral sequence, and tested on the sleep data, with TMR of both sequences during SWS. In Chapter 5, we investigated the roles of sleep and wakefulness on associative memory and subjective valence, arousal, and likeability ratings of happy, peaceful, sad, and scary musical stimuli after a period of 12 h, 24 h and 1 week. Finally, Chapter 6 is a general discussion acting like REM, we bring the findings of the previous chapters together, attempt to integrate them with the existing literature, and dream of future directions.

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2. Cued Memory Reactivation of Negative Memories during SWS Stabilizes their Consolidation and Enhances their Habituation

Maria-Efstratia Tsimpanouli, Rebecca Elliott, Isabel Hutchison, Ian M. Anderson, Penelope A. Lewis

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2.1 Introduction

Studies from humans and animals support a beneficial role of sleep in memory consolidation (Plihal & Born, 1997; Rasch & Born, 2013; Sara, 2017; Tucker et al., 2006). It is believed that the mechanism behind is the spontaneous reactivation of memories during slow-wave sleep (SWS) (Born, Rasch, & Gais 2006). Indeed, a large number of studies have shown enhanced memory consolidation and stabilization following cueing odours or sounds during SWS, to trigger targeted memory reactivation (TMR) (Cousins et al., 2014; Diekelmann et al., 2012; Fuentemilla et al., 2013; Oudiette et al., 2013; Rasch et al., 2007; Rudoy et al., 2009; Schreiner & Rasch, 2015a).

Items that are emotionally salient are better remembered than neutral ones across sleep or wake (Corsi-Cabrera & Poe, 2014; Dolcos et al., 2012; Payne et al., 2008). However, not all aspects of memory are enhanced by emotional salience. In contrast to recognition memory, associative memory can be impaired for emotional items (Bisby & Burgess, 2014; Maddock & Frein, 2009; Novak & Mather, 2009). According to the "Sleep to forget, sleep to remember" hypothesis, emotional memories are maintained across sleep, rapid-eye-movement sleep (REM) in particular, while their emotional component is decoupled (Walker, 2009). However, a study by (Groch et al., 2011) supports a role of SWS in the decrease of subjective arousal. If the latter is true, it remains unclear whether this emotional habituation relies on the reactivation of emotional memories during SWS. Conflicting findings come from TMR during SWS in fear conditioning paradigms. Fear memory was strengthened in animals (Barnes & Wilson, 2014; Rolls et al., 2013) and humans (Ai et al., 2015) or fear extinction was promoted in humans (Hauner et al., 2013; He et al., 2015).

In a study by (Rudoy et al., 2009) using neutral stimuli, participants learned object-location associations. Then, during a nap half of the sounds were cued during SWS. They reported a memory enhancement for the cued items. A later nap study (Cairney, Durrant, Hulleman, et al., 2014), examined the effects of TMR in SWS on associative memory of emotional stimuli, without assessing the change in emotional perception. In that study, no TMR effects were found in memory accuracy, but participants had faster reaction times for the negative cued items. Here, we used auditory TMR during overnight SWS to investigate sleep-dependent associative memory consolidation and emotional habituation of negative and neutral items. We also assessed whether TMR in sleep has a

unique role in memory consolidation and emotional habituation by using the same procedure in wakefulness too. Participants rated for valence and arousal matching pictures-sounds and learned their location on the screen. Half of the negative and half of the neutral sounds were replayed during SWS or active wakefulness. The next day, participants were tested again on their memory and rated the stimuli.

2.2 Materials and Methods

2.2.1 Participants

Forty healthy participants (19 females) aged 18-29 years old (mean age = 22.05, SD = ±2.70) took part. Originally, 22 participants (9 females) were recruited to test cueing during SWS, i.e. the sleep group. After the data collection was completed, we decided to run a control group to confirm that the findings were due to SWS TMR. For the control group, another 18 participants (10 females) were recruited and TMR was performed during active wake before sleep. All participants reported constant sleep-wake cycles for a month prior to the study, had no history of any neurological, psychiatric or sleep disorders, and abstained from caffeine and alcohol for 24 h prior to and during the study. All participants gave written informed consent and were compensated for their participation. This study has been approved by the University of Manchester research ethics committee.

2.2.2 Stimuli

Stimuli were taken from a previous nap study on emotional memory (Cairney, Durrant, Hulleman, et al., 2014). 72 pictures (36 neutral and 36 negative) were selected from the International Affective Pictures System (IAPS) (Lang, Bradley, & Cuthbert, 1997). 72 sounds, matching the content of each picture, were selected from the International Affective Digitized Sounds battery (IADS) (Bradley & Lang, 2007). Each sound was 6 s long. All pictures and sounds were rated on a Likert-like scale of 1 to 9 for valence and arousal. The two groups of stimuli differed significantly on valence ratings and on arousal ratings (Cairney, Durrant, Hulleman, et al., 2014).

After a pilot study, most of the sounds were modified, using a Praat script (Boersma, 2001), to make them be perceived as of equal loudness. Before starting the experimental tasks, a separate neutral noise was played to deter-

mine the appropriate sound volume level. The sounds were administered via noise canceling headphones (SONY mdr-nc7), during the tasks. During sleep, the sounds were administered through PC speakers (Dell A425). Brown noise was played throughout the night for both groups, to minimize arousals due to the auditory stimuli or any other external noise. To ensure that the sounds would not wake up the participants, they were further modified using the program Audacity in order to fade in during the first 2 seconds and fade out effect after the fourth second.

2.2.3 Experimental Tasks and Design

The experimental design is described in Figure 2-1. All participants filled the Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990), the Stanford Sleepiness Scale (SSS) (Hoddes, Dement, & Zarcone, 1972), and the 20-items Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) three times, at the beginning of the experiment, after the PSG wire-up, and before starting the morning experimental tasks. All tasks were performed on a computer screen with a resolution of 1024 x 768 pixels. At each task, the paired stimuli were presented in a pseudorandom order, neutral and negative stimuli alternating.

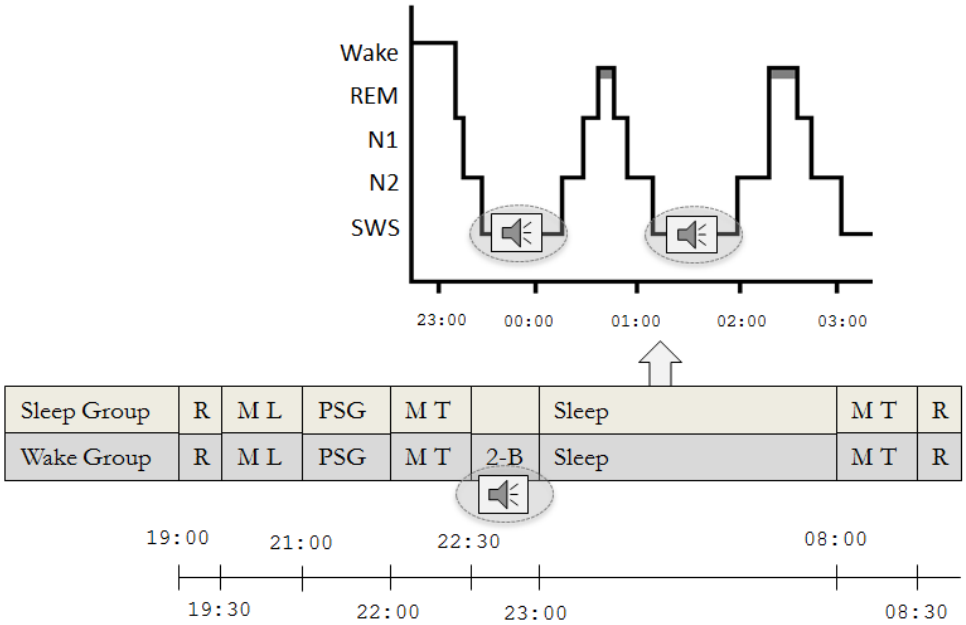

Figure 2-1 Experimental design: R = valence and arousal ratings, ML = memory learning and training tasks, MT = memory testing, 2-B = 2-back task

In the valence and arousal-rating task, stimuli were presented using Matlab and Cogent. Participants were instructed to rate the picture and sound combination

using a 9 items Likert-like scale, by pressing one of the numerical keys of the keyboard, according to their first impression without overthinking (1 being negative to 9 being positive for valence, and 1 being calm to 9 being exciting for arousal). The self-assessment manikins (SAMs) for arousal and valence (Bradley & Lang, 1994) were placed on the wall behind the computer as a reference and reminder about what is valence and arousal. Each picture was displayed full screen for 6 s, i.e. while its sound was playing, and after a 2 s gap, participants were asked to rate the pair for valence and arousal.

In the spatial memory task, the stimuli were presented on Eprime 1.0, based on a script developed by (Rudoy et al., 2009) modified for the needs of this study. Firstly, participants were instructed to memorize the location of each picture that was presented at a random screen location while listening simultaneously to its paired sound, having a grid background as reference. During the training session, each picture appeared in the centre of the screen and its sounds played for 6 s. Then the participants were instructed to move the picture to the location they thought to be correct using the left click of the mouse and press the right click to confirm. After confirming, feedback was provided by the picture moving to its correct location and its sound playing again. Participants completed several rounds training up to a criterion threshold through repeated testing with feedback. The first two rounds contained all 72 pairs. Once a pair was placed correctly, i.e. within 150 pixels from its correct location, in two subsequent runs, then it would not appear at the next run. The amount of training depended on the learning abilities of each participant. The electrodes for PSG were placed after the training session, allowing an at least 40 min gap between the training and testing for the spatial memory task.

The participants of the control group performed a working memory task for 30 min before going to sleep, during which TMR was administered. That was done in order to distract them from recognizing the TMR sounds, making this exposure similar to TMR in the sleep group. The working memory task was a 2-back recall task, where letters were presented and the participant had to indicate whether the letter before last was the same as the one on the screen. Participants were instructed to focus on the task and ignore any other sounds. To match the conditions of cueing during sleep, brown noise was played during this task.

The sounds were split into two sets having equal mean valence and arousal for neutral and negative stimuli. Once the participant had entered SWS for at least one minute, 6 sounds (3 neutral and 3 negative) of a set were played, with 2 s gaps between them. After at least one minute another 6 sounds of the same set were played. This procedure continued for as long as the participant remained in SWS. In case of an arousal during cueing, the sound was stopped and was continued after one minute. The aim was to play each sound at least once and as many times as possible.

The next morning, participants were woken up after approximately 8 h of sleep, when possible. The PSG electrodes were removed and participants were able to take a shower. Then, they performed once more the memory testing task and the valence and arousal ratings. After these tasks, it was revealed to them that some sounds were played while they were sleeping or doing the 2-back task. Subsequently, they were asked to indicate for each sound whether they believed that it was presented during these periods.

2.2.4 PSG Data Acquisition and Analysis

Silver-silver chloride electrodes were attached to the scalp and face of the participants. In total 15 electrodes were placed according to the 10-20 rule. The 7 electrodes on the scalp were placed on the regions F3, F4, C3, C4, Cz, O1, O2. The connection impedance was < 5 KOhms and the sample rate was 200 Hz. PSG activity was recorded through an Embla N7000 PSG amplifier using the RemLogic software. All PSG recordings were scored manually on RemLogic by two experimenters, who were blind on whether and when sounds were cued, according to "The AASM Manual for the Scoring of Sleep and Associated Events".

2.2.5 Statistical Analysis

Four participants, two from each group, were excluded from the analysis. Three did not complete the training task and one was not able to undergo PSG. Furthermore, three more participants, two from the sleep group and one from the wake group, were excluded from the valence and arousal analysis because the difference between pre- and post-sleep ratings was greater than 4 points in at least 1/3 of the total items or items of an emotion.

Furthermore, at the arousal and valence tasks, any stimuli that changed more than 4 points on the respective scale were excluded. Thus, 4.63% [±0.73] of

the stimuli were removed from the arousal task and 2.19% [±0.55] from the valence task. For the remaining stimuli, the overnight change was calculated by subtracting the pre-sleep ratings from the post-sleep ratings. The overnight % change for the memory task was estimated according to the function below:

$$\text{overnight \% change} = \frac{(\text{PostSleep Distance} - \text{PreSleep Distance})}{\text{Mean PreSleep Distance}_{\,Negative\ or\ Neutral}} * 100$$

A one factor (emotion: negative/neutral) repeated measures ANOVA was used to assess any differences in the number of rounds during the training session, valence and arousal ratings and error in spatial recall prior sleep. Furthermore, 2 x 2 x 2 repeated measures ANOVAs, with type of group (wake or sleep) as between-subjects factor and emotion (negative or neutral) and cueing (cued or non-cued) as within-subjects factors, were performed to assess the overnight changes of the valence and arousal ratings, and the spatial accuracy. For each group, a 2 x 2 ANOVA, with within-subjects factors valence and cueing, for each of the above measures was also performed. To determine any effects of the sleep stages, separate ANCOVAs, corresponding to the previous ANOVAs, were performed, having as covariates the mean-centred duration of SWS, REM, and N2 respectively. To assess any correlations we used two-tailed Pearson's correlations. The results from the task where participants had to indicate whether each sound was cued, were assessed by a 2 x 2 ANOVA based on their d' values (Lynn & Barrett, 2014; Macmillan & Creelman, 1990). Error bars and values in brackets refer to standard error of the mean (SEM) unless otherwise specified.

2.3 Results

2.3.1 Sleep and Questionnaires

A main effect of session was found in both sleepiness scales, SSS: F (2, 33) = 18.082, $p < 0.001$, $\eta_p^2 = 0.523$, and KSS: F (2, 33) = 43.133, $p < 0.001$, $\eta_p^2 = 0.723$. For the PANAS results, we observed a main effect of emotion, F (1, 34) = 251.159, $p < 0.001$, $\eta_p^2 = 0.881$, with higher ratings in the positive affect scale; and time, F (2, 33) = 13.562, $p < 0.001$, $\eta_p^2 = 0.451$, with higher ratings at the beginning of the experiment. Furthermore, there were interactions of emotion x group F (1, 34) = 19.356, $p < 0.001$, $\eta_p^2 = 0.363$, emotion x time, F (2, 33) = 8.681, $p = 0.001$, $\eta_p^2 = 0.345$, and emotion x time x group, F (2, 33) =

3.725, p = 0.035, η_p^2= 0.184. There was no difference among sleep stages between the two groups (Table 2-1).

Table 2-1 Total time spent in sleep stages

Sleep Stage (min)	Sleep Group [SD]	Wake Group [SD]	$\|t\|$ (34)	p
N1	24.46 [±2.75]	30.01 [±4.74]	1.014	0.320
N2	237.18 [±10.43]	229.43 [±10.20]	0.531	0.599
SWS	92.14 [±4.94]	103.67 [±7.69]	1.261	0.216
REM	83.85 [±5.54]	69.78 [±5.12]	1.865	0.071
WASO	40.53 [±5.29]	43.11 [±8.91]	0.249	0.805
TST	438.38 [±13.01]	432.89 [±12.04]	0.309	0.759

WASO = wake after sleep onset, TST = total sleep time

2.3.2 Valence and Arousal Ratings

First, we examined whether valence and arousal ratings differed between negative and neutral items prior to sleep (Table 2-2). An ANOVA on the valence ratings, with emotion as within-subjects factor, indicated a main effect of emotion, F (1, 32) = 501.414, p < 0.001, $p\eta^2$ = 0.940. Similarly, an ANOVA on arousal ratings indicated a main effect of emotion, F (1, 32) = 84.271, p < 0.001, $p\eta^2$ = 0.725. As expected, negative stimuli had higher arousal and lower valence ratings in comparison to the neutral stimuli.

Table 2-2 Mean valence and arousal ratings

Mean ratings [±SEM]	Negative cued	Neutral cued	Negative uncued	Neutral uncued
Valence before sleep	2.33 [0.13]	5.61 [0.11]	2.48 [0.16]	5.70 [0.12]
Valence after sleep	2.35 [0.17]	5.82 [0.13]	2.54 [0.19]	5.90 [0.16]
Arousal before sleep	6.17 [0.44]	4.67 [0.34]	6.04 [0.42]	4.43 [0.30]
Arousal after sleep	5.70 [0.42]	4.15 [0.33]	5.81 [0.43]	3.82 [0.35]

To investigate the effect of TMR during SWS on overnight changes in valence and arousal ratings, we used repeated measures ANOVAs with group as the between-subjects factor and cueing and emotion as the within-subjects factors.

We did not find any main effects or interactions on the change of valence ratings (Figure 2-2) suggesting that neither TMR nor emotion influenced valence overnight change. There was, however, an interaction of cueing x emotion x group on the overnight change of arousal ratings, F (1, 31) = 5.029, p = 0.032, η_p^2 = 0.140 (Figure 2-3), although there were no other significant effects. Additional ANOVAs with factors cueing and emotion on each group, showed a cueing x emotion interaction on the percentage change of arousal ratings in the sleep group only, F (1, 15) = 7.678, p = 0.014, η_p^2 = 0.339. Post hoc paired sample t-tests revealed trends for difference between negative cued and negative uncued items, t (15) = -1.935; p = 0.076, and between negative uncued and neutral uncued, t (15) = 1.954; p = 0.070. Further paired sample t-tests revealed significant differences between before and after sleep arousal ratings for negative cued, t (15) = 2.923; p = 0.011, neutral cued, t (15) = 2.454; p = 0.027, and neutral uncued items, t (15) = 3.553; p = 0.003, but not for the negative uncued ones, t (15) = 1.269; p = 0.224. These results suggest that TMR enhances significantly the arousal habituation of negative items.

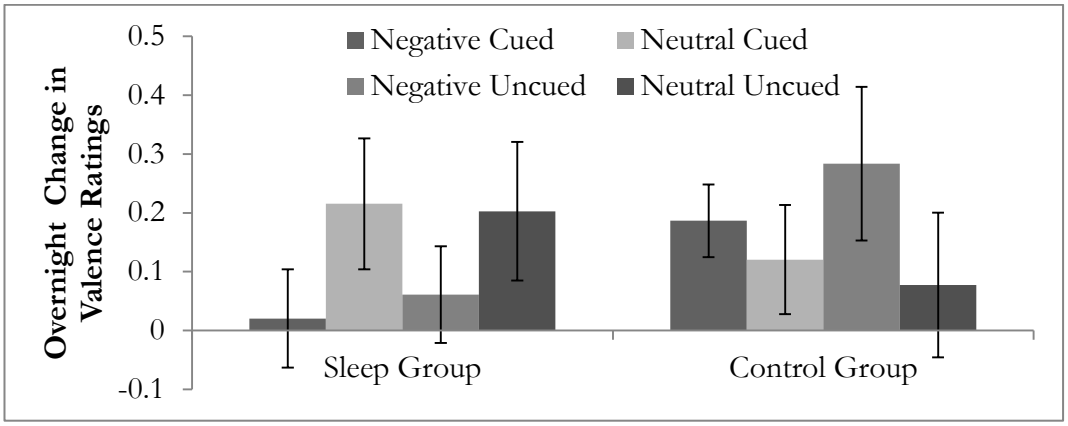

Figure 2-2 Overnight change in valence ratings

To test whether the different sleep stages have an additional effect on TMR related emotional processing, we repeated the above ANOVAs as separate ANCOVAs with the duration of N2, SWS, and REM as a covariate for each group. Once again, no effects were found on the wake group or the overnight valence changes. Furthermore, there were no significant results when REM or SWS were used as a covariate. When N2 was used as a covariate, we found a N2 main effect, with F (1, 14) = 15.549, p = 0.002, η_p^2 = 0.525. This was confirmed with a Pearson's correlation between N2 duration and mean overnight

percentage change of arousal ratings, r (16) = -0.726, p = 0.001, indicating that increased N2 duration correlated with a greater decrease in the arousal change.

To investigate whether the number of TMRs during SWS predicted post-sleep valence and arousal ratings or overnight changes, we run the respective Pearson's correlations. However, we did not find any significant correlations, all p > 0.05.

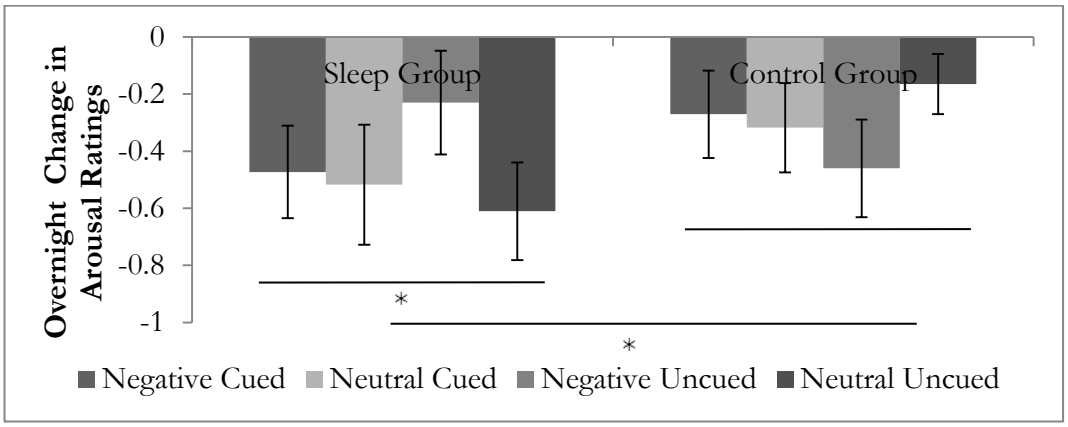

Figure 2-3 Overnight change in arousal ratings. Where *, statistical significance is p < 0.05.

2.3.3 Spatial Memory

To assess the effect of emotion on the spatial memory task we conducted two ANOVAs, with emotion as within-subjects factor, on the number of training rounds and on the accuracy error before sleep. In both cases, we found a main effect of emotion. Neutral items, compared to the negative ones, required fewer training rounds, F (1, 35) = 16.558, p < 0.001, η_p^2 = 0.321. Furthermore, participants remembered better the location of the neutral items than the negative items, F (1, 35) = 12.348, p = 0.001, η_p^2 = 0.261, (Table 2-3).

Table 2-3 Mean distance from correct location

Mean distance (pixels) [±SEM]	Negative Cued	Neutral Cued	Negative Uncued	Neutral Uncued
Before sleep	83.02	63.65	72.35	63.21
	[7.52]	[5.78]	[5.80]	[5.09]
After sleep	82.88	62.46	80.00	66.53
	[9.23]	[5.10]	[8.40]	[5.30]

To investigate the effect of TMR on overnight percentage change of spatial recall error, we conducted a repeated measures ANOVA with group, cueing, and emotion as factors. We found a cueing x group interaction, F (1, 34) = 7.143, p = 0.011, η_p^2 = 0.174 (Figure 2-4). To assess further the TMR effects on each group, we conducted an ANOVA on each group with factors cueing and emotion. We only found a cueing main effect on the spatial recall error percentage change of the sleep group, F (1, 17) = 5.494, p = 0.031, η_p^2 = 0.244. This effect appears to be driven by less forgetting of the cued items. Additional ANCOVAs with the sleep stages as covariates did not reveal any other main effects or interactions.

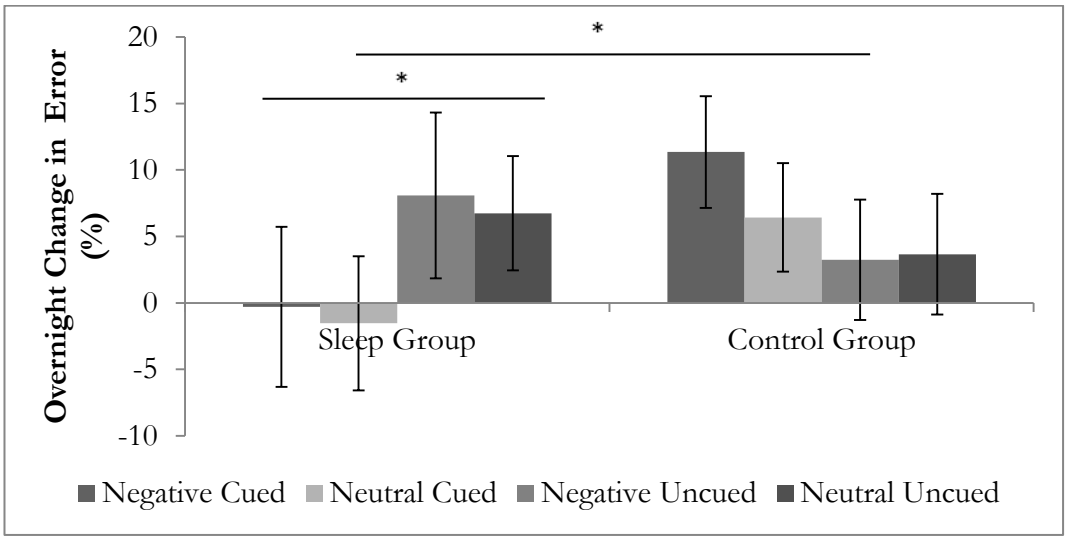

Figure 2-4 Overnight % change in spatial accuracy error. Where *, statistical significance is $p < 0.05$

To investigate whether the number of TMRs during SWS predicted post-sleep memory performance, we run the respective Pearson's correlations. However, we did not find any significant correlations, all $p > 0.05$.

2.3.4 TMR Awareness

All participants performed at chance when asked to recognize which sounds were cued, having a mean d' value of 0.11 [±0.05]. However, a repeated measures ANOVA having group and emotion as factors, showed a weak trend for a main effect of group, F (1, 30) = 3.535, p = 0.070, η_p^2 = 0.105, with the control group having a higher mean d' value, 0.18 [±0.06], than the sleep group, 0.01 [±0.07].

2.4 Discussion

In this study, we investigated for the first time the effects of TMR on the consolidation and habituation of negative and neutral associative memories during overnight SWS and wakefulness. We provide further evidence that TMR in SWS stabilizes the consolidation of object-location memory, regardless of the valence of the stimuli. Furthermore, we found enhancement of the overnight arousal habituation of negative stimuli, but there were no effects on valence. TMR during wakefulness did not affect valence and arousal ratings or memory performance.

In this object-location task, location memory of the negative items was worse than the neutral ones. This finding is in agreement with previous studies where associative memory was reduced for negative stimuli (Bisby & Burgess, 2014; Maddock & Frein, 2009; Mather et al., 2006; Mitchell et al., 2006; Novak & Mather, 2009). Negative emotion down-regulates the hippocampus, resulting in weakened associative representations (Bisby, Horner, Horlyck, & Burgess, 2016). At the same time, hippocampal activity mediates memory enhancement from TMR in SWS (Fuentemilla et al., 2013; Rasch et al., 2007). Therefore, in an associative memory task, cueing negative items during SWS could be more beneficial to their consolidation to a similar level as the neutral items. However, according to our findings, TMR during SWS stabilized equally the associative memory consolidation of negative and neutral items, whereas memory for the uncued items deteriorated.

Previous studies using SWS TMR on object-location memory tasks have also observed an enhancement and stabilization of the cued memories, protecting them from interference (Diekelmann et al., 2012, 2011; Rasch et al., 2007; Rudoy et al., 2009). However, these studies were using only neutral stimuli. In a later study, (Oudiette et al., 2013) used stimuli with low or high reward value. Cueing half of the low-value items during sleep rescued from forgetting all of the low value items, whereas cueing them during wake rescued only the cued ones. A nap study with TMR during SWS did not yield any effects on accuracy but SWS duration predicted faster response time for the negative cued items (Cairney, Durrant, Hulleman, et al., 2014). In a recent study, (Lehmann et al., 2016) found that emotional but not neutral memories benefit from TMR in NREM sleep, and not in REM. These studies show a selective enhancement on consolidation mediated by TMR, whereas in the current study TMR benefited

both negative and neutral items. The differences in our results may be accounted for by a number of reasons. One reason could be the use of different types of tasks, where emotional memories are better remembered. Another reason could be different testing times, (Cairney, Durrant, Hulleman, et al., 2014) tested participants after a nap, (Lehmann et al., 2016) after 3 h of NREM rich sleep, whereas in our design participants were tested after a full night sleep containing REM.

Although both arousal and valence ratings changed overnight, TMR did not have any effects on valence ratings. This might be because arousal reflects the emotional response and is closer to physiology, whereas valence is perceived as a category and is more stable. Our results support a role of SWS not only in the consolidation of emotional memories but in the habituation of their emotional component too. The observed overnight habituation might be influenced by the repeated exposure to the stimuli during the memory training session. A previous study has also provided similar evidence, reporting subjective arousal decreasing after SWS-rich early night sleep (Groch et al., 2011). Furthermore, it was found that blocking the release of noradrenaline during SWS diminished the arousal habituation (Groch et al., 2011). The effects of TMR on emotional response and habituation have also been studied using fear extinction paradigms. In such studies in rodents, TMR during SWS has been shown to strengthen (Barnes & Wilson, 2014; Rolls et al., 2013) or impair (B. Hars & Hennevin, 1987) fear memory. Similarly, conflicting results come from human studies where SWS TMR increased fear response (Ai et al., 2015) or promoted fear extinction (Hauner et al., 2013; He et al., 2015).

Not all studies though support a role of SWS in emotional habituation. A study by (Gujar et al., 2011) found that subjective arousal did not decrease if participants did not reach REM after a nap. Similarly, (Goldstein & Walker, 2014) found REM to be necessary for the dissociation of memories from their emotional tone. A role of REM in facilitating subjective arousal decrease is also supported by (Rihm & Rasch, 2015). Even though the above studies on SWS and REM seem to be conflicting, emotional habituation could be a synergistic effect of these sleep stages. In this regard, a review by (Hutchison & Rathore, 2015) suggests that REM sleep mediates the selection and subsequent integration of emotional memories, whereas SWS mediates their processing and consolidation.

However, while looking at the effects of different sleep stages on emotional habituation, we did not find any correlations with the duration of SWS or REM, but with the duration of N2. Duration of N2 correlated positively with the arousal habituation for all items when TMR was present in SWS but not in wakefulness. A study by (Rihm & Rasch, 2015) also found a decrease in perceived arousal of negative stimuli as a result of TMR during late night N2, using a Pavlovian conditioning paradigm. In contrast to our findings, though, they did not observe any effects on emotional memory. Most studies so far have focused on the role of REM, SWS or NREM on emotional memory processing and consolidation, but have not looked on N2 individually. N2 shares some of the characteristics of SWS that have been attributed to the processing and consolidation of memories, sleep spindles and slow waves. Sleep spindles are crucial for the stabilization and strengthening of a memory after cueing (Mednick et al., 2013). Sleep spindles have also been implicated in plasticity (Born et al., 2006; Diekelmann & Born, 2010; Niknazar, Krishnan, Bazhenov, & Mednick, 2015). Future studies should further investigate the distinct and shared properties at N2 and SWS in these memory functions.

The different, and sometimes even conflicting, effects of TMR on the consolidation and habituation of emotional memories from prior studies could occur because studies have assessed different types of emotions. Literature suggests that negative and positive emotions not only are processed differently but arousal levels might further modulate valence effects (Mickley Steinmetz, Addis, & Kensinger, 2010). The type of a stimulus and the experimental task can also influence the emotional effects on memory. Further research is necessary to elucidate the mechanisms behind TMR, methods of application, and the potential effect on consolidation and processing of emotional events in healthy people and patients. If results are encouraging, different types of TMR, e.g. during SWS vs REM, in combination with other therapeutic approaches might eventually have therapeutic potential for phobias, PTSD, anxiety disorders, and depression.

One potential limitation of this study is that the sleep group did not perform a working memory task before sleeping. Previous studies though show no effects in the processing of memory cues with TMR during either active or passive wake (Schreiner & Rasch, 2015a, 2015b). The memory training session may have had an effect on the initial subjective arousal and valence ratings, poten-

tially influencing their habituation. Nevertheless, we found TMR during SWS to modulate the subjective arousal. Finally, men and women differ on how they perform in memory tasks and process certain emotions (Dolcos et al., 2012). This should be considered in future studies investigating TMR treatment in female and male patients.

To conclude, we showed that TMR of negative and neutral memories during SWS stabilizes their consolidation. We also showed that TMR enhanced the habituation of subjective arousal ratings for the negative stimuli. Interestingly, N2 appears to enhance the arousal habituation of all stimuli.

3. The Neural Correlates of the Consolidation and Habituation of Negative Memories after Targeted Memory Reactivation during SWS: an fMRI study

Maria-Efstratia Tsimpanouli, Isabel Hutchison, Martyn McFarquhar, Rebecca Elliott, Jules Schneider, Ian M. Anderson, Penelope A. Lewis

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3.1 Introduction

Sleep plays an important role in the consolidation of memories (Rasch & Born, 2013; Sara, 2017). Declarative memory traces are believed to be initially stored in the hippocampus. It has been proposed that during slow-wave sleep (SWS) these traces are spontaneously reactivated and then are transferred to neocortical areas (Fuentemilla et al., 2013; Horner et al., 2012; Maingret et al., 2016; Takashima et al., 2009). A number of studies have shown that the underlying mechanism involves the activity of sleep spindles, slow oscillations, and sharp wave ripples (Inostroza & Born, 2013; Maingret et al., 2016). In addition, there is evidence that hippocampo-cortical connections get weaker after sleep whereas cortico-cortical connections get stronger (Takashima et al., 2009). This hippocampo-cortical dialogue results in the successful consolidation of the memories and their integration with previous information (Maingret et al., 2016).

Emotional memories are better consolidated than neutral memories. One of the mechanisms supporting this enhanced consolidation is the activation of amygdala during the stages of encoding, consolidation, and retrieval of emotional memories (McGaugh, 2004). Emotional memories are preferentially consolidated during sleep, as the amygdala may be tagging their traces and prioritize their reactivation (Hutchison & Rathore, 2015). However, at the same time, emotion may down-regulate the hippocampal activity (Bisby et al., 2016), which is important for context memory (Horner et al., 2012). As a result, associative memory and details of negative items, compared to neutral items, are remembered less (Bisby et al., 2016; Maddock & Frein, 2009; Mather et al., 2006; Mitchell et al., 2006; Novak & Mather, 2009; Phelps & Sharot, 2008). For example, in an object location task, the location of neutral items is more accurately remembered than that of the negative items (Maddock & Frein, 2009; Mitchell et al., 2006; Novak & Mather, 2009; Tsimpanouli, Elliott, Hutchison, Anderson, & Lewis, 2017).

Furthermore, sleep may be processing the emotional component of memories. Evidence for the role of SWS and rapid-eye-movement sleep (REM) in arousal processing is conflicting, some studies report a habituation, others a maintenance, and others an enhancement of arousal. According to the Sleep to Forget Sleep to Remember hypothesis (van der Helm & Walker, 2010) REM, prioritizes the consolidation of emotional memories and attenuates their salience.

In line with this hypothesis, (Gujar et al., 2011) found that sleep, mediated by REM, habituates reactivity to anger and fear. However, another study by (Groch et al., 2011) found that subjective arousal and heart-rate variability habituated across SWS. Conversely, (Baran et al., 2012) suggest that emotional reactivity is preserved during sleep, and this is mediated by REM. Similarly, (Groch et al., 2013) in a study with only male participants found that REM sleep preserved emotional arousal. A more recent study claims that REM attenuates any emotional habituation and might even enhance emotional salience (Werner, Schabus, Blechert, Kolodyazhniy, & Wilhelm, 2015). In favour of enhancement, (Wagner et al., 2002) reported that sleep, compared to an equal period of wakefulness, enhanced post-sleep arousal ratings. The lack of consistency in the results of the literature means that further studies are needed.

Experiments in animals and humans have triggered targeted memory reactivation (TMR) by cueing stimuli during sleep (Schouten et al., 2017). As a result, memories of the cued items may become stabilized or even strengthened. A number of studies have also investigated the effects of TMR during SWS or REM on emotional memories and fear extinction (Ai et al., 2015; Cairney, Durrant, Hulleman, et al., 2014; Hauner et al., 2013; He et al., 2015; Hutchison et al., under review; Rihm & Rasch, 2015). Results though remain inconclusive, possibly because these studies have used different experimental designs, tasks, and type of stimuli. Furthermore, it remains unknown whether TMR in SWS modulates hippocampal activity differently for negative and neutral memories. In two recent studies of our group, we used TMR to investigate further the role of sleep in emotional processing. In a previous study (Tsimpanouli, Elliott, et al., 2017), we used an altered version of the experimental task from (Rudoy et al., 2009), having negative and neutral pairs of sounds and pictures. Participants first rated the pairs for valence and arousal, then trained on a memory task with the same stimuli, and finally, half of the auditory stimuli were represented during active wakefulness or during SWS. The next day participants did the memory task and then rated again the stimuli. We did not observe any cueing effects when TMR was done during wakefulness. In the group that received TMR during SWS, we found that although participants remembered the location of neutral items better than that of the negative items, memory accuracy was preserved for both negative cued and neutral cued items (Tsimpanouli, Elliott, et al., 2017). Furthermore, we found that TMR enhanced

the habituation of negative stimuli. In another study (Hutchison et al., under review), we used TMR during SWS, REM, or wakefulness to assess processing of arousal both on the behavioural level, by subjective ratings, and on the autonomic system, by measuring pupil dilation. We only found a habituation on subjective arousal ratings when TMR occurred in REM.

The current study aimed to assess further the role of TMR during SWS on the consolidation and arousal processing of negative and neutral stimuli, by exploring the associated neural correlates. Following the design of (Rudoy et al., 2009), participants were trained to learn the location of negative and neutral pictures on the screen and were later tested. Each picture was presented with a semantically matching sound. Participants rated the pairs of stimuli for emotional arousal before and after the memory tasks. Then, participants went to sleep and during SWS half of the sounds from each emotional category were cued. The next day participants performed the arousal-rating task and the memory-testing task inside an MRI scanner. After approximately a week, participants had another session in the sleep lab, where they performed again the arousal and memory tasks. On the behavioural level, we expected to replicate the findings of our previous study. For the fMRI, we hypothesized that amygdala, hippocampus, orbitofrontal areas and other regions of the emotional and memory networks would show different activation patterns for negative and neutral items both for the arousal and memory tasks. The supplementary motor areas were also included in the memory analysis, as the task included procedural memory elements and a previous study has shown TMR to modify activity in motor areas (Cousins et al., 2016). Furthermore, we hypothesized that TMR might alter in different ways the neural correlates of negative and neutral stimuli.

3.2 Materials and Methods

3.2.1 Participants

Thirty healthy participants aged 18-37 years old (mean age = 24.43, SD = ±5.69) took part. All participants were female, right-handed, reported consistant sleep-wake cycles for a month prior to the study, had no history of any neurological, psychiatric or sleep disorders, and abstained from caffeine and alcohol for 24h prior to and during each study session. The choice of only female participants was based on previous research suggesting that women,

compared to men, find negative content to be more arousing, remain engaged to it for a longer period, and use different strategies to regulate emotions even at a neural level (Gard & Kring, 2007; Moriguchi, Touroutoglou, Dickerson, & Barrett, 2014; Spalek et al., 2015; Whittle, Yucel, Yap, & Allen, 2011). All participants gave written informed consent and were compensated for their participation. This study has been approved by the University of Manchester research ethics committee.

3.2.2 Stimuli

Stimuli, 72 pictures and 72 sounds, were the same as in our group's two previous studies on emotional memory (Cairney, Durrant, Hulleman, et al., 2014; Tsimpanouli, Elliott, et al., 2017). Half of the pictures were negative and the other half neutral. The sounds were matched semantically to the content of each picture (Cairney, Durrant, Hulleman, et al., 2014). All of the pictures were selected from the International Affective Pictures System (IAPS) (Lang et al., 1997) and all of the sounds from the International Affective Digitized Sounds (IADS) battery (Bradley & Lang, 2007). Each sound was 6 s long. Both sets of stimuli differed significantly on valence and arousal ratings, with negative stimuli being more arousing.

Before starting the experimental tasks, a separate neutral noise was played to determine the appropriate sound volume level. Sounds were delivered through overhead noise canceling headphones (Sony MDR-ZX110NA) during the experimental tasks in the sleep lab, through PC speakers (Dell A425) during sleep, and through an MR compatible noise-cancelling headphone unit developed by MR Confon (http://www.mr-confon.de/) inside the MR scanner. Brown noise was played throughout the night to minimize noise-induced arousals. To ensure that the sound stimuli would not wake up the participants, they were further modified using the program Audacity in order to fade in and fade out for the first two and last two seconds respectively.

3.2.3 Experimental Tasks and Design

The experimental design is described in Figure 3-1. All participants answered the Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990) and the 20-items Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) four times, at the beginning of the experiment, after the PSG wire-up, before entering the scanner, and before starting the final follow-up

session. Participants also answered the Depression, Anxiety and Stress Scale (DASS) (Lovibond & Lovibond, 1995), the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), the Edinburgh Handedness Inventory (Oldfield, 1971), and the Morningness-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976) at the beginning of the experiment, and filled a Sleep Diary for the night before each experimental day. The electrodes for PSG were placed after the training session, allowing an at least 40 min gap between the training and testing sessions for the memory task. All tasks were performed on a computer screen with a resolution of 1024 x 768 pixels.

For all tasks, the paired stimuli were presented in a pseudorandom order, with no more than two stimuli of the same category being presented after each other. Participants had the chance to perform at least one training round before each task, to learn how to use four keys in order to move a cursor for the arousal ratings or to place the picture for the memory task. Learning how to move the objects on the screen using four keys added a procedural learning component to both tasks. All stimuli were presented using Eprime 1.0.

For the arousal rating task, participants were instructed to rate each picture – sound pair using a 9 items Likert-like scale (1 being calm to 9 being exciting). A self-assessment manikin (SAM) for arousal (Bradley & Lang, 1994) was presented above the scale. Participants were instructed to decide what rating to give according to their first impression, while the stimuli were presented. The picture was displayed full screen for 6 s, i.e. as long as the sound duration. Then, they had a period of 5 s to give their rating. This task was performed twice at night, at the beginning of the experiment and after the memory test, below.

The spatial memory task was adapted from (Rudoy et al., 2009). During the learning session, participants were instructed to memorize the location of each picture that was presented at a random screen location while listening simultaneously to its paired sound, having a grid background as reference. For the training session, the picture would appear in the centre of the screen and its sounds would play. Then, the participants were instructed to move the picture to the location they thought to be correct within 8 s. After 8 s, feedback was provided as the picture moved to its correct location and its sound played

again. Participants completed several rounds of training up to a criterion threshold through repeated testing with feedback. The testing session was similar to the training session, with the difference of having only one round with all stimuli and no feedback was provided.

The sounds were split into two sets having equal mean valence and arousal for neutral and negative stimuli. Once the participant had entered SWS for at least 1 min, 6 sounds (3 neutral and 3 negative) of a set were played, with 2 s gaps between them. Another 6 sounds would be played after another 2 s, unless there was a sleep arousal or disturbance. In case of an arousal during a cueing period or a sleep stage change, the sound was stopped and was resumed once the participant was back in SWS. Each sound was played 5 times.

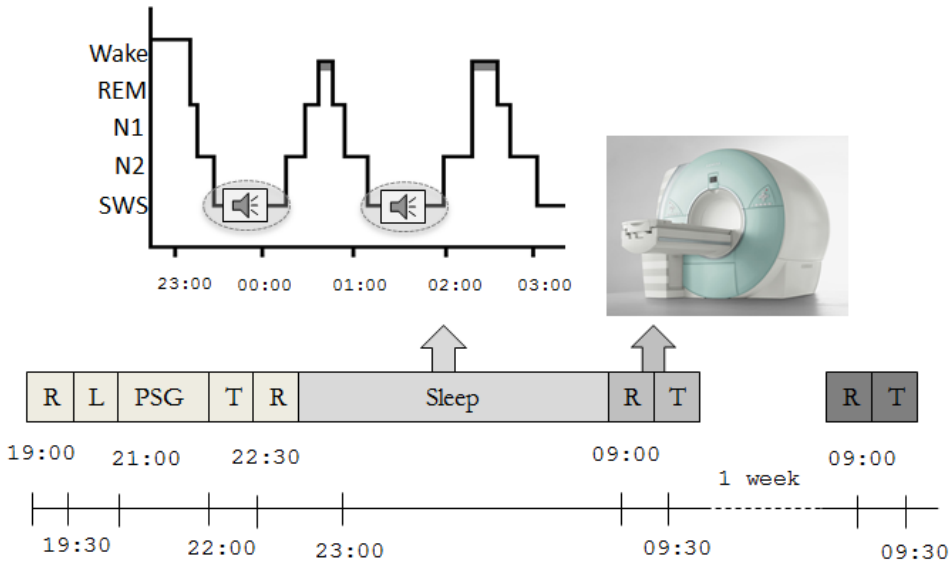

Figure 3-1 Experimental design: R = arousal ratings, L = memory learning and training, T = memory testing

Upon arrival, participants gave written informed consent and answered some questionnaires. After at least one training round, to get acquainted with how to use the keys to move the cursor, they performed the first session of the arousal rating task (t = 0 h). Then, they had the learning session of the memory task, at least one training round to learn how to move the picture within the grid, and then the training sessions. Once the training session was finished, the electrodes for the overnight polysomnography were placed. Following that, participants performed the memory testing session and the arousal rating task (t = 3 h). Then, participants were instructed to go to sleep while brown noise was delivered through a pair of speakers. The next morning, participants were

woken up after approximately 7 h of sleep, the PSG electrodes were removed, and participants were able to take a shower and have a light breakfast before the MRI procedure. During scanning, after a short structural scan and a training task to refresh their memory on how to use the four keys, they performed first the arousal rating task and then the memory task (t = 12 h). Each task was split into two equal length sessions. After scanning, participants were asked to indicate whether they considered each picture-sound pair to be negative or neutral. Finally, it was revealed to them that some sounds were played while they were sleeping and they were asked to indicate for each sound whether they believed that it was presented or not during their sleep, without receiving any feedback. After approximately one week, participants were asked to return to the sleep lab in the morning for a follow-up session. At this session, participants rated again the picture-sound pairs for arousal and performed the memory test (t = 1 week).

3.2.4 PSG Data Acquisition and Analysis

Polysomnography (PSG) activity was recorded through an Embla N7000 PSG amplifier using the RemLogic software. Silver-silver chloride electrodes were attached to the scalp and face of the participants according to the international 10-20 rule. The scalp electrodes were placed on the standardised locations F3, F4, C3, C4, O1, and O2, and each was referenced to the contralateral mastoid. The connection impedance was less than 5 KOhms and the sample rate was 200 Hz. All PSG recordings were scored manually on RemLogic by two experimenters, who were blind on whether and when sounds were cued, according to "The AASM Manual for the Scoring of Sleep and Associated Events".

3.2.5 Statistical Analysis

Seven participants were excluded from analysis due to technical errors during the TMR procedure at sleep.

The change (Δ) between different time points for arousal ratings was estimated by subtracting the mean rating of the earlier time point from that of the later time point. The overnight error Δ percentage for spatial memory accuracy was calculated for each item according to the function below. As we expected different performance between the negative and neutral stimuli, the normalization was done according to the respective emotional category of the stimulus.

$$error\ \Delta\ \% = \frac{(PostSleep\ Error\ -\ PreSleep\ Error)}{Mean\ PreSleep\ Error_{Negative\ or\ Neutral}} * 100$$

All statistical analyses of the behavioural data were done in SPSS © Version 22 (IBM Corporation 2015). Repeated measures ANOVAs were conducted to assess any cueing or emotion effects in performance on the arousal and memory tasks. The within-subjects factors were emotion (negative or neutral), cueing (cued or uncued), and where applicable time (0 h, 3 h, 12 h, 1 week). Post-hoc tests were Bonferroni corrected. When Shapiro-Wilks tests indicated a non-normal distribution, Wilcoxon signed rank tests were used for post-hoc analysis. To determine any effects of SWS and REM, we performed ANCOVAs, corresponding to the previous ANOVAs, having as covariates the mean-centred duration of SWS and REM. Any significant main effects or interactions were further assessed using two-tailed Pearson's correlation. If Pearson's correlation was not significant, the results from the ANCOVA are not reported below. Forced cueing remembrance was assessed based on the d' values (Lynn & Barrett, 2014; Macmillan & Creelman, 1990). All analyses were conducted at a 0.05 significance level. Error bars and values in brackets refer to standard error of the mean (SEM) unless otherwise specified.

3.2.6 fMRI Data Acquisition and Analysis

Imaging data were acquired on a 3T Philips Achieva scanner using an eight-element SENSE head coil with a SENSE factor of 2.5. We used a dual-echo sequence with a short_TE and long_TE of 12 and 35 ms, respectively, and a TR of 2800 ms. The short_TE was optimal for reduced signal loss and sufficient contrast sensitivity and the long_TE provided whole brain sensitivity (Poser, Versluis, Hoogduin, & Norris, 2006). The functional parameters were: 31 slices, 80 x 80 acquisition matrix, 240 x 124 x 240 mm FOV, in-plane resolution 3 x 3 mm^2, and slice thickness 4 mm (no gap) and an anterior-posterior (A-P) phase encoding direction. For the arousal task, 200 volumes were collected per scanning session and 244 for the memory task.

A high-resolution T1-weighted structural scan was also acquired using a 3D MP-RAGE pulse sequence, with in-plane resolution of 0.94 mm, slice thickness 0.9 mm, TR = 8 ms, TE = 3.9 ms, and 188 slices. The high-resolution T1-weighted structural image served for co-registration purposes.

Each task was split into two functional scans. Each scan had 5 null events, 12 s long for the arousal sessions and 15 s for the memory sessions. Before each picture, a black screen with a fixation cross in its centre was presented for a mean jittered time of 1 s.

Functional volumes were pre-processed and analysed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/; Wellcome Department of Imaging Neuroscience, London, UK).

First, we merged the data from both echoes by extracting an image volume for each echo and subsequently averaging the short and long echo for each TR. The resulting images were realigned to the first volume and the structural was co-registered to the mean functional image. The structural image was then segmented and the estimated transformations to MNI space were applied to all functional scans. All functional images were smoothed using a full-width half maximum Gaussian kernel of 8 8 8 mm and re-sampled to 3 x 3 x 4 mm using 4^{th}-degree interpolation. The Artifact Detection Toolbox (ART, http://www.nitrc.org/projects/artifact_detect/) was used to estimate per-volume movement outliers using > 3 SD from the mean signal intensity and volume-to-volume movement of 1.5mm. We excluded a scan if >15% of the number of volumes were classified as outliers. The remaining scans were scrubbed, as a separate regressor for each outlying volume was included in the first-level design matrix, concatenating the resultant time-series (Power 2012). Three participants were excluded due to missing data and another two from the memory task due to many outliers.

The first-level (participant level) models of the individual task conditions were fit using SPM12. The jittered time between blocks, as well as the null events, served as the baseline condition modelled implicitly in the block design. High-pass filtering was implemented in the design matrix using a cut-off period of 128 s to remove slow drifts from the time series. Movement parameters derived from the realignment of the functional volumes were also included as covariates of no interest. Each condition was modelled using a double-gamma haemodynamic response function with time and dispersion derivatives. For each task, we modelled the following blocks: negative cued viewing, neutral cued viewing, negative uncued viewing, neutral uncued viewing, negative cued responding, neutral cued responding, negative uncued responding, and neutral

uncued responding. We also modelled all key-presses as events of no interest. We also re-ran the first-level analysis with a first-level modulator for each of the viewing and responding blocks; the arousal ratings at 12 h for the arousal task, and the spatial accuracy error at 12 h for the memory task.

For the second-level models, which combine across participants, we used the multivariate and repeated measures (MRM) toolbox (McFarquhar et al., 2016) to specify a repeated measures model with within-subjects factors of cueing and emotion. This technique accounts for the error structure across the entire experiment rather than from a single condition or subtraction, as done by SPM. Therefore, MRM should allow for a more valid inference. The analysis was voxel-by-voxel, applying a multivariate general linear model. For the arousal task, we used the first-level contrasts from the viewing blocks and for the memory task from the responding blocks, to build the repeated-measure contrasts of main effects and interactions. Thresholding was at voxel level using 5000 permutations to generate p-values that were corrected using a false discovery rate (FDR) procedure. The multivariate test statistic used was Wilk's lambda. Small volume correction with five thousand permutations, at $p_{FDR} < 0.05$, extent 5 voxels. Further analyses were run for each task using as covariates the mean centered duration of SWS and REM or of stage 2 alone. We did not use all three stages as covariates in the same model to avoid collinearity issues (Mumford, Poline, & Poldrack, 2015), as SWS and stage 2 were correlated. Since analyses with stage 2 did not yield any significant results, they are not mentioned in the results section.

For both tasks, we conducted 2nd level inference restricted by a number of *a priori* defined regions of interest (ROI) using small volume correction. Both masks were created using the integrated AAL atlas (Tzourio-Mazoyer 2002) of the Wake Forest University PickAtlas toolbox (http://fmri.wfubmc.edu/software/PickAtlas). For the arousal task, ROI consisted of bilateral orbitofrontal cortex, amygdala, and insula. For the memory task, ROI consisted of the bilateral orbitofrontal cortex, supplementary motor areas, insula, hippocampus, parahippocampus, amygdala, cuneus, precuneus, thalamus, and caudate. These regions were selected from previous studies that have reported activations due to sleep, memory consolidation or emotional reactivity.

3.3 Results

3.3.1 Sleep and Questionnaires

All participants had mild to zero DASS scores and moderate to intermediate chronotypes. Participants reported worse sleep quality and more awakenings during sleep at the sleep lab. Duration of all sleep stages, wake after sleep onset (WASO), and total sleep time (TST) are displayed in Table 3-1. Duration of N2 was negatively correlated with the duration of SWS, r (23) = -0.637, p = 0.001, therefore subsequent ANCOVAs were conducted separately to prevent multi-collinearity errors. To assess whether positive or negative mood varied across the experiment, we conducted two ANOVAs on the respective PANAS scores with time as the between-subjects factor. Results indicated a main effect of time for the positive affect scores, F (3, 19) = 6.032, p = 0.005, η_p^2 = 0.488. According to post-hoc tests, positive affect scores decreased significantly 0 h to 12 h, p = 0.014. There was no main effect of time on the negative affect scores. To assess alertness levels at different stages of the experiment, we ran an ANOVA on KSS scores with time as a factor. We found a main effect of time on KSS scores, F (1, 22) = 9.596, p = 0.005, η_p^2 = 0.304. Post-hoc tests showed lower alertness at 3 h compared to 12 h, p = 0.010, and to 1 week, p < 0.001.

Table 3-1 Total time spent in sleep stages

Sleep stage	N1	N2	SWS	REM	WASO	TST
Mean duration (min) [±SD]	21.42 [9.10]	247.38 [38.01]	100.08 [28.61]	86.16 [22.28]	23.09 [23.39]	478.06 [35.59]

WASO: wake after sleep onset, TST: total sleep time

3.3.2 Behavioural Arousal

The mean arousal ratings across different time points are displayed in Figure 3-2. To assess the effect of TMR during SWS on how arousal ratings changed between different time-points, we used a series of repeated measures ANOVAs. The dependent variable was the change of arousal ratings between two time-points and cueing and emotion were the within-subjects factors. No significant main effects or interactions were observed on the change of arousal between any two time-points.

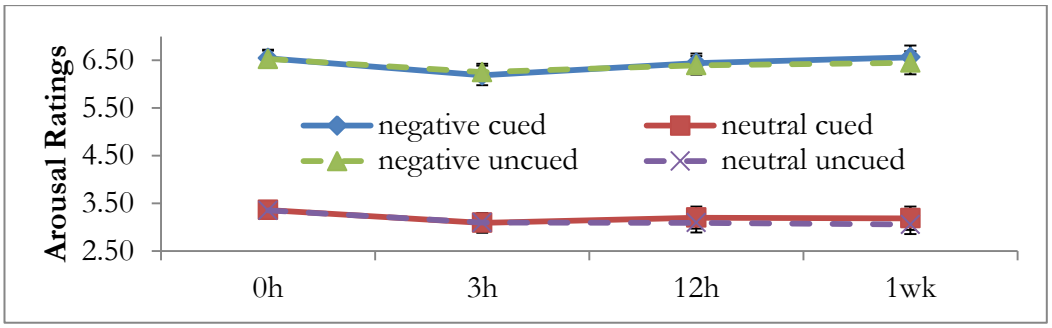

Figure 3-2 Arousal ratings across different time points

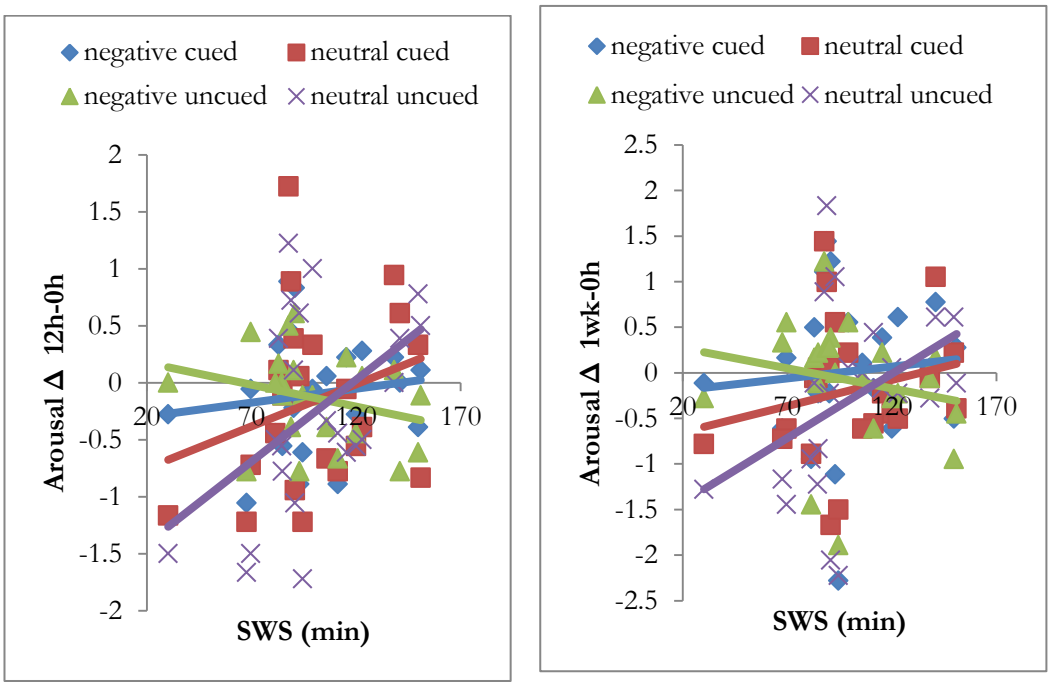

Figure 3-3 Correlation between SWS duration and arousal changes from 0 h to 12 h (left) and 0 h to 1 week (right)

To test whether the duration of the sleep stages had any effect on TMR related arousal changes, we repeated the above ANOVAs as ANCOVAs with the duration of SWS and REM as covariates. In the ANCOVA on the arousal change from 0 h to 12 h, we observed an emotion x SWS interaction, F (1, 20) = 4.515, p = 0.046, η_p^2 = 0.184. Increased duration of SWS was associated with neutral items becoming more arousing, whereas it did not have an effect on negative items. We also found a cueing x emotion x SWS interaction, F (1, 21) = 8.821, p = 0.008, η_p^2 = 0.306 (Figure 3-3 left). This was driven by the fact that longer SWS duration predicted a slight decrease in arousal for the negative uncued items and a slight increase in arousal for the negative cued ones. Conversely, SWS duration correlated with an increase in arousal ratings for all neu-

tral items, but more steeply for the uncued ones. A similar pattern was observed in the ANOVA on arousal changes from 0 h to 1 week with a cueing x emotion x SWS interaction, F (1, 20) = 6.002, p = 0.024, η_p^2 = 0.231 (Figure 3-3 right).

3.3.1 Behavioural Memory

To assess the effect of emotion on memory learning and memory performance, we used a paired-samples t-test to compare negative and neutral items on the number of training rounds and an ANOVA on accuracy errors with time, cueing and emotion as within-subjects factors. Neutral items required less rounds of training than the negative items, t (22) = 4.160; p < 0.001. The ANOVA on accuracy errors indicated a main effect of time, F (2, 22) = 33.595, p < 0.001, η_p^2 = 0.762, and a main effect of emotion, F (1, 22) = 20.163, p < 0.001, η_p^2 = 0.478. Participants remembered better the location of neutral items than the negative items (Figure 3-4). Post-hoc tests showed that accuracy deteriorated across time, with significant differences between all of the time points being p <0.001.

Next, we conducted repeated measures ANOVAs and ANCOVAs with cueing and emotion as the within-subjects factors and the duration of the sleep stages as covariates, to assess the effect of TMR during SWS on % changes between different time-points in memory accuracy. However, we observed no significant main effects or interactions.

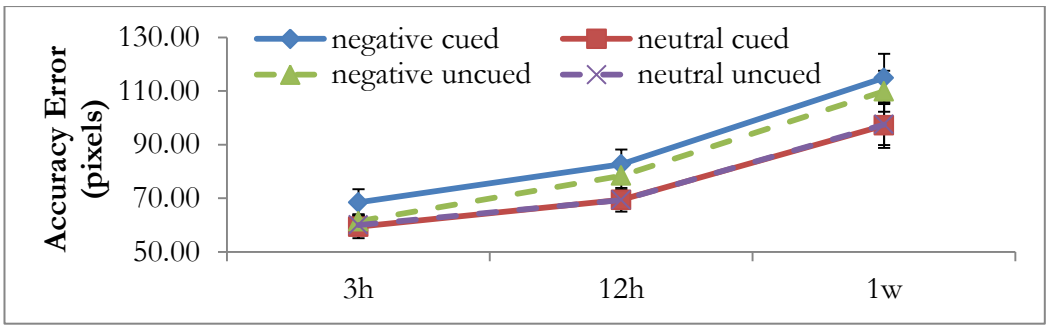

Figure 3-4 Location accuracy error across time

3.3.2 TMR Awareness and Valence Ratings

All participants performed at chance when asked to recognize which sounds were cued, mean d' = -0.03 [±0.07], with no difference between negative and neutral items. Regarding the forced choice of valence, all participants catego-

rized correctly the stimuli for their valence, 91.06% [±1.44]. A repeated measures ANOVA with cueing and emotion as factors, showed a main effect of emotion, F (1, 22) = 4.323, p = 0.049, η_p^2 = 0.165, with the neutral items having a higher recognition rate, 94.32% [±1.29], than the negative ones, 87.80% [±2.72].

3.3.3 Imaging Arousal Task

Firstly, we used a simple repeated-measures model with within-subjects factors cueing and emotion. We observed a cueing x emotion interaction in clusters including bilateral orbitofrontal areas and right insula (Table 3-2). Interestingly, as shown in (Figure 3-5) as an example, the BOLD signal of the above clusters was higher in the negative uncued items than in the negative cued. Conversely, for the neutral cued items there was a stronger signal than for the neutral uncued items.

Table 3-2 Coordinates of local maxima for brain regions where a main effect or interaction was found in the arousal task, design with no parametric modulator nor covariates

Contrast	Number of Voxels	Region	*F*-value	*p*	Coordinates X	Y	Z
Cueing x Emotion	29	Frontal Inf Orb R	22.89	0.044	36	29	-18
		Frontal Inf Orb R	14.65	0.044	48	32	-14
	11	Frontal Inf Orb L	18.19	0.044	-33	26	-18
	23	Frontal Inf Orb L	20.97	0.044	-51	23	-6
		Frontal Inf Orb L	16.4	0.044	-39	23	-10
	22	Frontal Inf Orb R	19.63	0.044	45	23	-6
		Insula R	17.04	0.044	33	20	-6

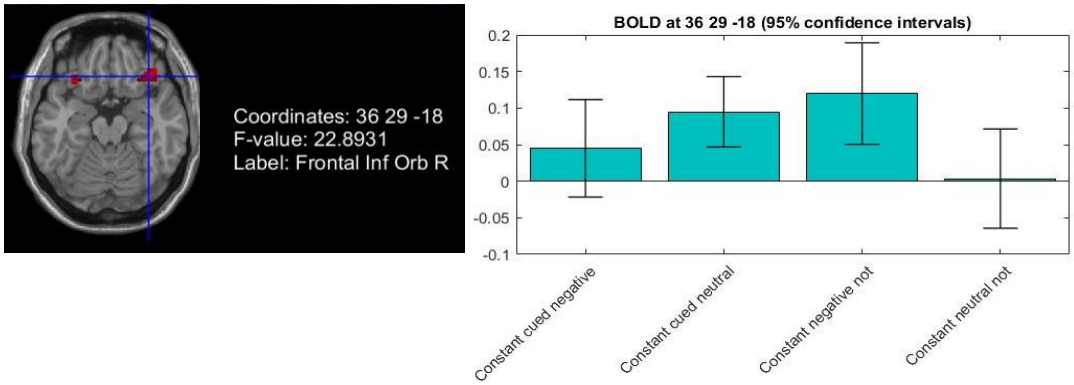

Figure 3-5 Cueing x emotion interaction in right inferior orbitofrontal lobe for the arousal task based on a design with no parametric modulator nor covariates

To investigate whether the duration of any of the sleep stages predicts the neural correlates, we added SWS and REM as second-level covariates. In this

design, we observed lower *p* values in the cueing x emotion interaction results. Furthermore, we also found significant results in the cueing x SWS interaction. The clusters where we observed a cueing x SWS interaction include areas of the bilateral insula and right orbitofrontal cortex (Table 3-3). As SWS duration increases, the BOLD signal becomes stronger for the uncued items whereas it remains unchanged for the cued items, e.g. (Figure 3-6).

Table 3-3 Coordinates of local maxima for brain regions where a main effect or interaction was found in the arousal task, design with no parametric modulators, SWS and REM as covariates

Contrast	Number of Voxels	Region	*F*-value	*p*	Coordinates X	Y	Z
Cueing x Emotion	78	Frontal Inf Orb L	29.108	0.029	-30	23	-18
		Frontal Inf Orb L	23.139	0.029	-51	20	-6
		Frontal Inf Orb L	17.946	0.030	-39	23	-10
	79	Frontal Inf Orb R	27.335	0.029	45	23	-6
		Frontal Inf Orb R	24.248	0.029	33	29	-22
		Insula R	16.341	0.032	33	20	-6
		Frontal Inf Orb R	13.928	0.038	48	32	-14
	10	Frontal Mid Orb R	18.750	0.029	27	47	-14
		Frontal Sup Orb R	13.030	0.036	21	53	-10
Cueing x SWS	5	R	26.956	0.045	18	53	-2
		Frontal Sup Orb R	22.275	0.045	15	56	-6
	8	Insula R	22.064	0.045	36	26	6
	11	Insula L	27.206	0.045	-33	26	10

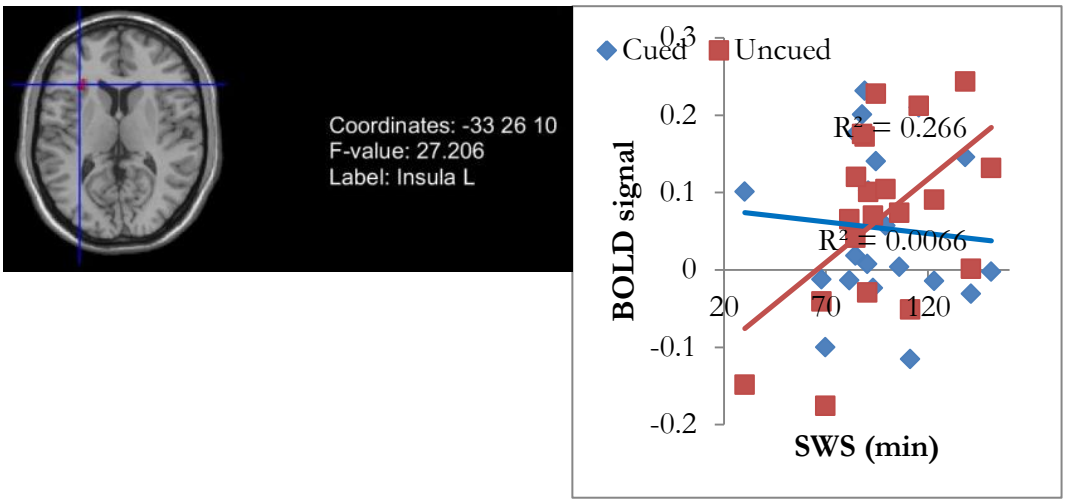

Figure 3-6 Cueing x SWS interaction in left insula for the arousal task based on a design with no parametric modulators, SWS and REM as covariates

Next, we used the arousal ratings at 12 h as a first-level parametric modulator to investigate whether the behavioural measures predict the observed neural

correlates, but did not find any results. However, when we added SWS and REM as second-level covariates in this design model, we found a main effect of SWS in the bilateral insula, Heschl's gyri, and left orbitofrontal areas (Table 3-4). There is a trend for a positive correlation between the BOLD signal and the arousal ratings, as the BOLD signal increases as participants give higher ratings, e.g. Figure 3-7. This relationship becomes more positive the more SWS one gets.

Table 3-4 Coordinates of local maxima for brain regions where a main effect or interaction was found in the arousal task, design with arousal ratings at 12 h as parametric modulator, SWS and REM as covariates

Contrasts	Number of Voxels	Region	*F*-value	*p*	Coordinates		
					X	Y	Z
SWS	284	Insula L	43.694	0.013	-45	5	6
		Insula L	30.065	0.013	-45	11	2
		Insula L	29.182	0.013	-36	26	6
		Insula L	27.366	0.015	-36	-7	18
		L	26.585	0.013	-30	14	-6
		Insula L	26.078	0.013	-30	29	6
		Insula L	24.486	0.015	-36	2	18
		Heschl L	22.755	0.015	-33	-25	14
		L	20.778	0.016	-51	17	-6
		Insula L	18.578	0.016	-39	8	-6
		Insula L	17.896	0.016	-39	20	-2
		Insula L	15.53	0.017	-36	-4	-10
		L	13.767	0.017	-36	-19	-2
		Frontal Inf Orb L	10.475	0.042	-39	35	-6
	173	Heschl R	35.029	0.013	33	-25	14
		Insula R	27.743	0.013	33	14	6
		Insula R	25.046	0.015	39	-19	2
	6	Frontal Inf Orb L	12.685	0.018	-24	35	-10
	6	Insula R	13.981	0.019	36	29	6

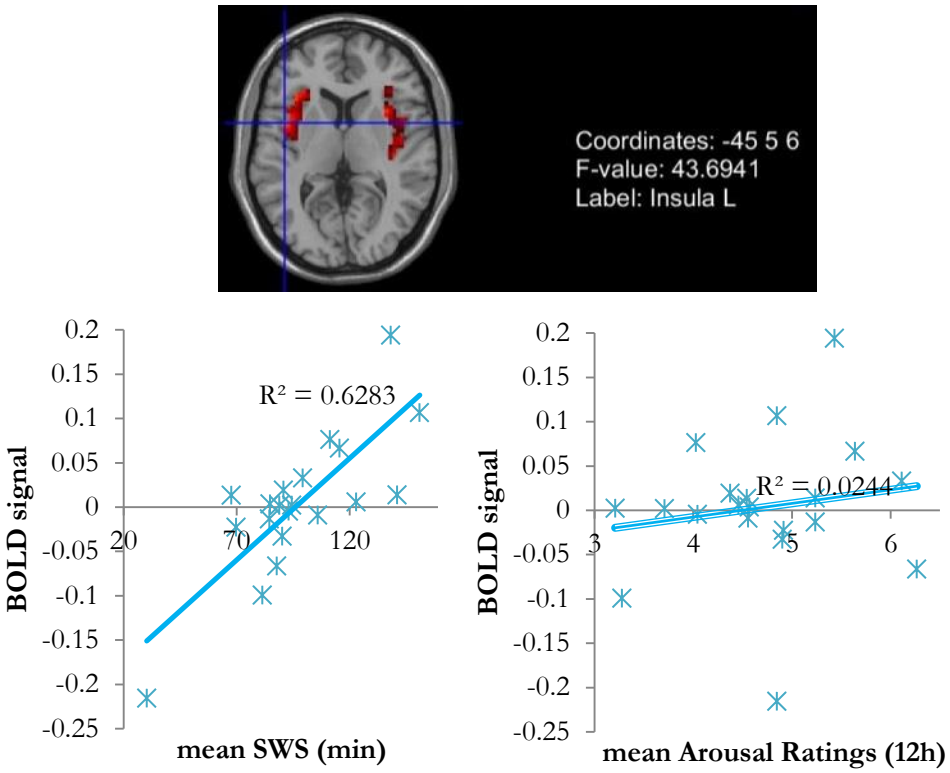

Figure 3-7 SWS main effect in left insula based on a design with arousal ratings at 12 h as parametric modulator, SWS and REM as covariates

3.3.4 Imaging Memory Task

As in the arousal task, we ran analyses on the memory task data without a first-level parametric modulator, but no main effects or interactions were observed. Similarly, when we used only sleep stages as first-level covariates there were no results. However, when accuracy error, as distance from correct location, at 12 h was used as first-level parametric modulator and SWS and REM as second-level covariates, there was a REM x emotion x cueing interaction at bilateral supplementary motor area, precuneus, thalamus, cuneus, insula, inferior orbito-frontal cortex, right temporal pole and parahippocampal areas, and left para-central lobule (Table 3-5). Plotting the BOLD values at each peak-voxel against the accuracy error values, showed a trend of decreasing BOLD signal with increasing error rates, e.g. Figure 3-8. As REM duration increases, the relationship between memory performance and the BOLD signal changes depending on whether the items were negative or cued. For the negative cued and the neutral uncued items, the relationship with REM is positive, such that the more REM one gets the more positive the relationship between the performance

error and the signal becomes in the areas above. For the negative uncued and neutral cued items, the opposite is true.

Table 3-5 Coordinates of local maxima for brain regions where a main effect or interaction was found in the memory task, design with distance from correct location at 12 h as parametric modulator, SWS and REM as covariates

Contrast	Number of Voxels	Region	*F*-value	*p*	Coordinates		
					X	Y	Z
Cueing x Emotion x REM	12	Temporal Pole Mid R	28.41	0.008	27	5	-34
		ParaHippocampal R	12.829	0.029	27	11	-30
	6	Temporal Pole Sup R	12.521	0.03	30	20	-26
		Frontal Inf Orb R	12.22	0.034	33	23	-22
	64	L	43.982	0.008	-36	-7	-10
		Insula L	18.059	0.019	-36	-7	6
		Insula L	17.391	0.013	-33	-19	6
		Insula L	13.284	0.029	-36	-19	14
	111	Insula L	40.506	0.008	-30	20	6
		Insula L	19.924	0.015	-42	14	-6
	80	Insula R	29.231	0.008	36	17	6
		Insula R	28.551	0.008	42	17	2
		Insula R	10.865	0.041	36	17	-10
	10	Frontal Inf Orb L	15.108	0.019	-39	35	-6
	50	L	44.534	0.008	-18	-10	-2
		Thalamus L	40.629	0.011	-12	-7	6
		L	11.866	0.033	-6	-22	-2
	14	Thalamus R	22.405	0.008	9	-7	2
		R	18.422	0.016	6	-22	-2
	6	Cuneus L	12.562	0.032	-15	-79	38
		Cuneus L	12.553	0.03	-18	-73	34
	29	Cuneus R	15.522	0.016	18	-70	38
	249	Precuneus L	53.214	0.008	-3	-43	58
		Precuneus L	34.262	0.008	-9	-49	66
		Precuneus R	24.77	0.008	9	-55	62
		Precuneus L	22.65	0.011	-15	-58	62
		Precuneus R	22.467	0.011	3	-70	58
		Precuneus R	18.408	0.018	3	-46	46
		Precuneus R	17.626	0.018	12	-64	58
	477	Supp Motor Area R	55.148	0.008	3	-10	66
		Supp Motor Area R	51.092	0.008	6	-13	70
		Supp Motor Area L	45.206	0.008	-9	2	54
		Paracentral Lobule L	40.529	0.008	-3	-13	70
		Supp Motor Area R	29.867	0.008	3	11	66
		Supp Motor Area L	26.512	0.008	-9	11	46
		Supp Motor Area L	25.064	0.008	-9	-1	70
		Supp Motor Area R	23.497	0.011	12	5	62
		Supp Motor Area L	20.321	0.011	-6	17	54
		Supp Motor Area L	18.085	0.015	0	20	58
		Supp Motor Area R	15.007	0.016	12	8	50
		Supp Motor Area L	14.257	0.018	-9	17	62

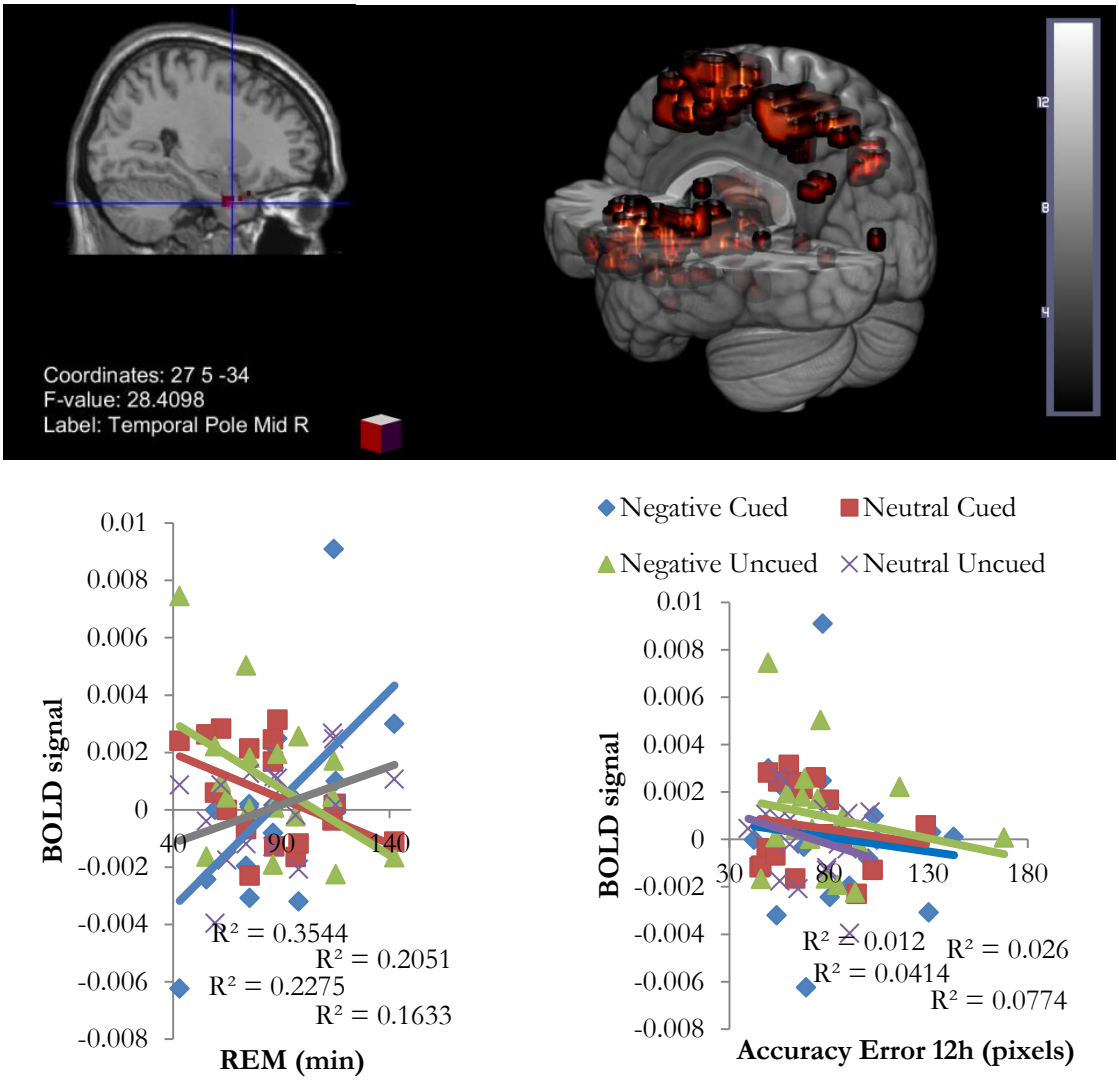

Figure 3-8 Cueing x emotion x REM interaction in right temporal pole based on a design with distance from correct location at 12 h as parametric modulator, SWS and REM as covariates. Top left: Local maxima at the right temporal pole. Top right: All the modulated brain areas

3.4 Discussion

This study provides evidence that TMR during SWS affects the neural correlates of subjective arousal ratings and associative memory consolidation of negative and neutral stimuli in different ways. Our results suggest that duration of SWS mediates TMR effects both at the behavioural level and on the neural correlates of subjective arousal. On the other hand, REM appears to mediate TMR effects on the neural correlates of emotional associative memory consolidation.

3.4.1 Arousal Processing

In the behavioural level, we did not observe any significant results without using SWS duration as a covariate. However, we found two significant interactions on the change of arousal ratings from 0 h (initial exposure) to 12 h. The first was between SWS duration and emotion, showing that longer SWS predicted an increase in the arousal of neutral items and had no effect on the negative items. The second interaction was between SWS duration, emotion and cueing, suggesting that the previous finding is more complicated. Here, a longer duration of SWS predicted an increase of arousal for the neutral items, especially for the uncued ones. A much weaker trend towards the same direction was observed for the negative cued items, whereas the negative uncued items had a tendency to habituate with longer SWS. Interestingly, we found the same interaction with SWS in arousal changes from 0 h to 1week, suggesting a long-term effect of TMR and SWS duration on subjective arousal processing. It is unclear why there were no effects on the arousal changes from 3 h to any of the post-sleep sessions. One explanation could be that the training session introduced temporary noise in the data.

Our results suggest that emotional arousal across sleep is regulated by SWS. We did not find any evidence supporting a role of REM as previous studies have in favour of arousal habituation (Gujar et al., 2011), maintenance (Baran et al., 2012; Groch et al., 2013), or enhancement (Werner et al., 2015). Yet, the role of SWS and TMR on arousal processing remains unclear and may depend on whether the stimuli are negative or neutral. Based on our results, it could be argued that TMR during SWS acts very differently on negative and neutral items as it inhibits emotional habituation in the former, and enhances it in the latter. These findings are out of keeping with both of our previous studies where we found that TMR in SWS enhanced arousal habituation of the negative items (Tsimpanouli, Elliott, et al., 2017) or that it had no effect on arousal ratings (Hutchison et al., under review).

Differences between neutral and negative stimuli and the effects of TMR were also observed on a neural level. Using a strict correction method with permutations, we found that in bilateral inferior orbitofrontal cortex and right insula, activity was higher for negative uncued items than negative cued ones. The opposite pattern was observed for the neutral items, with cued items having a high activation whereas activation for uncued items appears to be non-existent.

Insular activation has been associated with cognitively demanding emotional tasks, autonomic regulation, and interoceptive processing of emotions (Catani, Dell'Acqua, & de Schotten, 2013; Pais-Vieira, Wing, & Cabeza, 2016; Phan, Wager, Taylor, & Liberzon, 2002). Similarly, the orbitofrontal cortex has been implicated in the evaluation of emotional context (Faivre, Charron, Roux, Lehéricy, & Kouider, 2012) and the control of emotional behaviour (Catani et al., 2013).

SWS appears to modulate further TMR in bilateral insula and right orbitofrontal cortex. SWS correlated with increased activity for the uncued items in these areas but did not have any effect on the cued items. Additional results show that overall when stimuli were rated as more arousing SWS duration correlated with higher activation in bilateral insula, Heschl's gyri, and left orbitofrontal areas. As mentioned earlier both orbitofrontal cortex and insula are necessary for emotional regulation. Furthermore, the auditory cortex has been reported to project to the orbitofrontal cortex and limbic areas (Koelsch, 2014). The observed SWS effects may be mediated by sleep spindles, as sleep spindles during non-REM sleep modulate activity in the insula and orbitofrontal cortex, among other areas (Schabus et al., 2007). Another study reports that activation in the orbitofrontal cortex and insula is negatively correlated with slow wave activity (Dang-Vu et al., 2010).

Against our expectations, we did not find any main effects of emotion or cueing alone on brain activity. We also did not find any significant results on amygdalar activation. Our lack of results may be due to methodological limitations. Amygdala has been implicated in the processing of emotional salience as it is active both at encoding of emotional stimuli (Dolcos et al., 2004) and during REM (Maquet et al., 1996). Reportedly, REM mediates the decrease of amygdala reactivity (van Der Helm et al., 2011), and after a year, activity in amygdala does not differ between emotional and neutral stimuli (Dolcos et al., 2005). Therefore, the observed results may be mediated by amygdalar activity, as in a study with musical stimuli, the amygdala was found to drive the orbitofrontal cortex and the auditory cortex during the processing of emotional stimuli (Omigie et al., 2015).

Our imaging results support our behavioural findings that SWS duration and TMR have different effects on processing of arousal across sleep. These ef-

fects differed between negative and neutral stimuli when adjusting for sleep stage durations. This difference could stem from differences at encoding, as negative stimuli were perceived to be more arousing than the neutral ones. Furthermore, prior studies show that the prefrontal cortex and limbic areas are more responsive to negative stimuli during initial exposure (Dolcos et al., 2004). Our results suggest that TMR during SWS makes these areas more responsive to neutral items and reduces their activation for the negative ones. Further studies are needed to elucidate the underlying mechanisms.

3.4.2 Consolidation of Emotional Associative Memory

Our behavioural results do not support an enhancing role of emotion in the consolidation of associative memory. Neutral items, compared to negative items, required fewer training rounds and their location was better remembered. This result is not surprising, previous studies have also found worse associative memory for negative stimuli (Bisby & Burgess, 2014; Bisby et al., 2016; Maddock & Frein, 2009; Mather et al., 2006; Mitchell et al., 2006; Phelps & Sharot, 2008; Tsimpanouli, Elliott, et al., 2017). A study by (Bisby et al., 2016) provided further evidence that negative emotions elicit a down-regulation of the hippocampus causing weakened associative representations of the negative stimuli. Yet, they still found a greater amygdalar response during successful retrieval of negative items.

Unexpectedly, we did not find any effects of TMR during SWS on associative memory consolidation. Previous studies using the same experimental task have consistently shown a TMR mediated memory enhancement, (Creery et al., 2015; Oudiette et al., 2013; Rudoy et al., 2009; Tsimpanouli, Elliott, et al., 2017). The arousal rating tasks after the pre-sleep testing session and before the post-sleep testing sessions may have caused an interference in the associative memory consolidation mechanisms. The absence of TMR effects at 12 h could also be due to the memory-task taking place in a different environment, the MRI scanner. Another study using the same task as the current study, with neutral stimuli, (van Dongen et al., 2012) also did not find any behavioural cueing effects in an fMRI environment. Another factor could be the altered nature of the task as it included procedural memory components. Even though participants had to remember the location of the stimuli on the screen, it is possible they also learned implicitly the sequence of keys they had to press in order to move the stimulus to its proper location. This may have biased our paradigm

towards a procedural memory consolidation, which has been proposed to be mediated by REM (Fischer et al., 2002; Marshall & Born, 2007). Nevertheless, TMR during SWS of procedural memories, such as learning a motor sequence, has enhanced their consolidation and improved both explicit knowledge of the sequence and the associated procedural skills (Antony et al., 2012; Cousins et al., 2014, 2016). Therefore, TMR during SWS might have had an effect on the procedural components of our memory task, but we were unable to detect them on the behavioural level.

Two previous studies on TMR of emotional memories during SWS have shown that TMR enhanced selectively consolidation of the emotional stimuli (Cairney, Durrant, Hulleman, et al., 2014; Lehmann et al., 2016). A study by (Cairney, Durrant, Hulleman, et al., 2014) reported reduced reaction times for negative cued items. A study by (Lehmann et al., 2016) reported a memory enhancement only for the emotional items. Their results also suggest that emotional and neutral memories are processed differently during sleep. Cueing during SWS resulted to an increase of theta and spindle oscillations, which was stronger for the emotional items. However, cueing during REM increased theta activity for the neutral items. Finally, in our previous study we found that TMR during SWS stabilized memory accuracy for both negative and neutral items (Tsimpanouli, Elliott, et al., 2017).

In the imaging data, we did not find any main effects of emotion. We only found differences on neural correlates when using accuracy error at 12 h as a 1st parametric level modulator and duration of sleep stages as covariates. In fact, we observed an interaction of REM duration with cueing and emotion on the bilateral supplementary motor area, precuneus, thalamus, cuneus, insula, inferior orbitofrontal cortex, right temporal pole and parahippocampal areas, and left paracentral lobule. Most of these areas have an active role in emotional and memory networks starting from encoding up to long-term retrieval (Kober et al., 2008; Koelsch, Fritz, Cramon, Müller, & Friederici, 2006; Kumfor, Irish, Hodges, & Piguet, 2013; Mickley Steinmetz et al., 2010; Mickley Steinmetz & Kensinger, 2009; Murty et al., 2010; Payne & Kensinger, 2011; Phan et al., 2002; Sterpenich et al., 2007, 2009). Strangely, we did not observe any effects on the activation of the hippocampus, even though it has been reported to regulate associative memory representations and mediate memory enhancement by TMR in SWS (Fuentemilla et al., 2013; Rasch et al., 2007). We also did

not observe any direct effects on the activation of the amygdala, similarly to the arousal task findings. However, the observed effect on the supplementary motor areas, which are involved in complex cognitive motor programming and preparation of voluntary action plans (Koelsch, 2014), may be modulated through the amygdala in response to emotional stimuli, as the two areas share direct anatomical connections (Grèzes, Valabrègue, Gholipour, & Chevallier, 2014). Another explanation for the activation in the supplementary motor area could be the reflection of TMR and REM modulating procedural memory components (Cousins et al., 2016).

Overall, we observed a trend of weakened BOLD signal in the above areas as memory accuracy dropped. This trend was positively correlated with REM duration for the negative cued and neutral uncued items and negatively correlated for the negative uncued and neutral cued items. As expected, the neural correlates of negative and neutral stimuli appear to differ. It is not possible to conclude whether these differences are a result of differences at encoding of the stimuli or if TMR or REM further modulated activation in these areas differently. However, the different effects might not be due to the different emotional valence per se but because memory accuracy was better for the neutral items. Evidence suggests that the role of REM in memory consolidation might depend on whether memories have already been consolidated or not (Poe, 2017; Poe, Nitz, McNaughton, & Barnes, 2000).

Furthermore, we provide evidence supporting the sequential hypothesis (Giuditta, 2014) showing that SWS and REM may have different roles yet act synergistically on the regulation of the brain networks supporting associative memory consolidation. Additional evidence for this hypothesis comes from a study on emotional memory showing that SWS and REM served different roles (Cairney, Durrant, Power, et al., 2014). SWS predicted superior memory for remote negative images and a reduction in right hippocampal responses during the recollection of these items. REM predicted an increase in hippocampal-neocortical connectivity associated with negative remote memory. In contrast to our findings, (Groch et al., 2015) propose that REM mediates the emotional enhancement of item memory consolidation whereas SWS enhances associative memory independent of valence.

3.4.3 Conclusion

In sum, our results provide evidence that the effects of TMR during SWS on subjective arousal ratings and associative memory consolidation differ depending on their emotional salience. Behaviourally we found that SWS modulates further any cueing effects on subjective arousal. On a neural level, SWS appears to mediate cueing effects for arousal ratings whereas REM for associative memory. In both tasks, activation of the cued negative items is similar to the uncued neutral items, whereas uncued negative are similar to cued neutral. Even though we did not observe any effects on the amygdala or hippocampus, other emotional and memory related regions were modulated.

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4. Identification of Negative Memory Reactivation during Sleep by EEG Classification

Maria-Efstratia Tsimpanouli, Suliman Belal, Alessandra Tafuro, Jules Schneider, Rebecca Elliott, Ian M. Anderson, Penelope A. Lewis

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4.1 Introduction

Evidence that spontaneous reactivation of recently encoded memory traces during sleep promotes memory consolidation comes from a wide number of studies in animals (Ego-Stengel & Wilson, 2010; Ji & Wilson, 2007; Lee & Wilson, 2002; Nádasdy, Hirase, Czurkó, Csicsvari, & Buzsáki, 1999; Ramanathan et al., 2015; Singer & Frank, 2009; Wilson & McNaughton, 1994). Additional evidence comes from studies in humans using a variety of memory tasks, all showing that brain areas that were activated while learning, also had increased activity during post-learning rapid-eye-movement sleep (REM) (Maquet et al., 2000), non-REM (NREM) (Yotsumoto et al., 2009), or just slow-wave sleep (SWS) (Peigneux et al., 2004; Tamaki et al., 2013). Furthermore, increased activity during NREM or SWS correlated with enhanced post-sleep memory. In recent years, researchers managed to enhance post-sleep memory performance in humans by triggering targeted memory reactivation (TMR). TMR was achieved by presenting task-related auditory or olfactory cues during sleep (Antony et al., 2012; Cairney, Durrant, Hulleman, et al., 2014; Cousins et al., 2014, 2016; Oudiette et al., 2013; Rasch et al., 2007; Rudoy et al., 2009; Schönauer et al., 2014; Sterpenich et al., 2014). Some studies showed that TMR alters brain activity by increasing oscillations (Lehmann et al., 2016), EEG amplitude (Rudoy et al., 2009), or activation of memory-related areas (Rasch et al., 2007; van Dongen et al., 2012). In each of these studies, the increase of these measures during the cueing period correlated with post-sleep memory accuracy.

In a recent study, (Belal et al., submitted), we developed an index to quantify TMR during SWS on a trial by trial basis using an EEG linear classifier. Participants trained on a serial reaction time task (SRTT) sequence of finger presses in response to audio-visual cues. The SRTT has been previously used successfully in a number of TMR studies presenting auditory cues during SWS (Antony et al., 2012; Cousins et al., 2014, 2016), NREM (Schönauer et al., 2014) or olfactory cues in late stage 2 (N2) (Laventure et al., 2016). To minimise motion artefacts, participants were then re-exposed to the same SRTT audio-visual cues while imagining to move their fingers in response to the cues. Motor imagery can also promote brain plasticity and motor learning, which may be further enhanced by sleep (Di Rienzo et al., 2016). In subsequent sleep, the auditory tones were replayed during NREM to trigger TMR. An EEG clas-

sifier was trained on the wake imagery data and then applied separately on the SWS and N2 data to determine how successfully each tone elicited memory reactivation in each sleep stage. This found that classification was above chance only for tones that were presented during SWS. Furthermore, the classification accuracy correlated positively with better pre-sleep performance and negatively with overnight improvement.

Emotional memories are preferentially consolidated during sleep (Corsi-Cabrera & Poe, 2014; Dolcos et al., 2012; Payne et al., 2008). Results for TMR and emotional memories, however, are less consistent. In one study, TMR during SWS resulted in faster response times for the negative cued items (Cairney, Durrant, Hulleman, et al., 2014). In another study, TMR during NREM improved memory accuracy of cued negative items (Lehmann et al., 2016). In our own study, we found that the TMR during SWS enhanced equally the consolidation of negative and neutral memories, but only the arousal habituation of the negative memories (Tsimpanouli, Elliott, et al., 2017). In a follow-up study (Tsimpanouli, Hutchison, et al., 2017), we were not able to replicate that TMR effect, but we found an interaction effect of TMR, emotional valence, and REM duration on the activation of memory, emotion, and motor areas during the post-sleep memory testing session. The results of the above studies suggest that the effects of TMR on memory consolidation and the associated neural correlates may differ depending on the emotional content of the memories.

In the current study, we used the EEG classifier from (Belal et al., submitted) to investigate whether there is a difference between the triggered reactivation of memory traces of negative and neutral SRTT sequences during SWS. Before sleep, participants performed an SRTT and a motor imagery task with two sequences, one having negative visual cues and the other neutral. During sleep, we replayed the auditory tones of both sequences during NREM. The next morning, participants performed again the imagery task and the SRTT. We trained an EEG classifier for each sequence on the pre-sleep imagery data and applied it to the SWS data. Primarily, we were interested in whether the classification rate would be above chance for both sequences and if so whether it would differ between them. Furthermore, we examined whether the same type of features was selected for the classification of the negative and the neutral sequences. Finally, we looked whether there were any behavioural differences

between the two sequences and if the behavioural performance correlated with the classification rate.

4.2 Materials and Methods

4.2.1 Participants

Participants were nineteen healthy women (mean age = 23.58 years old, SD = ±4.5). Evidence suggests that women and men use different strategies to process emotional information and show differences in which brain areas get activated (Bianchin & Angrilli, 2012). All participants had normal hearing, normal or corrected-to-normal vision, reported a normal sleeping pattern for at least 4 weeks before participating, and abstained from caffeine and alcohol for at least 24 h prior to the experiment. Eighteen participants were right-handed and one was left-handed. No participants reported having a history sleep, motor, neurological, or psychiatric disorder or taking any psychologically active medications. All participants provided written informed consent. This experiment has been approved by the University of Manchester ethics committee.

4.2.2 Experimental Tasks and Design

Upon arrival, at 7 PM, participants were asked to complete the Morningness-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976), a Sleep Diary, the 22-items Ruminative Responses Scale (RRS) (Treynor, Gonzalez, & Nolen-Hoeksema, 2003), and the 21-items version of the Depression Anxiety and Stress Scale (DASS) (Lovibond & Lovibond, 1995). These questionnaires were administered to assess their sleep quality and habits, and their rumination, depression, anxiety and stress levels. Next, participants were fitted for polysomnography (PSG) recording and around 8 PM, they were ready to start the experimental tasks. The experimental design is shown in Figure 4-1. In the evening session, participants performed an SRTT and a motor Imagery (IMG) task with two sequences, one having negative and the other neutral coloured visual cues. Before each task, participants performed a short engagement task to enhance the emotional salience of the stimuli; and completed the Stanford Sleepiness Scale (SSS) (Hoddes et al., 1972), the Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990) and the 20 items Positive and Negative Affect Scale (PANAS) (Watson et al., 1988), to assess their alertness and mood. After the evening experimental tasks, participants were allowed to read in bed prior to sleep. During NREM sleep, tones of both sequences were cued as

many times as possible. The next morning, participants were awoken after 7-8 h of sleep and allowed 20 min to overcome sleep inertia. In the morning session, participants first performed the IMG task and next the SRTT. Once more, they completed the SSS, KSS, and PANAS before each task. All tasks were administered using Matlab 6.5 (The MathWorks Inc., Natick, MA, 2000) and Cogent 2000 (Functional Imaging Laboratory, Institute for Cognitive Neuroscience, University College London) on a computer screen with resolution 1024 x 768 pixels. Sounds were presented via noise-cancelling headphones (SONY mdr-nc7) during the experimental tasks and via computer speakers (Dell A425) during sleep.

Serial Reaction Time Task (SRTT)

The SRTT task was adapted from (Cousins et al., 2014, 2016; Nissen & Bullemer, 1987) to contain interleaved blocks of two 12-item sequences A (1 2 1 4 2 3 4 1 3 2 4 3) and B (2 4 3 2 3 1 4 2 3 1 4 1) that were matched for learning difficulty. Each block contained 3 repetitions of the sequence. No more than two blocks of the same sequence were presented consecutively. The blocks were separated by a 15 s gap, which could be prolonged if desired. During the break, performance feedback was displayed. Participants performed 24 blocks of each sequence and another 4 blocks with random sequences. Two of the random blocks had stimuli from sequence A and the other two from sequence B. "A", "B" or "R" appeared centrally on the screen to indicate the sequence.

Each sequence had neutral or negative visual cues that were accompanied by 200 ms long high- or low- pitched pure tones, all counterbalanced across participants. Visual cues were four objects, from the International Affective Pictures System (IAPS) (Lang, Bradley, & Cuthbert, 2008) or the internet, and four faces, from the Radboud Faces Database Trials (Langner et al., 2010). The neutral objects were a wooden chair and a pair of legs wearing socks, whereas the corresponding negative objects were a dirty toilet and a severed arm. The neutral faces were from one male and one female, both having neutral facial expression. The negative faces were from the same individuals, the female having a fearful expression and the male having a sad expression. High-pitched tones were musical tones grouped closely within the 5^{th} octave (A/B/C#/D), and low-pitched tones were within the 4^{th} octave (C/D/E/F).

For each trial, a visual cue would appear in one of the four corners of the screen accompanied by a tone. Semantically related visual cues appeared in the same position for each sequence (1 – top left corner = female face, 2 – bottom left corner = body, 3 – top right corner = male face, 4 – bottom right corner = sitting object). The spatial locations corresponded to keys of the same configuration to be pressed with individual fingers, either the index or the middle, of the left and right hands. Participants were instructed to press the corresponding key as quickly as possible while minimizing errors but were not asked explicitly to learn the sequences. They were also told that the nature of the cues (objects or faces) was irrelevant. Visual cues disappeared only after a correct response and were followed by an 880 ms inter-trial interval. The number of blocks and the inter-trial interval were optimized for the classifier analysis.

Imagery Task (IMG)

Participants were asked to repeat the previous SRTT but without pressing the corresponding keys for each cue. Instead, they were instructed to imagine they were moving their finger to press the key. For this task, 48 interleaved blocks, 24 from each sequence, were presented in the same order as in the SRTT, without any random blocks at the end. Cues were presented for 270 ms and the inter-trial interval was 880 ms. Furthermore, no feedback was provided between blocks.

Engagement Task

The purpose of this task was for the participants to engage emotionally with the visual stimuli to increase their emotional salience. Before the presentation of each stimulus, participants received appropriate instructions, e.g. mimicking facial expression, imagining self in a situation having to use the presented object, etc. The duration that the instructions were displayed was self-paced. After the instructions, each one of the visual stimuli was displayed in full screen for 5 s.

TMR during NREM

Brown noise was played throughout the night to minimize sleep disturbances due to external noises. Replay of sequence tones started after at least 20 min of stable NREM sleep. For all participants, tones from both sequences were presented, having the same duration of cue presentation and inter-trial interval as in the Imagery task. Tones of the two sequences were replayed in alternating

blocks. For six participants each block contained one repetition of a sequence and for thirteen participants it contained five repetitions. The interval between two sequences was at least 20 s long. In case of an arousal during the replay or a sleep stage change, then the replay was immediate. Replay was resumed after at least 1 min or when participants returned to stable NREM sleep.

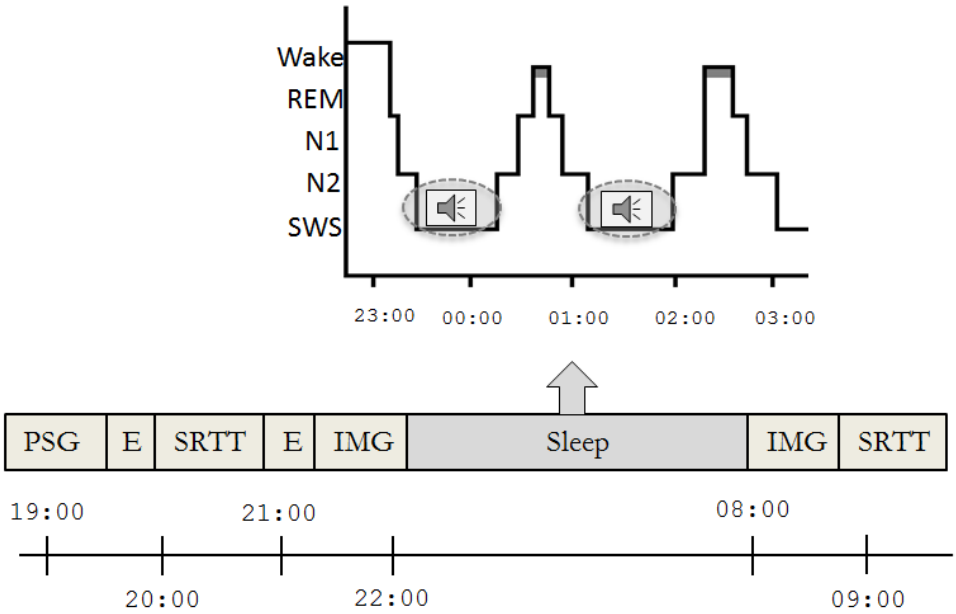

Figure 4-1 Experimental design: PSG = polysomnography, E = engagement task, SRTT = serial reaction time task, IMG = motor imagery task

4.2.3 PSG Data Acquisition and Analysis

Silver-silver chloride electrodes were attached to the scalp and face of the participants. In total 23 electrodes were placed according to the 10-20 rule. The 16 electrodes on the scalp were at the standard locations F3, F4, C3, C4, Cz, C5, C6, CP3, CP4, CP5, CP6, P7, P8, Pz, O1, and O2 and referenced at the contralateral mastoid electrode. Two electrodes were attached next to the eyes, two on the chin, and a ground electrode was at the forehead. Connection impedance was < 5 KOhms and the digital sampling rate was 200 Hz. PSG activity was recorded through an Embla N7000 PSG amplifier using the RemLogic software. All PSG recordings were scored manually on RemLogic by two experimenters, who were blind on when sounds were cued, according to "The AASM Manual for the Scoring of Sleep and Associated Events".

4.2.4 Classifier Analysis

We used an EEG classifier previously developed in our lab that was applied successfully on a single SRTT sequence during SWS (Belal et al., submitted).

The classifier was designed to identify the neural activity to each of the five possible classes, one for each finger and one of baseline EEG when no tone was presented – or a failure to trigger reactivation. For each participant two classifiers were developed and then applied, one on data from the negative sequence and one on data from the neutral. The training set of the classifier consisted of EEG data from the pre-sleep IMG task, as these data lack motor movement components and thus are more similar to sleep data.

Before training and applying the classifier, we pre-processed the EEG data to improve their quality. All electrodes were re-referenced to the mean of the two mastoids. We used Independent Component Analysis (ICA) to remove any artefacts. For the sleep data, we also removed manually arousals and movement artefacts during sleep. Following that, we selected sequences that were presented entirely during SWS and that were not interrupted by either an arousal or a sleep stage change. Finally, we baseline corrected the first 1000 ms after each tone onset by subtracting the mean of the 500 ms immediately before that onset for all trials in the IMG and sleep data.

Next, we extracted 1072 features from 1 s of EEG following the tone cue for each trial of the IMG and sleep data. The EEG features belonged to three distinct families, 512 were discrete wavelet transform (DWT) features, 64 were spectral features and 496 were event-related potential (ERP) time-domain features. We then applied a hybrid feature-selection algorithm on the extracted features from the IMG data to reduce data dimensionality and maximize classification accuracy of weak signals embedded in noisy EEG data. Features selection consisted of two stages. Firstly, the filter stage ranked the features based on joint mutual information (Yang & Moody, 1999) between each feature and the class labels. At the 2nd stage, a wrapper maximized classification accuracy be selecting the best combination of the ranked features. At the end, approximately 30 features were selected to be used by the classifier. Then, we trained a Linear Discriminant Classifier (Van der Heijden, Duin, De Ridder, & Tax, 2005) on the IMG data to distinguish between the five classes. Finally, we applied the classifier on the SWS data in order to select the dominant class label for each trial. As the reactivation occurrence could be delayed after the tone onset during sleep, we repeated feature extraction 120 times using a 400 ms sliding window for the sleep data. The class label with the longest uninterrupt-

ed run over the 120 extractions was chosen as the predicted class of that trial, following a modified majority voting strategy.

To evaluate the performance of the classifiers, we calculated the correct classification rate (CCR) as N_C/N_T. Where N_C is the number of correctly classified trials and N_T is the total number of trials to be classified. Chance level was at 0.2, as we were classifying 5 classes. To confirm further that the classification was above chance, we compared the performance of the classifier with the classification of the same features but with the class labels randomly shuffled. We performed this random analysis 100 times and calculated the CCR on a randomly selected 50% of the sequences each time. Finally, we compared the CCR for real and shuffled labels using a t-test.

4.2.5 Behavioural Analysis

Performance for the SRTT sequences was measured in terms of reaction time (RT) per item and accuracy, by calculating the percentage of errors within a sequence repetition. Trials with response latencies longer than 1000 ms were excluded from analysis, whereas trials that contained incorrect button presses, prior to the correct press, were included.

For each sequence, behavioural improvement across night was calculated for both RT and accuracy using the below four measures (where μ refers to mean value). For all measures, a resulting high positive value reflects greater improvement

(1) Early sequence improvement =

$$\mu\ (\text{last 4 blocks})_{\ pre-sleep} - \ \mu\ (\text{first 4 blocks})_{post-sleep}$$

(2) Early sequence-specific improvement =

$$[\mu\ (\text{last 4 blocks})_{\ pre-sleep} - \ \mu\ (random\ blocks)_{pre-sleep}] - [\mu\ (\text{first 4 blocks})_{post-sleep} - \ \mu\ (random\ blocks)_{post-sleep}]$$

(3) Late sequence improvement =

$$\mu\ (\text{last 4 blocks})_{\ pre-sleep} - \ \mu\ (\text{last 4 blocks})_{post-sleep}$$

(4) Late sequence-specific improvement =

$$[\mu \text{ (last 4 blocks)}_{pre-sleep} - \mu\,(random\ blocks)_{pre-sleep}] -$$
$$[\mu \text{ (last 4 blocks)}_{post-sleep} - \mu\,(random\ blocks)_{post-sleep}]$$

Early improvement identifies whether sleep, TMR, motor imagery, or a combination of these affects immediately the post-sleep SRTT performance. Late improvement identifies whether any of these effects are present toward the end of the post-sleep SRTT. The mean of sequence blocks contains information about the stimulus response mapping and the sequence specific skill, whereas the mean of random blocks represents the sensorimotor mapping learning alone. Therefore, the sequence-specific improvement measures identify the sequence-learning skill.

Mixed ANOVAs and paired samples t-tests were used for planned comparisons. Post-hoc tests were Bonferroni corrected. Where Mauchly's test indicated non-sphericity, the Huynh-Feldt (H-F) correction was used for $\varepsilon < 0.75$ and the Greenehouse-Geisser (G-G) correction for $\varepsilon > 0.75$. Associations between behavioural measures, CCR, and questionnaires responses were tested with Pearson's correlations. When Shapiro-Wilks tests indicated a non-normal distribution, Friedman's ANOVA, adjusted signed-rank tests, or Spearman's ϱ correlations were used. All tests were two-tailed and had statistical significance level $p < 0.05$. Error bars and values in brackets refer to standard error of the mean (SEM) unless otherwise specified.

4.3 Results

4.3.1 Questionnaires and Sleep

Participants were moderate evening, intermediate and moderate morning chronotypes according to the MEQ. They all reported normal to moderate levels of depression and anxiety, and normal to severe levels of stress in the DASS. Participants had higher positive affect scores than negative affect scores in PANAS. However, positive affect scores differed between the pre-sleep SRTT and the pre-sleep IMG sessions, and between the pre-sleep SRTT and post-sleep IMG sessions, both cases $p < 0.005$, having more positive scores at the pre-sleep SRTT session. Negative affect did not change significantly across time. Alertness also differed for both KSS and SSS between the pre-sleep SRTT and pre-sleep IMG sessions, and between the pre-sleep IMG and post-sleep SRTT sessions, having the lowest alertness scores at the pre-sleep IMG

session, all $p < 0.02$. Although participants reported more awakenings during the night in the sleep lab, 2.11 [±0.28], than in the previous night in their home, 0.95 [±0.26], F (1, 18) = 12.219, $p = 0.003$, $\eta_p^2 = 0.404$, their reported sleep quality and sleep duration did not differ between the two nights, both $p > 0.1$. Duration of sleep stages and total sleep are displayed in Table 4-1. There was no difference in the number of times that the tones of each sequence were presented during SWS, $p > 0.3$. The negative sequence was presented on average 146.22 [±12.22] times during SWS, accounting a 48.70% [±4.59] of total presentations. The neutral sequence was presented on average 149.59 [±11.22] times during SWS, accounting a 50.51% [±4.51] of all presentations.

Table 4-1 Total time spent in sleep stages

Sleep stage	N1	N2	SWS	REM	WASO	TST
Duration (min) [±SD]	17.76 [7.97]	246.42 [35.57]	105.84 [34.51]	103.45 [29.33]	15.97 [10.41]	489.45 [43.57]

WASO: wake after sleep onset, TST: total sleep time

4.3.2 Classifier

We trained the classifier on the pre-sleep IMG data and applied it to the SWS data for both sequences. To confirm that the classifier was successful we compared the CCR with a "random" CCR based on shuffled trial labels. Classification was significantly above this random control for the negative ($t = 9.777$, $p < 0.001$) and the neutral ($z = 3.823$, $p < 0.001$) sequences in comparison to the equivalent random sequences. However, at an individual level, for one participant classification was not significantly above chance for the emotional sequence, whereas for another participant it was not for the neutral sequence. The CCRs of these two sequences were excluded from subsequent analysis.

To investigate whether classifier performance differed between the two sequences and the 5 classes we conducted a repeated measures ANOVA with emotion and class as within-subjects factors. We found a main effect of class, (G-G) F (2.273, 36.362) = 21.050, $p < 0.001$, $\eta_p^2 = 0.568$. Post-hoc tests indicated significant differences between the 1st and 3rd classes, $p = 0.005$; 1st and 4th classes, $p = 0.041$; 2nd and 3rd classes, $p = 0.004$; 2nd and 5th classes, $p = 0.009$; 3rd and 5th classes, $p < 0.001$; and 4th and 5th classes, $p < 0.001$ (Figure 4-2).

Because classification was not equal in all classes, see (Figure 4-2), we performed a separate ANOVA on the four tone-related classes, with side of presentation and type of stimulus as within-subjects factors. We found a main effect of side, F (1, 17) = 10.350, p = 0.005, η_p^2 = 0.378. Items presented on the left side had a significantly higher CCR, mean = 0.24, SD = ±0.01, than the items presented on the right side, mean = 0.19, SD = ±0.01. Thus, the classifier was successful for the items corresponding to the non-dominant hand of the participants.

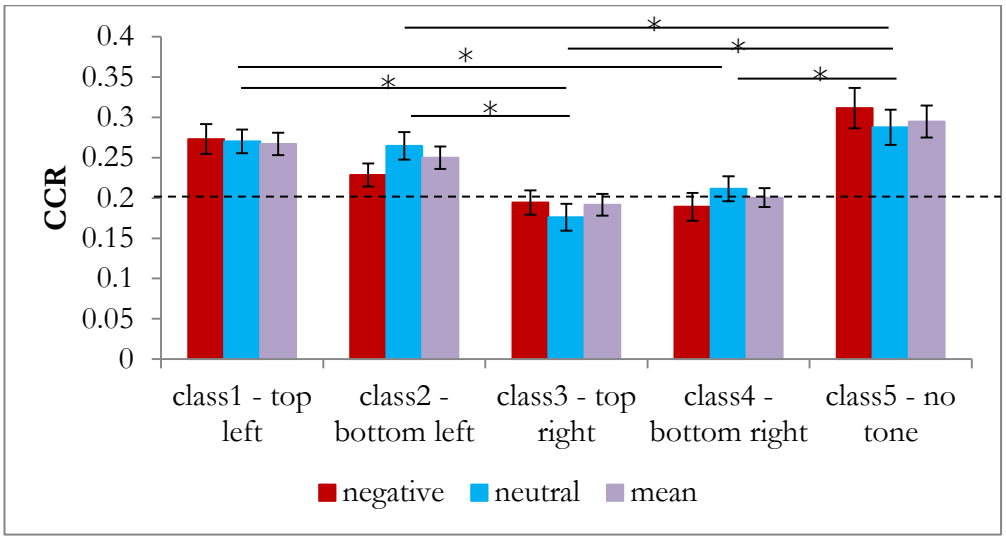

Figure 4-2 Correct Classification Rate of all classes. Dashed line corresponds to CCRs chance level. Where *, there is significant difference, $p < 0.05$.

To investigate further whether the classifier performance differed between the negative and the neutral sequence, we compared the number of selected features overall, per family of features, and per electrode. A paired-samples t-test on the number of selected features did not show any difference between the negative (mean = 25.72, SD = ±6.83) and the neutral (mean = 27.06, SD = ±6.78) sequences, $p > 0.7$. We then used an ANOVA on the number of selected features with emotion and type of family as within-subjects factors. We found a main effect of type of family type, F (2, 15) = 24.625, $p < 0.001$, η_p^2 = 0.767. According to post-hoc tests, fewer spectral power features, 4.03 [±0.79], were selected compared to the DWT features, 9.65 [±0.85], $p < 0.001$, and the time domain features, 12.80 [±1.12], $p < 0.001$. There was no significant difference between the DWT and time domain features. Although the spectral features were fewer in total than the other two types of features, in some cases, spectral features were not selected at all for classification.

Next, we ran an ANOVA on the number of selected features with within-subjects factors emotion and electrodes. We found a main effect of electrodes, (G-G) F (4.388, 70.201) = 6.756, $p < 0.001$, η_p^2 = 0.297, and an emotion x electrodes interaction, F (15, 2) = 30.810, p = 0.032, η_p^2 = 0.996, suggesting that not all electrodes contributed equally in the classification of each sequence. Post-hoc tests showed that for the negative sequence classifier, the number of times that an electrode was selected differed between the following electrodes: CP3 was selected fewer times than F3, p = 0.040, and P8, p = 0.006. Similarly, Pz was selected fewer times than P8, p = 0.019. For the neutral sequence classifier, the frequency that an electrode was selected differed between the following electrodes: P8 was selected more times than C3, p < 0.001; CP4, p < 0.001; CP3, p < 0.001; CP5, p = 0.005; CP6, p = 0.013; and Pz, p = 0.014, whereas O2 was selected more times than CP4, p = 0.002; CP3, p = 0.009; and C3 p = 0.015. Further tests indicated that CP4 was selected more times by the classifier of the negative sequence than the neutral one, p = 0.033; whereas the neutral sequence selected more times features of the electrodes O2, p = 0.014; and P8, p = 0.050 (Table 4-2). Our results suggest that even though electrode P8 was selected more frequently for both sequences, its selection frequency was much higher for the neutral sequence.

Table 4-2 Total number of times an electrode was selected by the classifier

Electrode	Negative Sequence	Neutral Sequence	*Z*	Asymp. Sig. (2-tailed) *p*
F3	47	31	-1.253	.210
F4	46	36	-0.418	.676
C3	20	8	-1.897	.058
C4	22	22	-0.768	.443
C5	22	23	-0.054	.957
C6	37	29	-0.777	.437
Cz	26	25	-0.228	.820
P7	33	41	-0.718	.472
P8	57	83	(*t*) -2.118	.050 *
Pz	12	18	-1.513	.130
CP3	10	11	-0.264	.792
CP4	16	10	-2.126	.033
CP5	13	16	-0.632	.527
CP6	14	18	0	1.000
O1	45	41	-0.237	.812
O2	43	57	(*t*) -2.748	.014 *

Where *, the values were normally distributed

Finally, we ran an ANOVA on the number of selected features with within-subjects factors emotion and side of electrode location. A main effect of side, F (1, 16) = 9.201, p = 0.008, η_p^2 = 0.365, indicated that more features were selected from the right side of the brain, mean = 13.5 [±1.06], than the left side, mean = 10.09 [±0.69]. This difference may be the reason why the items appearing on the left side of the screen had a higher CCR.

As N2, SWS and REM have all been implicated in the consolidation of procedural memory and or emotional memory, we also explored whether the CCR of each sequence would correlate with the duration of the different sleep stages. We found that REM duration correlated positively with the CCR of the neutral sequence, r (18) = 0.562, p = 0.015, but not of the negative sequence, r (18) = -0.086, p = 0.734. These two correlations differed significantly between them as assessed by the Fisher r-to-z transformation, z = -1.98, p = 0.0477. Thus, increased REM duration correlated with higher CCR of the neutral sequence.

4.3.3 SRTT

Mean RT and accuracy error % for all blocks are shown in Figure 4-3 & Figure 4-4. To confirm that sequence learning occurred before sleep, we compared the mean sequence performance of the last four blocks to the mean performance of the random blocks. Participants showed strong evidence of learning, as they were significantly faster while performing the main sequence blocks of both sequences compared to the equivalent random blocks, all $p < 0.05$ (Table 4-3). However, in accuracy measurements we only found a significant difference for the neutral sequence, $p < 0.05$ (Table 4-4). As this result could be due to the increased fatigue and sleepiness of the participants, we also compared the mean accuracy of all sequence blocks to the mean random accuracy. In this case, we found significant difference for both the neutral and the negative sequence $p < 0.05$ (Table 4-4). After sleep, participants performed better in the last four blocks compared to the random blocks for RT and accuracy for both sequences, all $p < 0.05$ (Table 4-3 & Table 4-4).

Next, we investigated whether there were any differences between the negative and the neutral sequences. In RT we found that participants were faster for the last 4 blocks of the neutral sequence than the negative sequence after sleep, $p < 0.05$ (Table 4-3). Regarding the accuracy performance, participants were

more accurate for the negative sequence compared to the neutral sequence before sleep, p <0.03 (Table 4-4). This difference was not present at the last 4 blocks before sleep, or at all after sleep, all p > 0.05.

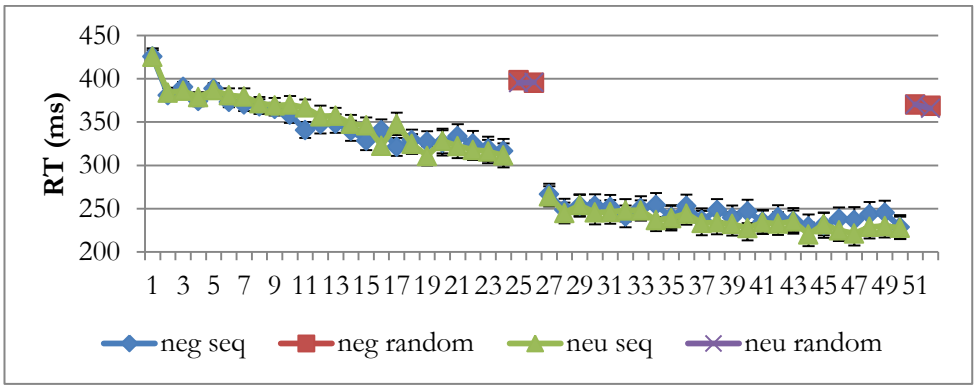

Figure 4-3 Reaction time across all blocks

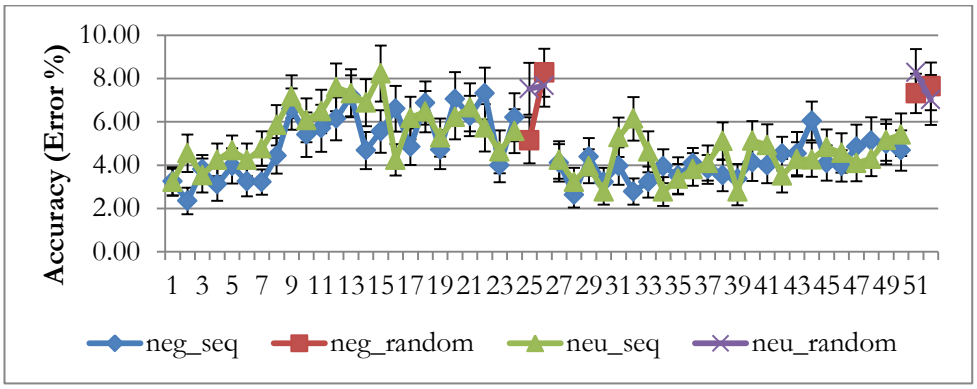

Figure 4-4 Accuracy error % across all blocks

To confirm whether performance improved overnight, we performed one-sample t-tests on the overnight changes in reaction time and accuracy. For the reaction time, all changes were significantly higher than zero (Table 4-3). However, for accuracy, only early changes were significant (Table 4-4). Looking at whether performance changed differently across sleep for the two sequences, we did not find a difference in early sequence change (last 4 blocks pre-sleep minus first 4 blocks post-sleep) in RT or accuracy, p > 0.05 (Table 4-3 & Table 4-4). Next, we compared late sequence change (last 4 blocks post-sleep subtracted from last 4 blocks pre-sleep), where we also did not find any significant differences between the two sequences in RT or accuracy, all p > 0.05 (Table 4-3 & Table 4-4). We also subtracted performance on the last 4 blocks or first 4 blocks from performance on the respective random blocks for both sequences, as a measure of sequence skill. However, we did not find any significant differ-

ences between the negative and neutral sequences in early or late sequence-specific changes, all $p > 0.05$ (Table 4-3 & Table 4-4).

Table 4-3 Mean reaction times in the SRTT and relevant statistics

mean RT (ms) [±SEM]	Negative	Neutral	Negative vs Neutral
Pre-sleep			
Last 4 blocks	320.40 [23.93]	315.29 [21.60]	$p = 0.659$
Random blocks	396.95 [5.32]	395.70 [4.83]	$p = 0.966$
Last 4 – Random blocks	75.45 [19.22]	80.75 [18.69]	$p = 0.638$
Last 4 vs Random blocks	$\|t\| = 3.926$ $p = 0.001$	$\|t\| = 4.320$ $p < 0.001$	
Post-sleep			
First 4 blocks	261.56 [21.00]	257.93 [20.51]	$p = .778$
Last 4 blocks	246.07 [22.45]	232.36 [22.10]	$\|t\| = 2.150$ $p = 0.045$
Random blocks	369.57 [4.38]	368.17 [3.92]	$p = 0.806$
Last 4 – Random blocks	123.66 [20.83]	136.41 [21.85]	$p = 0.092$
Last 4 vs Random blocks	$\|t\| = 5.396$ $p < 0.001$	$\|t\| = 6.244$ $p < 0.001$	
Overnight Change			
Early sequence	58.84 [10.63]	57.35 [9.96]	$p = 0.844$
t-test	$\|t\| = 5.534$ $p < 0.001$	$\|t\| = 5.757$ $p < 0.001$	
Late sequence	74.34 [10.93]	82.93 [12.70]	$p = 0.424$
t-test	$\|t\| = 6.799$ $p < 0.001$	$\|t\| = 6.529$ $p < 0.001$	
Early sequence-specific	32.72 [9.36]	30.08 [13.33]	$p = 0.777$
t-test	$\|t\| = 3.497$ $p = 0.003$	$\|t\| = 2.826$ $p = 0.011$	
Late sequence-specific	48.21 [12.89]	55.66 [14.26]	$p = 0.603$
t-test	$\|t\| = 3.740$ $p = 0.001$	$\|t\| = 3.903$ $p = 0.001$	

To investigate whether pre-sleep performance predicted overnight-improvement, we correlated mean performance of the last 4 blocks with the overnight changes. We only found that a higher error rate before sleep correlated positively with early sequence improvement for the negative sequence, ϱ (19) = 0.791, $p < 0.001$, and the neutral sequence, ϱ (19) = 0.490, $p = 0.033$. Furthermore, higher error rate before sleep had also a positive correlation with late sequence improvement for the negative sequence, ϱ (19) = 0.641, $p = 0.003$. However, we did not find any correlations between pre-sleep reaction time performance and overnight changes.

Next, we explored whether there were any speed-accuracy trade-offs by correlating RT and accuracy measures. We only found a negative correlation be-

tween the RT and accuracy error of the negative sequence before sleep, r (24) = -0.639, p = 0.001, suggesting that participants were less accurate the faster they responded.

Finally, we investigated whether overnight improvement correlated with any of the sleep stages but we did not find any significant correlations, all $p > 0.05$.

Table 4-4 Mean accuracy error rate % in the SRTT and relevant statistics

mean Accuracy as error rate % [±SEM]	Negative	Neutral	Negative vs Neutral
Pre-sleep			
Full sequence	5.10 [0.64]	5.66 [0.74]	$\|t\| = 2.539$ $p = 0.021$
Last 4 blocks	5.95 [0.90]	5.65 [1.10]	$p = 0.201$
Random	6.71 [1.12]	7.60 [1.03]	$p = 0.318$
Last 4 – Random blocks	0.76 [0.86]	1.96 [0.76]	$p = 0.316$
Full sequence vs Random	$\|t\| = 2.321$ $p = 0.032$	$\|t\| = 2.750$ $p = 0.013$	
Last 4 vs Random blocks	$p = 0.314$	$\|z\| = 2.311$ $p = 0.021$	
Post-sleep			
First 4 blocks	3.59 [0.55]	3.55 [0.62]	$p = 0.937$
Last 4 blocks	4.91 [0.87]	4.74 [0.94]	$p = 0.641$
Random	7.48 [1.03]	7.65 [1.16]	$p = 0.842$
Last 4 – Random blocks	2.57 [1.20]	2.91 [1.17]	$p = 0.783$
Last 4 vs Random blocks	$\|z\| = 2.115$ $p = 0.034$	$\|t\| = 2.946$ $p = 0.022$	
Overnight Change			
Early sequence	2.36 [0.73]	2.10 [0.90]	$p = 0.711$
	$\|t\| = 3.234$ $p = 0.005$	$\|t\| = 2.343$ $p = 0.031$	
Late sequence	1.04 [1.11]	0.91 [1.23]	$p = 0.903$
	$p = 0.360$	$p = 0.467$	
Early sequence-specific	3.13 [1.47]	2.15 [1.02]	$p = 0.732$
	$\|t\| = 2.133$ $p = 0.047$	$\|t\| = 2.116$ $p = 0.049$	
Late sequence-specific	1.81 [1.65]	0.96 [1.20]	$p = 0.613$
	$p = 0.287$	$p = 0.434$	

4.3.4 Classifier and Behavioural Performance

Finally, we were interested in the relationship between the behavioural findings and the CCRs. We did not find any significant correlations between the CCR of the neutral sequence and the behavioural performance pre-sleep or overnight changes. For the negative sequence, we found that the CCR correlated negatively with pre-sleep accuracy scores of last 4 blocks, ϱ (18) = -0.496, p = 0.036 (Figure 4-5). As the pre-sleep accuracy performance appeared to be

noisy, we ran further exploratory correlations. Their results indicate that the CCR correlated negatively also with the pre-sleep accuracy scores of the mean sequence, ϱ (18) = -0.550, p = 0.018; and the mean random blocks, ϱ (18) = -0.547, p = 0.019 (Figure 4-5). These findings indicate that the more accurately participants had learned the individual stimuli, regardless of whether they were presented in the sequence blocks or the random blocks, the classification rate was higher. Furthermore, we found a negative correlation between CCR and early sequence change, as measured both by RT, ϱ (18) = -.0546, p = 0.019, and by accuracy, ϱ (18) = -0.521, p = 0.027 (Figure 4-5). We also found a positive correlation between CCR and early sequence-specific improvement of RT, ϱ (18) = 0.479, p = 0.044 (Figure 4-5). However, when we tested late sequence improvement and late sequence-specific improvement we did not find any significant correlations with CCR.

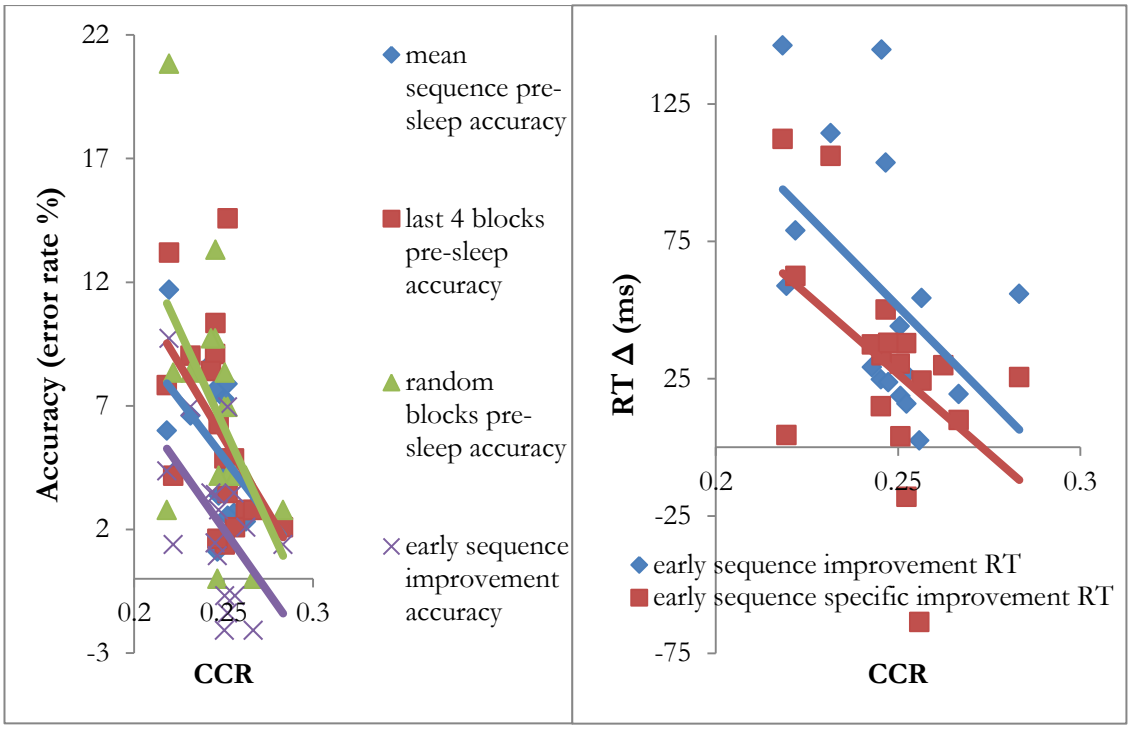

Figure 4-5 Correlations between CCR and accuracy error rate % (left) or RT (right) for the negative sequence

To confirm whether the above correlations were specific or stronger for the negative sequence we used the Fisher r-to-z transformation to assess the significance of the difference between the negative and neutral correlation coefficients. This exploratory analysis revealed a significant difference in the early sequence improvement when measured by accuracy, z = 2.290, p = 0.022. Additionally, in the early sequence improvement measured by RT, there was a very

weak trend of difference between the two sequences, $z = 1.790$, $p = 0.074$. Therefore, at least in the correlation between the CCR and early sequence improvement of accuracy, the negative and neutral sequences are showing a different pattern.

To summarise, our results suggest that higher CCR correlates with lower overnight improvement for the negative sequence. Although in pre-sleep the individual item consolidation was important, the overnight early improvement was sequence-specific for RT but not accuracy. This effect, however, was no longer present by the end of the post-sleep SRTT session.

4.4 Discussion

In this study, we used an EEG classifier to detect the cued replay during SWS of memories associated with negative and neutral stimuli in SRTT sequences. Both sequences were classified above chance. However, the CCR did not differ between the negative and the neutral sequences. Similarly, we did not find any differences between the negative and the neutral sequences on the overnight behavioural change. However, our results suggest that cueing may have different effects on the induced behavioural changes depending on whether the items of the sequence had negative or neutral content.

4.4.1 Effects of Emotion on SRTT Performance

On the behavioural level, we observed higher mean accuracy for the negative sequence before sleep. However, this difference disappeared at the last four blocks before sleep and completely in the post-sleep session. The accuracy data appear to be noisy. Yet, mean accuracy of the negative sequence was significantly higher than the random blocks. These effects could be explained as a result of a trade-off between accuracy and speed. Regarding performance in terms of reaction time, we did not find a difference between the two sequences before sleep. After sleep, the reaction time for the neutral sequence was faster compared to the negative sequence in the last four blocks. This difference might have developed as a result of additional training and is unlikely an effect of prior sleep. In accordance with previous studies on motor sequence learning (Fischer et al., 2002; Walker et al., 2002), we found that reaction time and accuracy performance improved after sleep. TMR has also been shown to enhance procedural memory consolidation (Antony et al., 2012; Cousins et al., 2014, 2016; Schönauer et al., 2014). However, we cannot say whether the observed

improvement is a result of sleep, TMR, motor imagery, or a combination of the above as we lack appropriate controls. Interestingly, accuracy and reaction time performance improved across night for both sequences equally. Our finding differs from a previous study using a different procedural memory task, mirror tracing, where they found greater offline improvement in accuracy when the content was negative (Javadi, Walsh, & Lewis, 2011). In this SRTT task, emotion appears to enhance accuracy performance before sleep and slow down reaction time after extensive training.

4.4.2 Classifying Negative and Neutral SRTT Sequences

We observed a significant classification for cued negative and neutral sequences during SWS on a total number of 19 participants. This result validates the findings of our previous study where we used the same classifier on a neutral sequence with fewer participants (Belal et al., submitted). It is also in accordance with the results of a study reporting preservation of task-specific preparatory responses on both hemispheres during sleep, for motor-response tasks that participants practiced during wake (Kouider, Andrillon, Barbosa, Goupil, & Bekinschtein, 2014). Contrary to our expectations, we did not observe a difference between the CCRs of the two types of sequence. Furthermore, the number or family type of selected features by the classifier did not differ between the negative and the neutral sequences. Furthermore, the EEG characteristics of negative visual stimuli did not appear to add information that could improve the CCR. The selected features were, possibly, not reflective of the emotional EEG properties of the stimuli but based on other properties. This could be due to the nature of the classifier we used, as it was not built to detect differences between emotional categories. Potentially, using a different type of classifier or training a single classifier on items of both sequences simultaneously could yield different results between a negative and a neutral sequence. Furthermore, conducting the study with male participants instead of female could also produce different results as men and women show differences in their sleep quality and may use different strategies and brain networks to process emotional stimuli or acquire motor skills (Andreano & Cahill, 2009).

As in our previous study (Belal et al., submitted), we found that the features selected by the classifier were consistently from the wavelet transform and ERP families and less frequently from the spectral family. Furthermore, features from electrode P8 were selected more frequently, especially for the neu-

tral sequence. Our results suggest that although the classifier achieved similar CCR for the negative and neutral sequences, the frequency and distribution of selected features, in terms of electrodes, differed between the two types of sequences. Unexpectedly, we found that CCR differed between the classes of stimuli depending on which side of the screen they were presented. Stimuli on the left side, corresponding to the non-dominant hand, had a significant CCR whereas stimuli on the right side did not. A reason for this difference could be the fact that the classifier selected more frequently features from electrodes on the right brain side, again corresponding to the non-dominant hand. It is unclear why this happens, as one would hypothesize that the dominant hand should have more fine-tuned motor representations and thus be better classifiable.

4.4.3 Correlations between Behaviour and Classification Accuracy

Our findings replicate the work of (Belal et al., submitted) by indicating that for the negative sequence the more accurate one was before sleep, the higher the subsequent classification accuracy will be. However, we build on past work by showing that the sensorimotor-mapping and not the sequence-specific skill is driving this effect, as the accuracy of the random blocks was also following the same correlation pattern. We did not observe any similar significant effects for the neutral sequence or the reaction time performance before sleep. Furthermore, again in line with (Belal et al., submitted), our results indicate that a higher CCR predicted less early sequence improvement for the negative sequence, both for reaction time and accuracy performance. Interestingly, a dissociation appears between the nature of learning for reaction time and accuracy measures. We observed the same correlation with the sequence-specific skill improvement for reaction time performance but not for accuracy. We did not observe any correlations between the classification accuracy and any of the late sequence improvement measures. The reason behind the lack of correlations with late sequence improvement could be the long duration of the post-sleep session. The post-sleep session was as long as the pre-sleep session and thus additional learning may have occurred, overriding any sleep or cueing effects.

The above correlations are similar to the findings in (Belal et al., submitted), with an EEG classifier on a neutral sequence during SWS. Furthermore, in this

study we had random blocks after the main blocks, clarifying thus that CCR correlated with the sensorimotor-mapping learning component of accuracy. Interestingly, in the current study, unlike the prior study, we did not find any correlations with reaction time pre-sleep performance, although we did find parallel correlations with accuracy. However, a crucial difference is that the current correlations were found in the negative sequence only. When comparing the correlations of the negative sequence to the ones of the neutral sequence, we did not find any significant differences. Thus, we cannot conclude that accuracy learning of the negative sequence affects the CCR differently than the neutral sequence. However, we could suggest that the pre-sleep accuracy performance effects on the CCR are stronger for the negative sequence. This difference could be stemming from the pre-sleep accuracy difference between the two sequences across all the main blocks. However, on the behavioural level, there were no differences between two sequences in the last 4 blocks or the random blocks, even though we observed correlations with CCR for these types of blocks for the negative sequence. Previously, it was argued that the pre-sleep performance correlation could be explained as either that the participants who had learned better the sequence were more responsive to TMR, or that their brain activity was easier to identify during sleep (Belal et al., submitted). Evidence supporting the former argument comes from a study using TMR during SWS with a declarative memory task (Creery et al., 2015). Their results indicated that TMR induced memory enhancement was greater for participants who had better pre-sleep performance, except if their pre-sleep memory accuracy was nearly perfect. Yet, it remains unclear which of the two hypotheses is correct in this experimental setup, and further research is necessary to elucidate how pre-sleep performance is related to classification accuracy during SWS.

Regarding the overnight performance improvement, we found that early sequence improvement of the negative sequence, measured by both reaction time and accuracy, was negatively correlated with the CCR during SWS. Furthermore, for the negative sequence, we found that early sequence-specific improvement of reaction time had a negative correlation with CCR. Therefore, CCR appears to correlate with the stimulus-response mappings for accuracy improvement, and with the sequence-specific learning skill for reaction time improvement. Why these correlations are negative could be explained if we

take into account pre-sleep performance. Our behavioural data indicated that more errors before sleep correlated with a larger early sequence improvement. Meaning that there might be a ceiling effect, as participants who already had high accuracy performance before sleep, and thus higher CCR, were less likely to improve. However, we did not find such correlations for the reaction time improvement. In our previous study, we observed a similar negative correlation between CCR and performance improvement, as a composite score of accuracy and reaction time, for a neutral sequence. In this study, when comparing correlations between the negative and the neutral sequences, we found a significant difference for the correlations between CCR and early sequence improvement of accuracy and a trend for reaction time. Therefore, it appears that sleep or cueing act differently on the consolidation of motor sequences; depending on whether there is only one sequence with neutral items or if there are two sequences, one of them having neutral and the other negative items.

4.4.4 Conclusion

We used an adapted SRTT task and an EEG classifier to detect neural reactivation of negative and neutral memories during SWS. First, we showed that classification rate was above chance for both sequences but did not differ between them. Next, we showed that the classifier was not always using the same type of features for the negative and the neutral sequences. On the behavioural level, we did not find any differences on the overnight performance change between the two sequences. Finally, our findings suggest that the correlation between the classification rate of TMR in SWS and the behavioural performance may differ between negative and neutral memories.

5. Investigating the Roles of Sleep and Wake in Emotional Perception and Memory of Musical Excerpts

Maria-Efstratia Tsimpanouli, Rebecca Elliott, Ian M. Anderson, Penelope A. Lewis

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5.1 Introduction

Music can induce strong emotions with either positive or negative valence (Krumhansl, 1997) by modulating activity in a number of brain structures that are involved in emotion processing (Koelsch, 2014). Music can also enhance the emotional experience when presented simultaneously with congruent pictures (Baumgartner, Lutz, Schmidt, & Jäncke, 2006). Furthermore, the emotional content of music may modulate the emotion elicitation in movie scenes (Pehrs et al., 2014). Listening to music can also enhance spatial skills and cognitive abilities by modulating mood and arousal levels (Husain, Thompson, & E. Glenn, 2002; Schellenberg, 2005; Schellenberg, Nakata, Hunter, & Tamoto, 2007). Interestingly, patients with Alzheimer's dementia can recognize auditory but not facial emotions (Drapeau, Gosselin, Gagnon, Peretz, & Lorrain, 2009) and may still remember how to play a musical instrument even if they cannot recognize familiar melodies (Baird & Samson, 2009; Fornazzari, Mansur, Acuna, Schweizer, & Fischer, 2017). Emotional appreciation of music was even spared in a case of extensive brain damage (Peretz, Gagnon, & Bouchard, 1998). However, a patient with amygdala damage was not able to recognize scary and, to a lesser extent, sad music (Gosselin, Peretz, Hasboun, Baulac, & Samson, 2011). Therefore, musical stimuli could be a valuable tool to study emotional processing and memory in healthy and clinical populations.

Emotion has a dual role in memory consolidation. Emotional items are better remembered than neutral items (Dolcos et al., 2004). Negative emotion though may disrupt the formation of associative memory (Bisby & Burgess, 2014; Bisby et al., 2016; Maddock & Frein, 2009; Novak & Mather, 2009; Tsimpanouli, Hutchison, et al., 2017; Tsimpanouli, Elliott, et al., 2017). However, not all negative, or positive, emotional stimuli are processed by the same brain areas or evoke the same physiological responses (Elliott, Zahn, Deakin, & Anderson, 2011; Krumhansl, 1997; Levine & Pizarro, 2004; Olofsson, Nordin, Sequeira, & Polich, 2008). A common element of emotional memory processing is that emotional memories are preferentially consolidated during sleep (Hu et al., 2006; Van Der Helm & Walker, 2011). Furthermore, sleep enhances associative memory (Diekelmann, Wilhelm, Wagner, & Born, 2013; Talamini et al., 2008; van Dongen, Takashima, Barth, & Fernández, 2011). In associative emotional memory, though, the effect of sleep is less clear and may depend on the type of task (Mather, 2007). In an associative memory para-

digm, where memory performance was better for the negative stimuli, sleep enhanced only the neutral paired associates (Alger & Payne, 2016). In another study, sleep promoted the memory of emotional items but memory for their neutral backgrounds was decreased (Payne et al., 2008). In our previous study, targeted memory reactivation during sleep stabilized memory for both negative and neutral stimuli, although location of neutral stimuli was overall better remembered than the location of negative stimuli (Tsimpanouli, Elliott, et al., 2017). In these studies, the emotional stimuli were negative, but it is unclear what the sleep effects would be on different types of negative stimuli, or on positive emotional stimuli. In addition to memory consolidation, sleep has been proposed to have a significant role in the processing of emotional affect. However, once more, the consensus is not uniform as some studies suggest that sleep enhances emotional responses (Baran et al., 2012; Lara-Carrasco et al., 2009; Wagner et al., 2002) and other that it habituates them (Gujar et al., 2011; Pace-Schott et al., 2011; van Der Helm et al., 2011).

Most studies on emotional music and memory are assessing either if participants remember the music stimuli (Aubé, Peretz, & Armony, 2013; Drapeau et al., 2009; Gosselin et al., 2011; Narme, Peretz, Strub, & Ergis, 2016) or music-evoked autobiographical memory (Belfi et al., 2015; Janata, 2009; Janata, Tomic, & Rakowski, 2007; Van den Tol & Ritchie, 2014). In this study, we aimed to investigate the effects of emotion on how associative memory and subjective ratings of musical excerpts change across a period of nighttime sleep compared to a period of daytime wakefulness. We recruited two groups of participants, one group starting in the morning and one in the evening, to rate a set of peaceful, happy, scary and sad musical excerpts for arousal, valence, and likeability in four different sessions. During the 1st session, participants were also trained, and subsequently tested in all the sessions, on an explicit and implicit associative memory task. The 2nd and 3rd sessions took place 12 and 24 h later, respectively, and the 4th after a week. We were also interested in understanding better how different emotions and subjective arousal may enhance or disrupt associative memory. Finally, we sought to investigate whether going to sleep or staying awake immediately after the 1st session could have an impact on how emotional ratings and associative memory change a week later, after several nights of sleep.

5.2 Materials and Methods

5.2.1 Participants

Thirty-nine healthy female volunteers participated in this study. Twenty were randomly assigned to the APAA (sessions taking place in AM → PM → AM → AM) group and 19 to the PAPP (sessions taking place in PM → AM → PM → PM) group. Participants were instructed not to nap for the duration of the experiment or consume any caffeine for at least 24 h before each experimental session. Five participants were disqualified from analysis based on non-compliance with criteria regarding sleep during the experiment or because of a history of sleep disorders. Analyses were performed on data from 34 subjects, 19 in the APAA group (mean age = 25.21 years old [±0.92]) and 15 in the PAPP group (mean age = 22.27 years old [±1.27]). Three participants were excluded from the analysis of the memory tasks because they performed badly in the training session, completing it after 20 or more rounds. Finally, location memory data of one participant could not be used due to technical errors. All participants gave written consent to participate at the beginning of the experiment and received a financial compensation for their participation. This study has been approved by the University of Manchester research ethics committee.

5.2.2 Stimuli

Stimuli were 56 musical excerpts that convey four emotions, happiness, sadness, fear, and peacefulness, adapted from (Vieillard et al., 2008). All excerpts were modified to be 6 s long so that participants learned to recognize them from other characteristics than their duration. It has been shown that a duration as short as 5 s was sufficient to recognize the correct emotion (Vieillard et al., 2008).

Each musical excerpt was randomly paired with one out of seven different possible colours. Thus, each colour was paired to two musical excerpts from an emotional category. The selection of colours was based on their of their red-green-blue (RGB) decimal code values. The mean value was 127 per red/green/blue dimension (Table 5-1).

Table 5-1 Colours for implicit memory test

R	G	B	colour
0	255	0	
0	255	255	
0	0	255	
127	0	255	
255	0	127	
255	127	0	
255	255	0	
127	127	127	mean

5.2.3 Experimental Tasks and Design

A summary of the design is shown in Figure 5-1. All participants completed 4 experimental sessions. The first session was in the morning for the APAA group and in the evening for the PAPP group. The second session (t = 12 h) took place approximately 12 h later, and the third session after another 12 h (t = 24 h). The APAA group slept between sessions 2 and 3, whereas the PAPP group slept between sessions 1 and 2. Finally, the fourth session (t = 1 week) took place after about a week, in the morning for the APAA group and evening for the PAPP group.

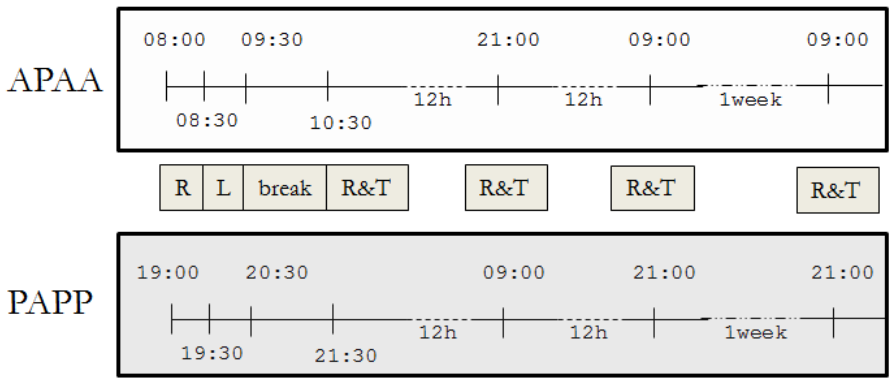

Figure 5-1 Experimental Design: R = ratings task, L = memory learning and training tasks, R&T = ratings task and memory tasks

All tasks were performed using E-prime 1 on a computer screen with a resolution of 1024 x 768 pixels. The musical excerpts were delivered binaurally through noise-cancelling headphones (Sony MDR-ZX110NA). Before starting each session, a neutral sound was presented in order to adjust the volume of

the headphones. In all tasks, the musical excerpts were presented in pseudo-randomized order to ensure that no more than two excerpts of the same emotion category or paired colour were presented consecutively.

At the beginning of the first session, participants filled the consent form, a copy of the Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990) and the 20-items Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) (t = 0 h). They then received instructions for the Ratings task (t = 0 h). Participants were asked to rate each stimulus for arousal, valence, and liking by clicking on 0-9 continuous scales. Above each scale, a self-assessment manikin (SAM) was displayed (Bradley & Lang, 1994). For the liking scale, thumbs-down/thumbs-up symbols were used (Koelstra et al., 2012). The arousal scale was from 0 having very low arousal/intensity up to 9 having very high arousal/intensity. In the valence scale, 0 was very negative, 5 neutral, and 9 very positive. The likeability scale was from 0 not liking it at all up to 9 liking it extremely. Before starting the task, to ensure that participants understand the difference between valence and arousal, they heard musical excerpts from the soundtracks of the movies *Jaws* and *Schindler's List* as examples of music with low valence and high or low arousal, respectively. During the Ratings task, each musical excerpt was preceded by a black screen with a white fixation cross in the centre for 500 ms. The musical excerpt was then presented for 6 s, while the black screen with the fixation cross remained. Then, a white screen appeared with the three scales and their SAMs (Figure 5-2). Once participants had marked all three ratings using left-click, they pressed the right-click of the mouse to continue with the next musical excerpt.

Following the Ratings task, participants performed the Learning and Training memory tasks. The stimuli were presented using a script developed by (Rudoy et al., 2009) modified for the needs of this study. Participants had to learn to associate each of the 56 musical excerpts with a location of a box on a background grid. Each box was coloured with one of the seven possible colours, but participants were instructed not to base their learning strategy on the colour of the box. For the Learning task, a black screen with a fixation cross was displayed for 500 ms before the presentation of the stimuli. Then, the musical excerpt was delivered while a box was displayed on a random location on a grid for 6 s. For the Training task, the box was presented in the centre of the grid. Once the musical excerpt finished, participants moved the box using left-click

to the location they thought to be correct and right-clicked to confirm. The box would then move to its correct location. Participants performed several rounds of the Training task until they placed each box within a criterion threshold twice.

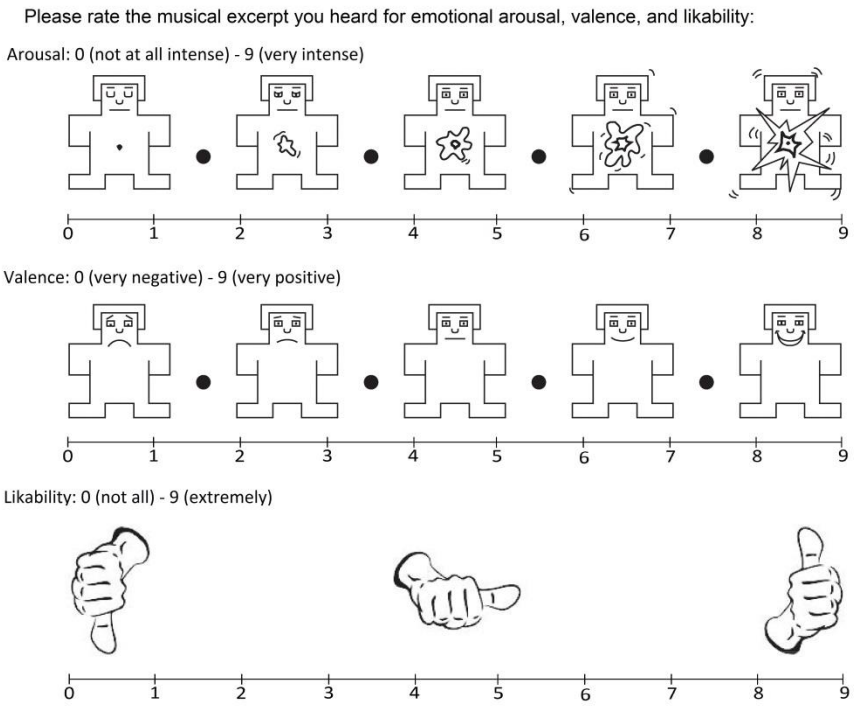

Figure 5-2 Ratings task

After the Training task, participants had a break, during which they answered questionnaires. The questionnaires were the Depression, Anxiety, and Stress Scale (DASS) (Lovibond & Lovibond, 1995), the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), a Sleep diary, the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), the Morningness-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976), a sleep quality questionnaire, the 22-items Ruminative Responses Scale (RRS) (Treynor et al., 2003), the Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996), the Edinburgh Handedness Inventory (Oldfield, 1971), a screening questionnaire, the Emmanuel College Musical Background Questionnaire (Zhao, Mauer, & Doyle-Smith, 2012), and the PANAS and the KSS, (t =2 h).

Then, participants rated again the musical excerpts for arousal, valence, and likeability and were tested on their memory for the location of the box related to a musical excerpt and its colour (t = 2 h). To test explicit memory participants had to place a black box on the correct location corresponding to the

musical excerpt they just heard. To test implicit memory participants had to indicate which colour matched the musical excerpt. The Ratings task was as described above. After participants pressed right click, a black screen with a white cross was displayed for 250 ms. Then, the grid of the memory tasks was displayed with a black box on its centre while the same musical excerpt was presented again. Participants moved the box to its location and then pressed right-click to confirm. A white screen would then appear with a colour wheel in the centre and a box below changing colour according to the point indicated on the colour wheel (Figure 5-3). The colour wheel consisted of a continuous gradient, colour changing every 2 °, among the maximum decimal code RGB values. Participants had to indicate the colour that matched the musical excerpt by left-clicking on the colour wheel and then right-click to confirm. Upon completion of this task, participants were allowed to resume their daily activities or go to their home to sleep.

For the next three sessions, participants answered the PANAS, KSS, and when appropriate the sleep diary and sleep quality. In the fourth session, they also answered the DASS. After the questionnaires, they completed the Ratings task and the Memory testing tasks for location and colour.

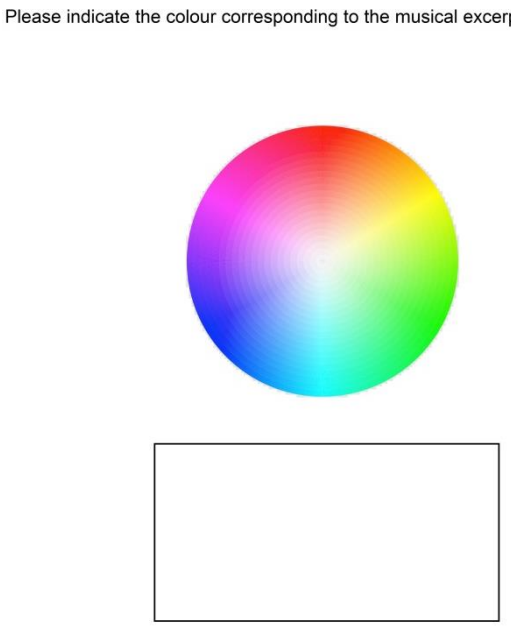

Figure 5-3 Associative colour memory testing task

5.2.4 Statistical Analysis

For the location memory task, performance was calculated as accuracy error based on the 2-D distance between the X and Y coordinates of the correct location and the given location. Similarly, for the colour memory task, the accuracy error was based on the "3-D distance" between the given decimal code RGB values and the correct decimal code RGB values. Therefore, in both location and colour measures, a larger value equals to lower accuracy.

The accuracy change for each item was calculated as error change percentage by subtracting the error at the earlier session from the error at a later session, then dividing the difference by the mean error of the emotional type at the 1st session and multiplying it by a hundred. Therefore, a positive value means that the accuracy got worse and a negative value that it got better. An example is given below for the accuracy change from 12 h to 24 h of a happy stimulus:

$$\text{Happy Error } \Delta\,\% = \frac{(\text{Happy Error}_{24h} - \text{Happy Error}_{12h})}{\text{Mean Happy Error}_{2h}} * 100$$

Both memory tasks were designed and analysed as described above in order to obtain continuous measurements of memory performance and thus allow for a better comparison of their results. However, processing of colours is categorical and a categorical design and analysis, e.g. correct/incorrect, may have been more accurate.

To investigate effects of group, emotion, and type of (sessions') interval we ran a series of ANOVAs. Usually, the between subjects factors were group – APAA or PAPP – and the within-subjects factors were type of interval – sleep (24 h from 12 h for the APAA group and 12 h from 2 h for the PAPP group) or wake (12 h from 2 h for the APAA group and 24 h from 12 h for the PAPP group) –, and emotion – peaceful, happy, scary, sad. If the results indicated a main effect or an interaction with group, we ran additional ANOVAs for each group with the appropriate within-subjects factors. Post-hoc comparisons were examined using Bonferroni correction. When Mauchly's test of sphericity was violated, the Huynh-Feldt (H-F) correction was used for $\varepsilon < 0.75$ and the Greenehouse-Geisser (G-G) correction for $\varepsilon > 0.75$. In some cases, we ran one-sample t-tests to confirm whether the change of ratings or accuracy increased or decreased significantly. When necessary, we ran independent samples t-test to test whether the two groups differed significantly. We also ran a

number of Pearson's correlations. If Shapiro-Wilk tests indicated a non-normal distribution of data, then we ran Spearman's correlations. All tests were two-tailed and we adopted a statistical significance level $p < 0.05$. Error bars and values in brackets refer to standard error of the mean (SEM) unless otherwise specified.

5.3 Results

5.3.1 Questionnaires

We used independent samples t-tests to verify that the two groups did not differ on their interest in music, hours listening per week, hours practicing per week, or having received any training, all $p > 0.05$. Similarly, there were no differences between the two groups in the DASS, STAI, BDI, and MEQ scores. However, the two groups differed significantly on their reflection type RRS scores, $t(32) = 2.283$, $p = 0.029$, with the APAA having lower values than the PAPP group. There were no significant differences between the other types or the sum of RRS scores. Furthermore, there were no differences between the mean age of the two groups. Both groups slept a similar amount of time within the first 24 h of the experiment, either from 12 h to 24 h for the APAA group or from 2 h to 12 h for the PAPP group, averaging at 7.68 h [±0.14], $p > 0.05$. However, the APAA group slept significantly fewer hours than the PAPP group before the 1st session, $t(18) = 3.964$, $p = 0.001$, and before the 4th session, $t(22) = 2.416$, $p = 0.025$. Alertness levels, according to the KSS scores, did not differ between the two groups after 12 h of wakefulness or 12 h of sleep, or at 0 h or at 1week, all $p > 0.05$. However, the PAPP group was less alert than the APAA group at 2 h, $t(32) = 2.361$, $p = 0.024$. Finally, positive and negative mood, according to PANAS scores, did not differ between the two groups at any time point, all $p > 0.05$.

To test whether the alertness at 2 h could have an impact on the given ratings or memory accuracy, we ran correlations between the KSS scores and the given ratings or accuracy errors for each emotion at 2 h. We only found a negative correlation between the alertness scores and likeability ratings of the happy excerpts at 2 h, $\varrho(34) = -0.410$, $p = 0.016$; all other correlations were non-significant, $p > 0.05$. These findings indicate that lower alertness levels in the PAPP group at 2 h are not responsible for any behavioural differences.

5.3.2 Change of Ratings across Training

To confirm that the training task had the same effect on ratings regardless of group we ran three ANOVAs, one for each type of ratings, on the change of ratings across the training session (0 h subtracted from 2 h) with between-subjects factor group and within-subjects factor emotion.

On the arousal ratings we found a main effect of emotion, (G-G) F (2.343, 74.965) = 7.163, p = 0.001, η_p^2 = 0.183. After the training session, arousal ratings of happy excerpts decreased significantly more than the peaceful excerpts, p = 0.001; and the sad excerpts, p = 0.009 (Figure 5-4). The same effect of emotion was observed at the change of valence ratings, F (3, 30) = 5.871, p = 0.003, η_p^2 = 0.370. Valence ratings of the happy excerpts became more negative after the training session in comparison to the peaceful excerpts, p = 0.002; and to the sad excerpts, p = 0.022 (Figure 5-5). We did not observe any main effects or interactions on the change of likeability ratings across the training session.

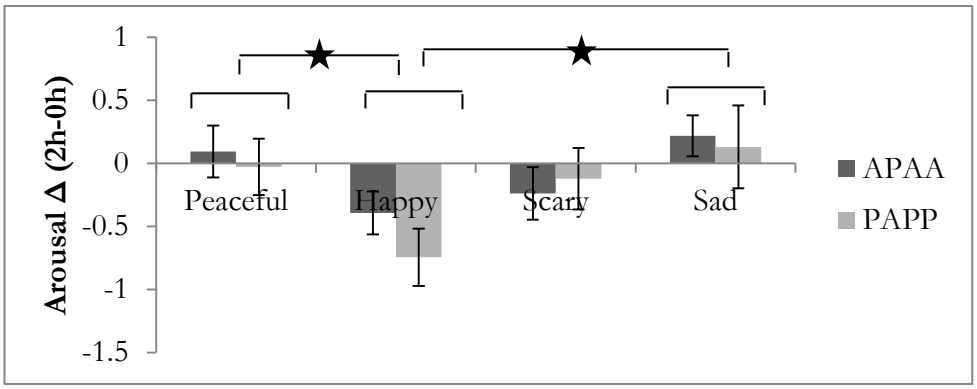

Figure 5-4 Arousal ratings changes across training for both groups

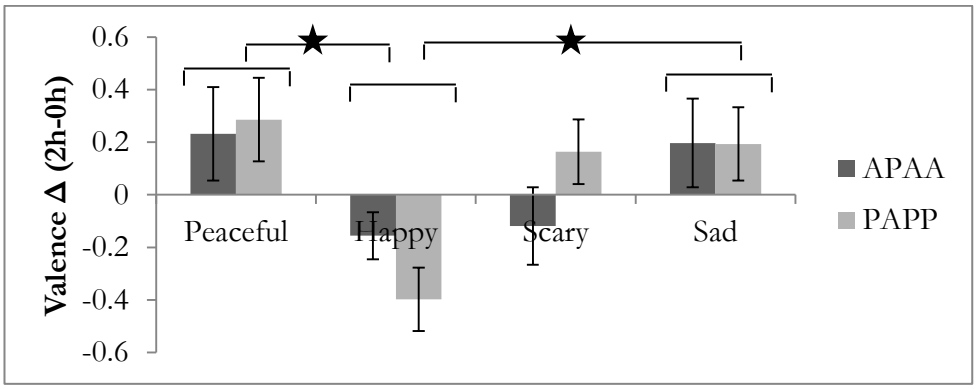

Figure 5-5 Valence ratings changes across training for both groups

Next, we used one-sample t-tests to determine how ratings changed after the training task, across both groups. Overall, arousal and likeability ratings decreased following the training task, t (135) =-2.107, p = 0.037, and t (135) = -2.443, p = 0.016, respectively. Additional tests per emotion showed that only the arousal of the happy excerpts decreased significantly, t (33) = -4.171 p < 0.001. For valence, ratings of the peaceful excerpts increased, t (33) = 2.127, p = 0.041, whereas ratings of the happy stimuli decreased, t (33) = -3.511, p = 0.001. Finally, only the likeability ratings of the peaceful stimuli decreased significantly after training, t (33) = -2.071, p = 0.046.

5.3.3 Change of Ratings across 12 h with Sleep or Wakefulness

Next, we tested whether the various ratings changed differently across 12 h of wakefulness or sleep. To do so, we ran another three ANOVAs having the change of ratings as dependent variable, group as the between subjects factor, and interval and emotion as the within-subjects factors.

In the arousal ratings changes, we found an interval x group interaction, F (1, 32) = 6.396, p = 0.017, η_p^2 = 0.167, suggesting that how much the arousal ratings change might depend on the order of the sessions rather than the type of interval (Figure 5-6). Indeed, one sample t-tests indicated that mean arousal ratings of both groups increased across the first 12 h, t (135) = 3.454, p = 0.001, and did not change across the next 12 h, t (135) = -1.547, p = 0.124. To investigate further the above interaction, we ran two ANOVAs, one per group, on the change of arousal ratings having the type of interval and emotion as within-subjects factors. In the APAA group, we found an interval main effect, F (1, 18) = 6.280, p = 0.022, η_p^2 = 0.259 (Figure 5-6). Arousal ratings of the APAA group got significantly higher across 12 h of wake compared to 12 h including sleep. However, in the PAPP group, we found a main effect of emotion, F (3, 12) = 4.906, p = 0.019, η_p^2 = 0.551. Here, the arousal of scary excerpts increased significantly more than the arousal of the peaceful excerpts, p = 0.019 (Figure 5-7).

In the changes of valence ratings, we found a main effect group, F (1, 32) = 6.034, p = 0.020, η_p^2 = 0.159 (Figure 5-8). The APAA group had a significantly more positive change in valence ratings than the PAPP group. One-sample t-tests indicated that only the APAA group had a significant increase in valence ratings across wake, t (65) = 2.389, p = 0.020.

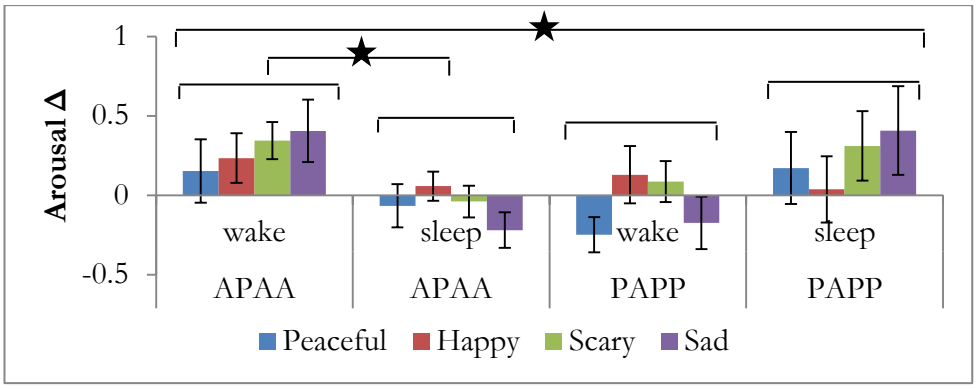

Figure 5-6 Arousal ratings changes across sleep and wakefulness for both groups

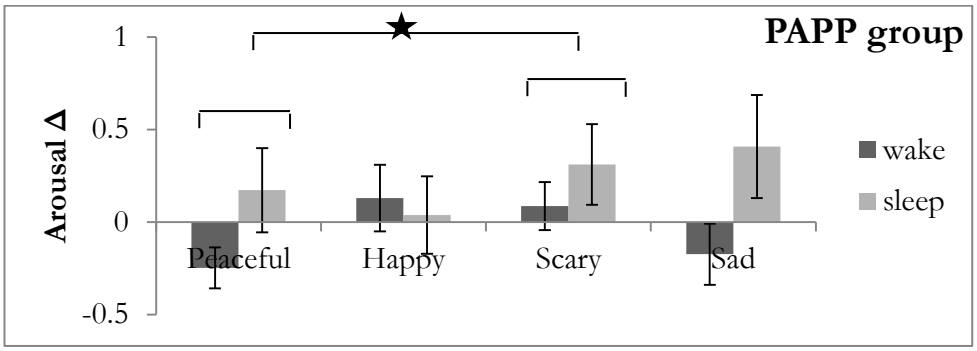

Figure 5-7 Arousal ratings changes across sleep and wakefulness for the PAPP group

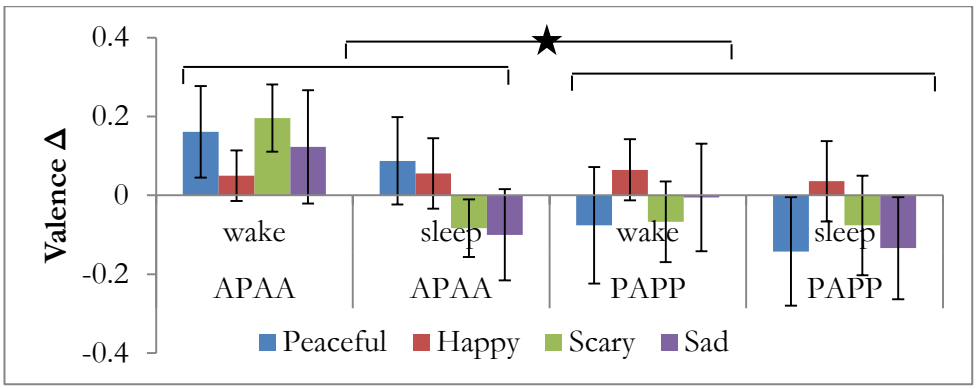

Figure 5-8 Valence ratings changes across sleep and wakefulness for both groups

Regarding the changes of likeability ratings, we found an interval x group interaction, F (1, 32) = 4.657, p = 0.039, η_p^2 = 0.127 (Figure 5-9). Similar to the arousal ratings changes, this finding suggests that the change of likeability ratings for both groups depends on the sessions' order rather than the interval type. One sample t-tests indicated that for both groups mean likeability ratings

increased across the first 12 h, t (135) = 5.404, $p < 0.001$, and did not change across the next 12 h, t (135) = 0.052, p = 0.958. To investigate further the above interaction, we ran two more ANOVAs, one per group, on the change of arousal ratings having the type of interval and emotion as within-subjects factors but did not find any other significant main effects or interactions.

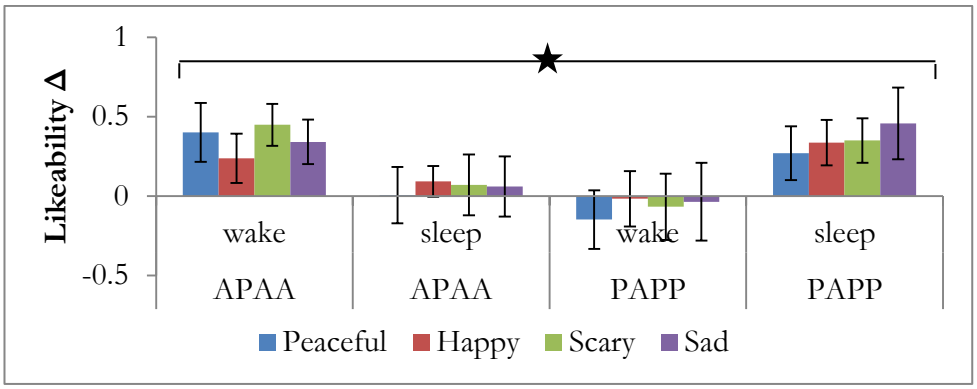

Figure 5-9 Likeability ratings changes across sleep and wakefulness for both groups

5.3.4 Change of Ratings across a Week

To investigate whether sleeping or staying awake within the 12 h after the 1st session could have an impact on how the ratings change across a week, we ran three ANOVAs on the changes from 2 h to 1 week with group as the between-subjects factor and emotion as the within-subjects factor.

We found a trend for a main effect of group on the arousal ratings change across one week, F (1, 32) = 3.927, p = 0.056, η_p^2 = 0.109 (Figure 5-10). One sample t-tests showed that the arousal ratings of the APAA group increased significantly, t (75) = 2.749, p = 0.007, whereas they did not change for the PAPP group, t (59) = -1.245, p = 0.159.

We found a significant main effect of group on the valence ratings change across a week, F (1, 32) = 4.429, p = 0.043, η_p^2 = 0.122 (Figure 5-11). One sample t-tests showed that the arousal ratings of the APAA group increased significantly, t (75) = 1.998, p = 0.049, whereas they did not change for the PAPP group, t (59) = -1.740, p = 0.087.

Separate ANOVAs for each group, with emotion as between-subjects factor, for valence and arousal changes across a week did not show any significant results. Furthermore, we did not find any significant main effects or interactions

on the change of likeability ratings across one week. We then used a one-sample t-test to check whether likeability ratings changed after a week, and we found that they increased, t (135) = 3.763, $p < 0.001$.

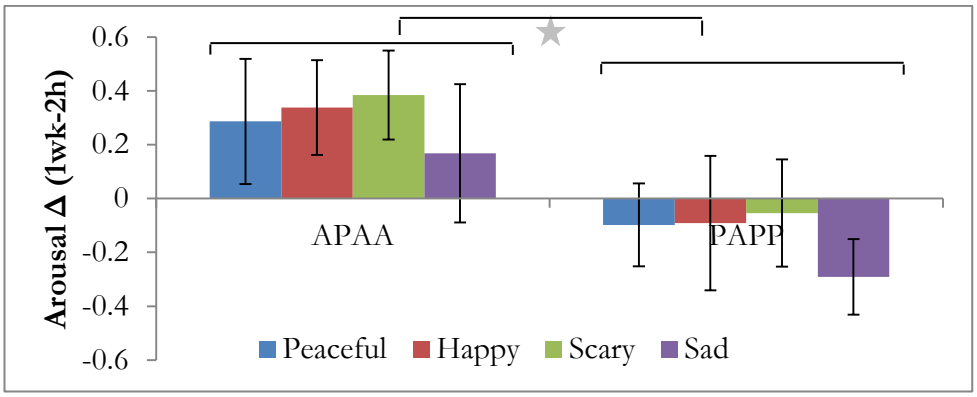

Figure 5-10 Arousal ratings changes across a week for both groups

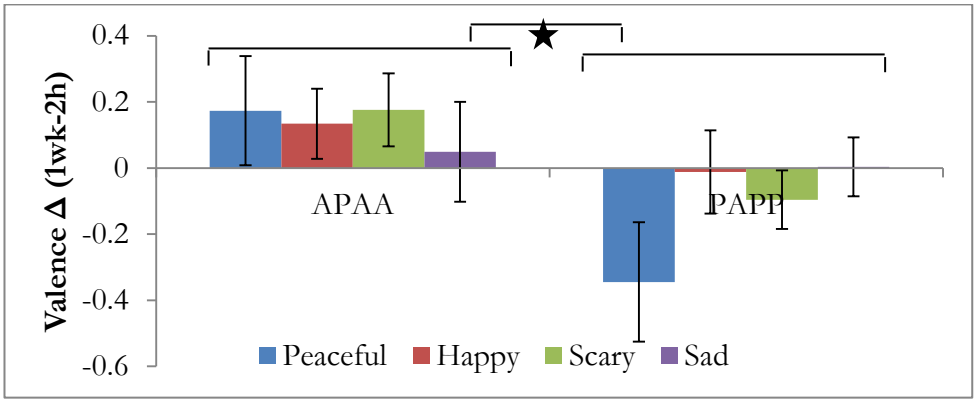

Figure 5-11 Valence ratings changes across a week for both groups

5.3.5 Effects of Emotion on Associative Memory

To investigate whether memory accuracy was different between the four emotions, we ran an ANOVA on the average number of rounds at the training task with group and emotion as the between- and within-subjects factors respectively. We also ran a series of ANOVAs on the accuracy errors of each task with group as the between subjects factor and emotion as the within subjects factor.

The ANOVA on the number of rounds at the training task indicated a main effect of emotion, F (3, 27) = 6.845, p = 0.001, η_p^2 = 0.432. According to the post-hoc tests, scary excerpts required significantly fewer rounds than the peaceful excerpts, p = 0.046, and the sad excerpts, p = 0.001. To investigate whether the number of rounds had an effect on memory accuracy or emotion-

al ratings, we ran a number of correlations between the number of rounds and the behavioural measures at 2 h. We only found a significant correlation between the number of training rounds and location accuracy, r (120) = 0.179, p = 0.050.

The ANOVA on location accuracy at 2 h indicated a main effect of emotion, F (3, 26) = 3.704, p = 0.024, η_p^2 = 0.299, group, F (1, 28) = 6.028, p = 0.021, η_p^2 = 0.177, and an emotion x group interaction, F (3, 26) = 4.526, p = 0.011, η_p^2 = 0.343. As shown in Figure 5-12, the PAPP remembered worse the locations of the stimuli than the APAA group. Post-hoc tests showed that memory for the scary excerpts was significantly worse than for the peaceful excerpts, p = 0.020. To investigate further these effects, we run two more ANOVAs, one for each group, with emotion as the between-subjects factor. We only found a main effect of emotion in the PAPP group, F (3, 12) = 6.391, p = 0.008, η_p^2 = 0.615. According to the post-hoc tests, the location of the peaceful stimuli was better remembered than the scary stimuli, p = 0.011, or the sad stimuli, p = 0.010.

The ANOVAs on location accuracy errors at the session following a sleep interval, or a wake interval, or after a week, did not show any significant results. Similarly, there were no significant results for the colour accuracy error ANOVAs at any session.

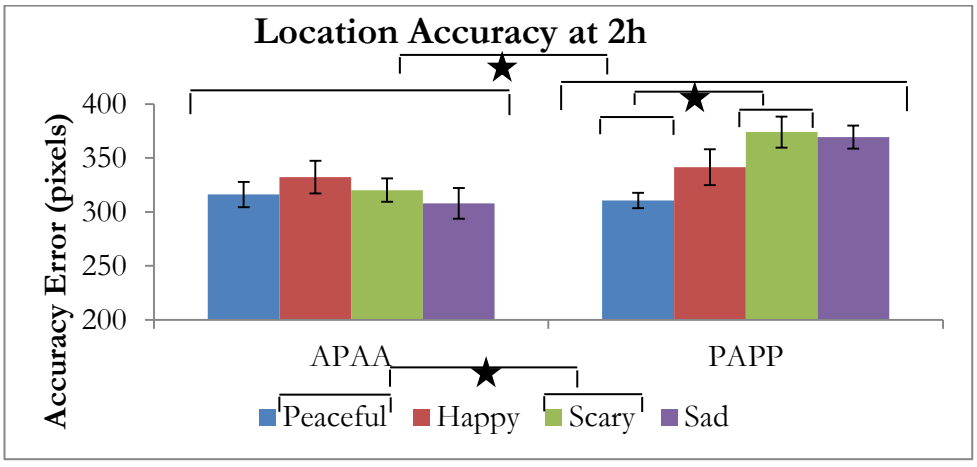

Figure 5-12 Location accuracy at 2 h for both groups

Since previous studies have shown that arousal and valence may mediate the memory effects of emotion, we ran a series of correlations between the emotional ratings and the memory performance across the different sessions. At 2

h, we found a positive correlation between arousal ratings and location accuracy error, ϱ (120) = 0.200, p = 0.029; and a negative correlation between likeability ratings and location accuracy error, ϱ (120) = -0.182, p = 0.047. After the sleep or wake intervals, we did not observe any significant correlations. After a week, location accuracy error was negatively correlated with the given valence ratings, ϱ (124) = -0.227, p = 0.011.

5.3.6 Change of Memory Accuracy

To investigate whether the location memory accuracy changed differently across 12 h of wakefulness or sleep, we ran an ANOVA on the error percentage changes with between-subjects factor group and within-subjects factors emotion and type of interval. We found a main effect of emotion, F (3, 26) = 3.355, p = 0.034, η_p^2 = 0.279, group, F (1, 28) = 5.290, p = 0.029, η_p^2 = 0.159, and an emotion x group interaction, F (3, 26) = 4.158, p = 0.016, η_p^2 = 0.324 (Figure 5-13). On average, the accuracy of the APAA group got worse than that of the PAPP group. Post-hoc tests revealed that the accuracy of the scary excerpts improved compared to the peaceful ones, p = 0.027.

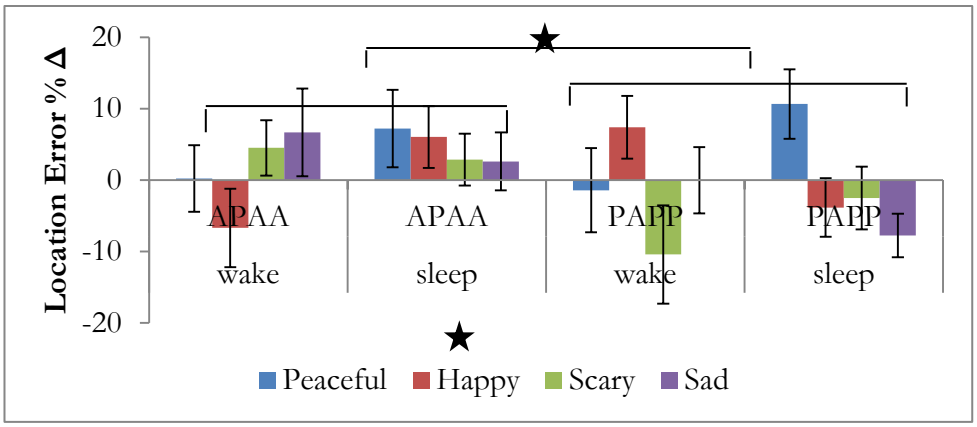

Figure 5-13 Location error change % across sleep and wakefulness for both groups

To understand better the above findings, we ran two more ANOVAs, one per group, with within-subjects factors emotion and type of interval. We did not observe any significant main effects or interactions for the APAA group, but we found a significant main effect of emotion for the PAPP group, (G-G) F (2.180, 30.518) = 4.539, p = 0.017, η_p^2 = 0.245 (Figure 5-14). Again, post-hoc tests showed that the accuracy of the scary excerpts got better than that of the peaceful ones, p < 0.001, suggesting that the interaction observed in the main ANOVA was driven by the PAPP group.

Next, we ran an ANOVA with error change percentage from 2 h to 1 week as dependable variable, group as between-subjects, and emotion as within-subjects factor, to investigate whether sleeping or staying awake within the 12 h after the 1st session could have an impact on how the location memory accuracy changed across a week. However, we did not find any significant main effects or interactions. We then repeated the same type of ANOVAs for the colour-memory accuracy changes but there were no significant findings.

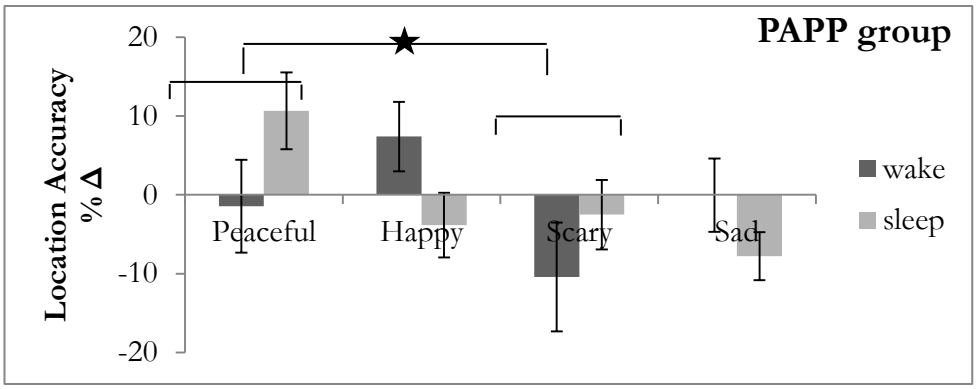

Figure 5-14 Location error change % across sleep and wakefulness for the PAPP group

Finally, we used correlations to explore whether the change of emotional ratings was related to the accuracy error changes. Across both groups, we found that the change of arousal ratings was negatively correlated with the location accuracy error change across an interval with sleep, ϱ (120) = -0.235, p = 0.010. To test whether these correlations are specific for the across sleep interval, we compared them with the equivalent correlations for the across wakefulness interval, using Fisher's r-to-z transformation. We found a significant difference for the location accuracy correlations with arousal ratings across a period of sleep vs a period of wakefulness, z = 2.87, p = 0.004. We also found a significant positive correlation between the arousal ratings change and the colour accuracy error change across a week for the APAA group, ϱ (64) = 0.247, p = 0.049. When compared to the equivalent correlation for the PAPP group we observed a significant difference, z = 2.14, p = 0.032.

5.4 Discussion

In this study, we examined the effects of sleep and emotion on the subjective emotional ratings and associative memory of musical excerpts.

5.4.1 Emotional Ratings of Musical Excerpts

The two groups did not differ on how much their ratings changed across the training task. Overall, participants rated as less arousing and less likeable the musical excerpts after the training. However, our results suggest that these changes were not uniform across all emotions. Both arousal and valence ratings of the happy excerpts decreased more than the peaceful and sad excerpts. These differences are unlikely to be an effect of frequency of exposure, which may cause familiarity and over-familiarity effects (Schellenberg, Peretz, & Vieillard, 2008), as we did not observe a correlation between the change of these ratings and the number of training rounds. Time of day and tiredness have also been reported to affect the perception of emotions, although not in terms of arousal or valence, in musical excerpts (Brabant & Toiviainen, 2014). Here, we found a difference in alertness levels between the two groups after the training task. The more tired participants were at 2 h, the less they liked the happy musical excerpts. Therefore, alertness levels after the training task could explain the observed decrease of the likeability ratings, but not any of the changes in arousal and valence ratings.

Regarding the effects of wakefulness or sleep following the first session, we found results in all three emotional ratings. In valence ratings, we observed a difference between the two groups, most likely driven by the increase of valence ratings for the APAA group across the wakefulness interval. However, for arousal and likeability ratings the order of sessions seems to be more important than the type of interval. In both groups, the arousal and likeability ratings increased after the first 12 h and did not change within the next 12 h. The increase of arousal and likeability ratings within 12 h after the first session could be a rebound from the training-evoked decrease. Interestingly, the change of arousal ratings could be more complicated as we found different effects in each group. In the APAA group, the change of arousal ratings across these two periods was significantly different. However, in the PAPP group we found that arousal ratings increased more for the scary than the peaceful musical excerpts.

The effects of immediate sleep on valence and arousal ratings are still evident at the 4th session. We found that ratings of the PAPP group did not change after a week, but the ratings of the APAA group increased. Thus, sleep within the 12 h following the first session has long-term effects, as it stabilizes valence

and, to some extent, arousal ratings of emotional musical excerpts, regardless of their emotional type. If there is no sleep within that period, then both valence and arousal ratings appear to increase after a week. This is in line with the results of (Baran et al., 2012; Groch et al., 2013) who suggest that sleep preserves emotional reactivity. Finally, participants liked the musical excerpts more after a week, compared to the end of the first session, regardless of whether they slept or stayed awake after it.

5.4.2 Associative Memory of Emotional Music

In recognition memory of musical stimuli, high arousal enhances memory compared to low arousal (Aubé et al., 2013; Eschrich, Münte, & Altenmüller, 2005, 2008; Samson, Dellacherie, & Platel, 2009; Vieillard & Gilet, 2013). Three recent studies have also provided evidence for a role of valence in remembering musical melodies. In the first one, researchers suggest that after a week, memory was enhanced for musical stimuli with positive valence when arousal was high (Altenmüller, Siggel, Mohammadi, Samii, & Münte, 2014). The second study provided a more complex interaction between valence and arousal. In immediate testing, there was better recognition for positive excerpts compared to negative excerpts for low arousing music. Testing at 24 h showed that high arousing stimuli were better remembered than low arousing, and negative better than positive (Alonso, Dellacherie, & Samson, 2015). Finally, (Narme et al., 2016) suggest that recognition memory is better for positive melodies compared to negative ones, and for higher arousal memories than lower arousing ones.

Little is known though about the associative memory of musical stimuli. One study claims that music may disrupt source memory by disrupting the feature-binding processes, (El Haj, Omigie, & Clément, 2014). However, others report better memory for title or performer of songs that elicit a stronger emotional response (Schulkind, Hennis, & Rubin, 1999). Here, we investigated the associative memory of participants using an explicit and implicit test. We only found significant results for the explicit task. Firstly, we were interested in assessing whether using emotional musical stimuli alone, without semantically related images, would have similar effects on associative memory as observed in previous studies. Participants required fewer rounds of training for the scary than the peaceful or sad excerpts, suggesting that they had learned better the location of the scary excerpts. Furthermore, a correlation analysis indicated that

location memory was worse at 2 h the more rounds one required in the training task. However, when participants were tested at 2 h they had worse location accuracy for the scary excerpts compared to the peaceful ones. This effect though appears to be driven by the PAPP group, which also had worse location accuracy than the APAA group. Even though both groups had different alertness levels at 2 h, we did not find a correlation between alertness and memory accuracy. Therefore, the location memory difference between the two groups at the first session could be attributed to circadian effects. Interestingly, we did not observe any more differences between the two groups or the emotional types in later sessions.

Regarding the effects of an interval of sleep or wakefulness on how location accuracy changed, we found that across both intervals, the memory of the APAA group seems to have deteriorated more than the PAPP group. This is in agreement with the results of (Talamini et al., 2008) who report that sleep benefits the consolidation of spatial associative memory, whereas after an equally long period of wake recall was worse. However, the sleep effect might be mediated by how strong the memory traces are at sleep onset. Therefore, one could argue that our finding indicates a stabilizing effect of sleep on memory; however, the PAPP group already had worse memory than the APAA group at the first session. Furthermore, we found that memory of the peaceful stimuli deteriorated compared to the scary stimuli, and this effect was likely driven by the PAPP group. However, once more, location of scary stimuli was worse than the peaceful at the first session. Therefore, the results on how the memory changed after the first session seem to be driven by the performance of the participants in the first session and not by the presence or absence of sleep.

Correlations between memory performance and arousal, valence, or likeability ratings were used to understand better the role of emotional perception on associative memory. At the first session, participants remembered worse the location of stimuli that they had rated as more arousing. This is in agreement with the results of other studies that suggest a disruptive role of arousal on the binding of associated information (Bisby & Burgess, 2014; Bisby et al., 2016; Madan, Caplan, Lau, & Fujiwara, 2012; Mather et al., 2006; Novak & Mather, 2009; Tsimpanouli, Hutchison, et al., 2017; Tsimpanouli, Elliott, et al., 2017). However, likeability seems to enhance memory, as participants remembered

better the location of stimuli they liked more. After a week, though, arousal or likeability ratings are no longer influencing the memory accuracy. Instead, valence appeared to modulate memory, as stimuli that were rated as more negative were better remembered. The interaction between arousal ratings and memory performance becomes more complicated when looking at their changes. We found that a decrease in arousal ratings across 12 h containing sleep predicted deterioration in memory accuracy. This effect appears to be significantly different in comparison to the 12 h interval of wakefulness. Thus, it is possible that even though arousal at immediate test disrupts associative memory, when is enhanced by sleep then it results in improved memory.

5.4.3 Limitations and Future Perspectives

The lack of findings on the implicit test is more likely because the task was too difficult and participants did not manage to learn successfully the colour associations. It is unlikely that there were no effects of emotion, sleep, or an interaction between them. A beneficial effect of sleep, compared to wakefulness, on both implicit and explicit memory, using though a different task, has been reported previously, (Weber, Wang, Born, & Inostroza, 2014). Whereas another study, using musical stimuli, reports stronger exposure effects on implicit memory than on explicit memory (Narme et al., 2016). Thus, we may assume that the use of a simpler implicit memory task with the same stimuli could yield significant results. Furthermore, a larger number of participants could have produced more significant and statistically stronger results, as we observed several trends in the current analysis.

Another caveat of this study is that we did not take into control for possible hormonal variations by the menstrual cycle of the participants. Evidence suggests that emotional perception (Derntl, Windischberger, et al., 2008; Derntl, Kryspin-Exner, Fernbach, Moser, & Habel, 2008; Guapo et al., 2009) and memory performance (Bayer, Schultz, Gamer, & Sommer, 2014; Genzel, Kiefer, et al., 2012) may vary across the menstrual cycle. Furthermore, there is evidence that men and women differ in perception of musical emotion (Flores-Gutiérrez et al., 2009) and spatial memory (Arce, Ramos, Guevara, & Corsi-Cabrera, 1995). Therefore, future studies should address the male population too and control for effects of the menstrual cycle.

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6. General Discussion

In this thesis, I have presented four studies exploring the role of sleep in the consolidation of memories related to emotional stimuli and in the processing of their salience. At the beginning of this thesis, most of the studies using TMR on humans were nap studies and had used neutral stimuli. Studying TMR during overnight sleep was the next logical step, as it would allow cueing items more times and would be a more natural paradigm of sleep-dependent consolidation. Another intriguing question was to investigate the effects of TMR on the consolidation and processing of emotional items. Emotion not only appears to enhance sleep-dependent consolidation but also sleep disturbances may lead to mood disorders. However, the literature also had, and still has, gaps on the interaction of sleep and emotion and the consolidation of associated memories. Therefore, these three key points guided the development of four studies. My methodology toolbox to investigate emotion, memory, and sleep included cued memory reactivation, three neuroimaging techniques, PSG, EEG, and fMRI, and behavioural measures assessing declarative memory, procedural memory, and emotional salience. The output of these studies has filled some of the gaps in the literature and raised additional important questions for future research. In this final chapter, I will initially summarise the key findings within the thesis and attempt to integrate them into a general conclusion. Then, I will discuss methodological limitations. Finally, I will outline some of the remaining questions in the field and suggest future work.

6.1 Summary of Results

In Chapter 2, we investigated cued reactivation of negative and neutral stimuli during SWS and wakefulness. Participants rated matching picture-sound pairs for arousal and valence and trained on an associative memory task. The following day, we found that cueing half of the stimuli during SWS stabilized their consolidation, regardless of valence, and enhanced arousal habituation of negative stimuli. Overall, memory accuracy was worse for the negative stimuli, which were rated as more arousing and more negative.

Chapter 3 aimed to explore the underlying neural correlates supporting the TMR effects observed in Chapter 2 and further investigate whether TMR effects would be detectable at the behavioural level after a week. We adapted the

experimental protocol of Chapter 2 in order to control for any habituation effects due to the memory-training task and to make it MRI-compatible. We did not replicate the behavioural results of the previous chapter, but we found that SWS modulated the TMR effects, increasing arousal ratings 12 h and 1 week after initial exposure for all the stimuli but the negative uncued ones. At the neural level, we found that cueing modified activity in orbitofrontal areas and insula for negative and neutral stimuli differently, increasing activation for neutral items when cued and decreasing activation for negative items when cued. SWS further modulated cueing effects on arousal. However, the TMR effects on memory of negative and neutral stimuli were modulated by REM in areas of the limbic and memory systems as well as in supplementary motor cortex.

Chapter 4 built upon the findings of Chapter 3 showing different modulation after sleep of the neural correlates of negative and neutral stimuli by TMR during SWS. We used an EEG classifier to investigate whether there is a difference in the activation of negative and neutral procedural memory traces during SWS. Although the classification accuracy and overnight behavioural improvement were similar for negative and neutral sequences, we only found correlations of classification accuracy with pre-sleep behaviour and overnight improvement for the negative sequence. Higher prior performance predicted higher classification accuracy, which in turn predicted lower overnight improvement.

Finally, the aim of Chapter 5 was to explore the effect of sleep on the consolidation of associative memory and emotional ratings, investigate the effects of training on emotional ratings, and assess the suitability of happy, peaceful, sad, and scary musical excerpts as stimuli in sleep related studies. We found that arousal and valence ratings did not change in the same way for different emotions. Furthermore, sleep appeared to stabilize valence and arousal ratings whereas wake made items more arousing and more positive. We also found a correlation of arousal ratings and memory accuracy. Finally, our results indicate that sleep might enhance memory accuracy compared to wakefulness.

6.2 Integration and Implications of the Current Findings

6.2.1 Emotion and Associative Memory

In all the studies of this thesis emotionality was not the direct target of the memory tasks but part of the context. Previous studies have shown that when

emotion is part of the context it might not enhance memory consolidation but rather impair it (Bisby & Burgess, 2014; Chiu et al., 2013; Mather, 2007; Novak & Mather, 2009; Pierce & Kensinger, 2011). Our findings confirm the latter in both declarative and procedural tasks. The results of the first two chapters unanimously show better location memory accuracy for the neutral items than the negative ones. Mather had argued that whether the effect of emotion is beneficiary or detrimental for the memory depends on the nature of the task. When learning is incidental emotional memories are better remembered (Mather & Nesmith, 2008), whereas when it is intentional and participants have multiple training rounds, as in our task, neutral pictures are better remembered (Novak & Mather, 2009). Associative memory of negative items is inferior than the neutral items because of impairments during encoding (Otani, Jaffa, Libkuman, Goernert, & Kato, 2012). Furthermore, the original item-context binding is stronger for negative items and less likely to be corrected when erroneous (Novak & Mather, 2009). Our training task results are in agreement with these observations, as the training threshold criterion was reached faster for the neutral stimuli.

Another question is whether associative memory is impaired by negative emotion or high arousal. Most studies have used only negatively stimuli, which are inherently more arousing than their neutral counterparts are. This applies for the stimuli we used in our first three studies. Therefore, in Chapter 5 we used four emotional categories of emotional stimuli that differed between them in arousal and valence. As shown in (Vieillard et al., 2008) happy and peaceful stimuli are more positive than scary and sad, and scary and happy stimuli are more arousing than peaceful and sad. At immediate testing, we found that location accuracy was worse for the scary than the peaceful items. Furthermore, we found that higher arousal correlated with higher accuracy error at 2 h whereas after a week negative valence correlated with lower accuracy error. These results suggest an interaction of valence and arousal on associative memory accuracy that might evolve across time. However, another study found enhanced memory for both negative and positive visual stimuli with high arousal (Mather & Nesmith, 2008). In another study, though, with negative, neutral and positive items, effects of arousal were non-linear (Anderson & Shimamura, 2005). However, the type of context binding might also be influencing memory impairment effects. In a between-object binding (extrinsic) context high impair-

ment was caused by arousal regardless of valence, whereas in a within-object binding (intrinsic) context impairment was observed only for high arousing negative stimuli (Mackenzie, Powell, & Donaldson, 2014). Therefore, we may conclude that whether arousal or a combination of arousal with valence is impairing associative memory depends on the type of task and stimuli used.

Furthermore, emotion in associative memory might interact with memory networks in different ways than in item memory. Indeed, negative emotion was found to down-regulate the hippocampus in an associative memory task, although it was not spatial context (Bisby et al., 2016). Simultaneously, emotion up-regulated amygdala activity resulting in enhanced item memory. Indeed, amygdala activity during encoding was associated with item and not source memory for negative and positive stimuli (Kensinger & Schacter, 2006). Furthermore, another study found that negative emotion attenuated activity in areas involved in working memory and feature integration (Mitchell et al., 2006). In our imaging results, we did not find emotion effects in amygdala, hippocampus, or any other area. However, as our design was more complicated, we found an interaction of emotion with cueing and REM duration, which will be discussed later.

6.2.2 Emotion and Procedural Memory

Regarding the emotion effects on the procedural task, we found that only after a night of sleep and extensive training response time was faster for the neutral sequence. Conversely, accuracy was higher for the negative sequence than the neutral sequence across the first training session only. As our task was not designed to detect differences between the two sequences at a behavioural level, we tentatively suggest that negative emotion may enhance accuracy, as in item memory, but may also lead to impairment of response time, as in associative memory. Further research is needed, controlling for learning strategies and the accuracy-speed trade-off effect, to determine how emotion affects performance at procedural tasks and emergence of explicit knowledge of the sequence.

6.2.3 Sleep, Emotion, Associative Memory, and TMR

In Chapter 5 our results suggest that memory accuracy got worse for the group that did not sleep immediately after the 1st session compared to the group that did. However, this difference might be driven by a baseline difference. In

Chapter 2, we found that TMR during SWS stabilized the consolidation of cued stimuli regardless of their valence. This indicates that the associative traces were enhanced equally and TMR did not alter the context-binding properties of the memories that could have differentiated memory between negative and neutral stimuli. Nevertheless, Chapter 2 results are in agreement with the literature suggesting a beneficial role of SWS in the consolidation of associative declarative memories (Lau et al., 2010). However, these behavioural results were not replicated in Chapter 3. We found though effects at the neural level, our fMRI results suggest an interaction between REM duration, cueing, and emotion on a number of areas in the limbic network, memory network, and supplementary motor cortex.

Previous imaging studies have shown that the hippocampus supports contextual details of memories (Bisby et al., 2016; Yonelinas & Ritchey, 2015) but we did not find any effects in that region. Nevertheless, we found activation of the parahippocampal areas to be modulated. The parahippocampus has also a role in contextual associations as well as in visuospatial processing and episodic memory (Aminoff, Kveraga, & Bar, 2013; Ross & Slotnick, 2008). We also observed a modulation in the activation of the precuneus, which might reflect processes of visuo-spatial imagery and episodic memory retrieval (Cavanna & Trimble, 2006). Another region was the orbitofrontal cortex, whose activation can be influenced by emotion, (Lewis et al., 2007). Furthermore, evidence suggests that it takes part in decision making processes, in collaboration with other areas such as the amygdala, insula, and somatosensory cortex (Bechara, Damasio, & Damasio, 2000). Interestingly the areas where we observed modulated activity have been shown to be activated during SWS (Dang-Vu et al., 2008). Furthermore, we observed a large cluster of modulated activity in the supplementary motor cortex, an area that is connected with and modulated by the insula and the amygdala. Thus, its modulation could reflect emotional network effects or procedural memory effects on motor learning.

Our results indicate that the BOLD signal in these areas tends to increase the more accurately people remembered the location. This was further enhanced by longer REM duration for the negative cued and neutral uncued items. Conversely, longer REM has a deleterious effect on BOLD signal for the negative uncued and neutral cued items. Therefore, we have direct evidence that associative memory traces that have been cued during SWS are further modulated by

REM, thus supporting the sequential hypothesis (Giuditta, 2014). A previous study on declarative memory consolidation has also shown that SWS and REM have complementary roles in modulating brain activity for the negative stimuli (Cairney, Durrant, Power, et al., 2014). Furthermore, similar to our findings, two studies using TMR during SWS found that the two sleep stages have distinct roles on brain activity for a procedural memory task (Cousins et al., 2016), and that REM predicted integration of learning for cued words (Tamminen et al., 2017). Other studies, though, did not find any effects on declarative or procedural memory by TMR during REM (Cordi et al., 2014; Laventure et al., 2016). However, (Groch et al., 2015) argue that REM and SWS have separate roles in emotional memory, processing of item memory and processing of contextual information, respectively.

Overall, it has been well established that SWS consolidates hippocampus-dependent memories. Conversely, there is not a consensus regarding the role of REM. Among the different proposed theories on REM there are some common recognized functions, which may depend on the consolidation level of the memories. These functions include integration of memories, processing of emotional memories, by modulating activity in the amygdala and the hippocampus, and interacting with NREM stages resulting in changes at the cortical level (Genzel et al., 2015; Hutchison & Rathore, 2015; Llewellyn & Hobson, 2015; Poe, 2017). Our results suggest that SWS and REM are synergistically modulating associative memory traces of negative and neutral stimuli at the neural level, but we cannot infer what the exact role of each sleep stage is.

6.2.4 Repeated Exposures Effect on Arousal

The results of Chapter 2 suggest that sleep promotes an arousal habituation, which is enhanced for the negative cued items. However, this change might be influenced by the training task. In Chapter 3, participants rated the stimuli after the training session. Our results suggest that arousal ratings habituated after the training task. A slight arousal habituation after repeated presentation of the same stimuli has also been reported by (Wagner et al., 2002). Although we did not find any significant changes, the post sleep ratings tended to be less arousing than the pre-training ratings but more arousing than the post-training ratings. The same trend was observed with the arousal ratings after a week. To understand better the effect of the training task to subjective arousal, in Chapter 5 we tested how arousal ratings change for four distinct emotions during

daytime and nighttime. We also assessed these ratings after 12 h, 24 h and 1 week. Interestingly, in this dataset only the arousal of the happy stimuli decreased across training, regardless of time. Furthermore, arousal ratings for both groups increased after 12 h and then remained relatively stable after another 12 h. Yet, after a week, arousal ratings increased compared to the post-training ratings, if the 1st session was in the morning, whereas they did not change if it was in the evening. Therefore, it appears that repeated exposure to the stimuli through the training task may lead to a temporary habituation, but arousal ratings bounce back up within 12 h. The role of sleep on processing of arousal is unclear within this 12 h period. Ratings after a week may give a clearer picture.

6.2.5 Sleep, Subjective Arousal, and TMR

As discussed earlier, our interpretation of the sleep effects on subjective arousal is altered by the training task. Originally, we interpreted our findings in Chapter 2 as TMR during SWS enhancing habituation of the negative stimuli, agreeing with findings of (Groch et al., 2011). However, considering a potential training-task induced habituation, we could attempt an alternative interpretation. The arousal is already habituated by the training task and TMR stabilizes this habituation for the negative cued stimuli. Conversely, arousal ratings of the other stimuli tend to recover during sleep from the training-induced habituation. Our findings in Chapter 5 also indicate that sleep may stabilize subjective arousal ratings, although we cannot tell if SWS or REM mediates the stabilization. For participants who slept after the 1st session, arousal ratings of musical stimuli did not change a week later. Whereas our results in Chapter 3 indicate that SWS predicts an increase in arousal for the neutral stimuli after 12 h, but does not affect the negative stimuli. This effect was further modulated by cueing; SWS predicted a decrease in the arousal of the uncued negative items, both after 12 h and 1 week. However, cued negative items had a tendency to become more arousing relatively to the uncued ones. Regarding the neutral items, SWS predicted a higher increase in arousal for the uncued stimuli. Other studies however have indicated a role of REM, and not SWS in the modulation of affective tone, either enhancing habituation (Gujar et al., 2011; Hutchison et al., under review; Rihm & Rasch, 2015), stabilizing (Baran et al., 2012; Groch et al., 2013), or increasing arousal (Werner et al., 2015).

Our fMRI results also suggest that cueing has different effects on the underlying neural correlates of negative and neutral stimuli. Previous studies show a role of orbitofrontal cortex in the processing of valence and of amygdala for arousal (Bensafi et al., 2002; Lewis et al., 2007; Small et al., 2003). However, in our study stimuli with negative valence also had high arousal. Higher activation in these areas for negative stimuli, as demonstrated by uncued items. However, cueing appears to decrease activation for the negative stimuli and increase it for the neutral. We also observed an interaction between SWS and cueing. SWS predicted an increase of the BOLD signal for the uncued items, but did not change significantly the cued items. Furthermore, SWS predicted an increase in activation the more arousing stimuli were rated.

It is worth discussing potential reasons that could cause the apparently contradicting results of our studies. Firstly, in Chapter 2 participants did not have a follow up session after a week. Being aware of an upcoming session, in Chapters 3 and 5, may have tagged these stimuli as future relevant and thus activated a different mechanism for their processing. Secondly, the order of the tasks might have influenced the sleep-dependent processing, as rating arousal before a retention interval may bias subsequent ratings (Groch et al., 2013). In Chapter 2 participants performed the arousal rating at the beginning of the session, in Chapter 3 right before they went to sleep, and in Chapter 5 in parallel with the memory task. Thirdly, Chapter 5 had different stimuli than the other two studies. The arousal properties of emotional musical excerpts may differ from pictures-sounds pairs.

6.2.6 Using an EEG Classifier to Detect Memory Traces of Negative and Neutral Stimuli during Cueing in SWS

In Chapters 2 and 3, our findings suggest that TMR may have different effects on negative and neutral stimuli at both the behavioural level and the underlying neural correlates. In Chapter 5, we set to investigate whether we could detect differences between negative and neutral memory traces while they are being reactivated during SWS using an EEG linear discriminant classifier. This classifier had been used before successfully to detect memory traces of a single SRTT sequence using neutral items while cueing in SWS (Belal et al., submitted). The SRTT task can elicit strong signal changes at the motor cortex areas, even during motor imagery, that are relatively easy to detect on EEG. We found that both sequences were classified accurately above chance but their

classification rate did not differ. However, the two classifiers differed on how frequently they were selecting features from different electrodes. If a single classifier was to be trained and applied on data of both sequences simultaneously, it could potentially show differences between negative and neutral stimuli during cueing.

Nevertheless, even though the classification rate did not differ between the two sequences, we found that only the pre-sleep performance and overnight improvement of the negative sequence was correlated with the classification accuracy. Furthermore, these correlations were replicating the previous findings on the single neutral sequence (Belal et al., submitted). This may suggest that processing of the negative sequence during sleep is prioritized over the neutral sequence, even though we were not able to detect any differences on the EEG traces. Differences on the memory traces and involved memory pathways between the two sequences may exist since their initial encoding and evolve across time and sleep. However, there is no prior literature examining the binding of emotional context on a motor sequence learning task. Based on the associative memory literature, as discussed earlier, emotion may disrupt context-binding learning processes in the hippocampus. Furthermore, the original emotional item-context binding may be rather strong and harder to update. If that were the case though, we would expect a correlation between behavioural measures and classifier accuracy for the neutral sequence. Another point is that the above effects usually depend on the arousal of the stimuli and probably the extensive exposure to the stimuli over 2 h habituated the perceived arousal, despite the engagement tasks.

Although we did not find any correlations with the behavioural performance for the neutral sequence CCR, we found a correlation with the duration of REM. Longer REM duration correlated with higher CCR accuracy for the neutral sequence only. When comparing this correlation of the neutral sequence to the equivalent of the negative sequence we found a significant difference. As we performed TMR throughout the night, and not only during early sleep, which is SWS-rich, our results could be interpreted as that increased presence of REM between cueing periods may result in increased response to TMR or facilitate detection of brain-activity. Further analysis of our data is required to test this hypothesis. If we confirm this hypothesis, it would provide further evidence that TMR has different effects on the processing of memories de-

pending on whether their content is negative or neutral. Additionally, this correlation between REM duration and classification accuracy of TMR during SWS may support the sequential sleep hypothesis, which proposes that SWS and REM have complementary roles in the processing of memory traces (Ambrosini & Giuditta, 2001; Giuditta, 2014; Giuditta et al., 1995).

6.3 Limitations

6.3.1 The Current Sample

Our results cannot be generalized for the whole population, as our participants were young, healthy, highly educated females in three out of the four studies. The study that included male participants, they were also healthy, young and highly educated. Sleep, memory, and emotional processing differ between males and females. For example, there are differences between the two genders in memory processing (Guillem & Mograss, 2005), memory of emotional and neutral information (Bloise & Johnson, 2007; Glaser, Mendrek, Germain, Lakis, & Lavoie, 2012), emotion effects on item and source memory (Wang & Fu, 2010a) and attention (Syrjänen & Wiens, 2013), the effect of a nap on declarative memory (Wang & Fu, 2009), (Wang & Fu, 2010a), the relationship between sleep spindles and intelligence (Ujma et al., 2014), the effects of sleep deprivation (Dai et al., 2012) and many more. Changes also occur throughout a person's life and further differences can be observed in various types of clinical populations.

6.3.2 Study of Sleep in a Laboratory

Sleeping for a first time in a foreign environment having electrodes attached on the head and face can be a stressful experience and alter the sleep quality. This has been verified by studies comparing sleep quality between two nights in a sleep laboratory and it is referred to as the "first night effect". The first night effect may cause changes in the quality of sleep, increasing awake periods, delaying the first occurrence of REM and shortening REM duration (Agnew, Webb, & Williams, 1966; Mendels & Hawkins, 1967). As we did not use an adaptation night to acclimate participants in any of the studies we recorded PSG, it is possible that our results are biased. Sleep quality may have an impact on emotional memory processing and valence ratings (Tempesta, De Gennaro, Natale, & Ferrara, 2015). Furthermore, our data may be biased by time of the year effects as their collection occurred in different periods around the year.

We were not able to control the temperature, humidity, ventilation or natural lighting in the rooms, which may also influence sleep quality.

Finally, in modern society we are continuously exposed to the electromagnetic field of our mobile phones, even while sleeping if the phone is nearby. Exposure to electromagnetic field of mobile phones before and after sleep may alter regional cerebral blood flow and sleep EEG. These changes include an increase in α frequency prior to sleep, spindle frequency range during N2, and spectral power during NREM (Borbély et al., 1999; R. Huber et al., 2002; Reto Huber et al., 2000). These changes could have an impact on sleep-dependent consolidation processes. Even though we asked participants to turn off their phones, we are not sure whether they complied.

6.3.3 Some Limitations of the Experimental Protocols and Analysis

The training session of the associative memory task in Chapters 2, 3, and 5 was long, tiresome and sometimes causing feelings of frustration and exasperation. Negative mood may impair memory of spatial context (Zlomuzica, Preusser, Totzeck, Dere, & Margraf, 2016) and thus influence the memory performance of the participants. The PANAS mood ratings were collected before the training session and before the testing session, which took place at least 40 min after the completion of the training allowing for a recovery of mood. As discussed earlier, the training task may also have interfered with the arousal ratings. Additionally, there might be order effects on both arousal and memory tasks, before and after sleep.

Furthermore, in Chapter 5 the associative memory task was rather hard and after a short pilot study, we lowered the training session requirements. However, appropriate learning levels might not have been reached, as reflected by the performance of the participants. Mean distance from the correct location in Chapter 2 was 74.22 pixels [±4.85] before sleep and 77.19 pixels [±5.22] after sleep, and in Chapter 3, it was 62.34 pixels [±2.88] before sleep, 74.99 pixels [±3.94] the next day, and 104.89 pixels [±7.23] after a week. In Chapter 5, though, the corresponding values were 334.01 pixels [±4.95] at 2 h, 329.42 pixels [±4.98] at 12 h, 331.03 [±4.77] at 24 h, and 329.73 [±4.89] at 1 week.

The setup of the SRTT sequences was adapted to meet requirements of the classifier regarding the minimum number of trials required for training, as well

as the minimum duration of a trial. These settings were not optimal to study the effects of negative stimuli on SRTT performance. Furthermore, the SRTT task and the imagery task were one hour long each, causing fatigue to participants, as demonstrated by their alertness scores.

Regarding the data analysis, multiple comparisons correction was not applied in certain cases, e.g. when conducting additional ANOVAs for each group. In addition, it is debatable whether correlations are the best way to assess certain effects.

6.3.4 Some Limitations of Current Neuroimaging Methods

Regarding the collection of fMRI data, a weakness is the limited temporal resolution of fMRI. Furthermore, there might be signal dropout and spatial distortion in ventral, temporal and prefrontal areas, even though we used dual-echo (Glover, 2011). The scanner is producing a very loud noise and participants might have not heard all of the auditory stimuli, despite wearing noise-cancelling headphones. If the picture-sound pair was not perceived as in the pre-sleep session, then this could have an impact on behavioural responses, skewing them and altering any sleep or TMR effects. To analyse the data, we used a novel methodology, MRM. MRM addresses some of the drawbacks by SPM, in regards of repeated-measures analysis, but more studies and further investigation are required to confirm its reliability. We used a complicated model for our analysis, including 1st-level parametric modulators and 2nd-level covariates, thus making hard the interpretation of our results. As fMRI does not measure directly neural activity, a change, either increase or decrease, in BOLD signal does not necessarily reflect a behaviour-associated change at the same direction; it could also be a composite result of cortical excitation and inhibition networks (Logothetis, 2008).

A drawback of EEG is its low spatial resolution. This does not impose a problem for the PSG analysis, but it limits the classifier. Furthermore, the type of electrodes, paste, etc., we used in Chapter 4 was optimized for collection of PSG data, lasting over 8 h. As a result, there was increased noise in the data, decreasing the signal to noise ratio, and thus could have a negative impact on the performance of the classifier. The placement of electrodes for Chapter 4 was focused on the parietal areas, since we used a motor task. Emotion related effects could be detectable in more frontal cortical areas, or in deeper brain

structures, e.g. the amygdala. Furthermore, the features selected by the classifier possibly were not reflective of the emotional EEG properties of the stimuli; either because of the data was not available, due to the prior limitations, or because of the nature of the linear discriminant classifier.

6.4 Future Directions

The results of this thesis raise additional questions regarding the mechanisms of emotion, memory, and sleep. Furthermore, they may serve as a stepping-stone for future studies investigating these mechanisms. Below I will suggest directions for future work in this field.

To improve the existing TMR protocols, I would suggest either using another emotional memory task that would not interfere with the arousal ratings task, or conducting separate experiments on emotional memory and emotional processing. Furthermore, it would be interesting to use TMR with a task assessing both emotional item- and context-memory to understand better the effects of emotion on emotional and memory brain networks. Additionally, cueing different emotional sub-categories, e.g. sad and scary, would elucidate any valence vs arousal effects.

A first general direction would be to repeat the studies in different populations, assessing for gender or age effects. Although most human and animal studies are usually conducted on males (Beery & Zucker, 2011; Mazure & Jones, 2015), gender is an important biological variable that can add valuable information and allow for a better interpretation and reproducibility of results (Shansky & Woolley, 2016). As discussed earlier, there is ample evidence for gender differences in sleep, memory, and emotion processes. Furthermore, sleep architecture and duration change throughout one's life. Infants spend most of their day sleeping, REM being the dominant sleep stage, and SWS has not yet fully developed (Davis, Parker, & Montgomery, 2004). Once developed, SWS reaches its maximum duration in young children (Carskadon & Dement, 2011). As children grow older, they sleep less, having less REM and SWS. In adulthood, SWS continues decreasing, as does REM percentage, whereas the percentages of N1 and N2 increase (Carskadon & Dement, 2011; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). In parallel, the learning abilities and memory demands change from infancy to old age. As people grow old their emotional memories are less depended on hippocampal-amygdala structures and more on

dorsolateral prefrontal cortex, parietal cortical, and amygdala structures (Murty et al., 2009). Furthermore, their overall memory abilities become worse and they develop a memory "positivity effect" (Carstensen & Mikels, 2005; Charles, Mather, & Carstensen, 2003; Mikels, Larkin, Reuter-Lorenz, & Carstensen, 2005; Sakaki, Nga, & Mather, 2013).

Future research on TMR could also generate new ways that might be relevant in understanding mood disorders, such as depression. Different types of depression have been associated with various sleep-related complaints and symptoms, including changes in sleep architecture (Armitage, 2007; Coble, Mcpartland, Kupfer, Spiker, & Neil, 1979; Hickie, Naismith, Robillard, Scott, & Hermens, 2013; Kupfer, 1995; Tsuno, Besset, & Ritchie, 2005). Furthermore, people with sleep disturbances are at high risk of onset, relapse, and recurrence of depression (Benca & Peterson, 2008; Holsboer-Trachsler & Seffritz, 2000). Women have two to three times higher prevalence of depression (Kessler, 2003; Marcus, Yasami, van Ommeren, Chisholm, & Saxena, 2012; K. Wilhelm, Parker, Geerligs, & Wedgwood, 2008) and gender-specific abnormalities of sleep may contribute in developing depression (Armitage & Hoffmann, 2001). Furthermore, depressed patients show a negative bias in attention and memory processes (Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Gotlib, Jonides, Buschkuehl, & Joormann, 2011; Levens & Gotlib, 2010; Murphy et al., 1999; Ridout, Astell, Reid, Glen, & Carroll, 2003), and have increased rumination (Joormann & Gotlib, 2010). Basal activity in the amygdala and prefrontal regions of depressed patients is increased compared to healthy individuals (Drevets, Price, & Furey, 2008). Interestingly, major depression disorder patients, compared to healthy controls and non-medicated patients in steady remission, have increased activity in bilateral amygdala when seeing sad faces but not for fearful ones (Arnone et al., 2012). Using TMR would allow us to better study the emotional processing and memory consolidation functions during sleep, to observe any differences in comparison to non-depressed people, and potentially to uncover new treatment pathways. Other mood disorders that could benefit from this direction of research include anxiety, phobias, and post-traumatic stress disorder.

To improve the classifier protocol, I would suggest investigating whether a different type of classifier would be more suitable in detecting differences between negative and neutral sequences. For example, support vector machines

have been shown to have superior accuracy compared to linear discriminant analysis classifiers in classifying different emotions (Bhardwaj, Gupta, Jain, Rani, & Yadav, 2015) and different types of mental tasks (Garrett, Peterson, Anderson, & Thaut, 2003), including movement imagery (Lotte, Congedo, Lécuyer, Lamarche, & Arnaldi, 2007). Alternatively, train a single classifier on items of both sequences simultaneously. In addition, combining EEG with fMRI recordings would be useful in uncovering the function of deeper brain structures, such as the hippocampus, in various sleep stages. Another option to address this question would be applying a TMR classifier on sleep data from intracranial EEG (iEEG) recordings of epilepsy patients. A single-trial iEEG classifier has been previously used successfully in detecting whether SRTT trials belong to the pre-sleep or post-sleep session (de Lucia et al., 2011). A first study should apply the TMR detecting iEEG classifier using one SRTT sequence as its protocol has significantly shorter duration, and it would be less tiresome for the patients.

Another research area that has been overlooked so far is studying the effects of emotion on procedural memory. Future experiments may assess how emotion influences encoding, binding-properties, learning, consolidation, integration, and retrieval of procedural memories. Furthermore, studying sleep-dependent music consolidation and use of emotional musical stimuli may expand our knowledge on mechanisms of sleep, emotion, and memory mechanisms as well of music therapy and its applications. Finally, repeating all of the above by applying TMR during REM would provide immense help in understanding how SWS and REM function and collaborate.

6.5 Conclusion

This PhD thesis set out to explore the mechanisms of sleep, emotion, and memory. Our results, in line with previous research, support the role of sleep in emotional processing and memory consolidation. We demonstrated that cued reactivation during SWS can influence how the brain processes arousal and consolidates emotional memory both at the behavioural and at the neural level. Interestingly, the effects of sleep on memory may differ depending on the emotional content of the memory. In addition, our results suggest that SWS and REM may be functioning synergistically in modulating memory and the attached emotions. Overall, these findings enhance our understanding of the underlying mechanisms of the emotional sleeping brain.

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sleep

that knits up the ravell'd sleave of care,

the death of each day's life,

sore labour's bath,

balm of hurt minds,

great nature's second course,

chief nourisher in life's feast

William Shakespeare, *Macbeth, Act II, sc. 2*