Aus dem Institut für Medizinische Psychologie und
Verhaltensneurobiologie der Universität Tübingen

Testing the Effects of Targeted Memory Reactivation during Rapid Eye Movement Sleep and Wakefulness on Problem-Solving

Dissertation
submitted for a doctoral degree in
medicine

at the
Faculty of Medicine
of the Eberhard Karls Universität
Tübingen

Submitted by

Valentin, Anthony St. Clair

2019

Dean: Professor Dr. I. B. Autenrieth

First Reviewer: Privatdozentin Dr. S. Diekelmann
Second Reviewer: Professor Dr. A. Bartels

Date of oral examination: 02.07.2019

Table of Contents

List of Abbreviations

AASM	American Academy of Sleep Medicine
AccDist	Recognition accuracy of stimulation distractor sounds
ANOVA	Analysis of variance
APST	Analogical Problem-Solving Test
BiOtA	Broader form of the information overlap to abstract
CorrRecSGSound	Corrected recognition accuracy of stimulation game sounds
DSpan	Digital Span Task
ECG, EKG	Electrocardiogram
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
GBQ	Gaming Background Questionnaire
GEQ	Gaming Experience Questionnaire
HNH	Hear-No Hear Task
LRP	Lateralized readiness potentials
LTP	Long-term potentiation
M	Mean
MANOVA	Multivariate analyses of variance
MDBF-A	Multidimensional Mood State Questionnaire Short-Form A
Mdn	Median
MSQ	Mental State Questionnaire
MT	Movement Time (during polysomnography)
MWU	Mann-Whitney U test
NREM	Non-rapid eye movement sleep stages
NRT	Number Reduction Task
PGO waves	Ponto-geniculo-occipital waves

PS	Practice session
PST	Problem-Solving Test
RAT	Remote Associates Test
REM Sleep	Rapid eye movement sleep stage
REM Stim	REM sleep TMR group
RRTT	Random Reaction Time Task
S1	Sleep Stage 1
S2	Sleep Stage 2
S3	Sleep Stage 3
S4	Sleep Stage 4
SD	Standard deviation
SE	Standard error
SF-A-R	Sleep Quality Questionnaire
SRTT	Serial Reaction Time Task
SSS	Stanford Sleepiness Scale
SWS	Slow wave sleep
TLPI	Training Level Performance Index
TMR	Targeted memory reactivation
TS	Testing session
TTS	Time to solve
VT	Vigilance Task
W	"Wake Stage" (during polysomnography)
Wake Stim	Activated wakefulness TMR group

1. Introduction

The idea of having to sleep on a problem to arrive at its solution is engrained into our society. When we talk to somebody about a difficult problem we cannot seem to solve, however much effort we invest into it, one common advice is to “have a night’s sleep over it”. Sleep is generally viewed as the predominant absence of consciousness and of behavioral control for a self-limited time period. This presents a stark contrast to wakefulness, when our conscious mind handles much of the information we can extract from our surroundings, which is then processed and consecutively either forgotten or retained for a later date. We are aware of some of the mechanisms and title this “thinking”. Naturally, if we perceive information, that is processed and deemed to be a problem in need of solving, we analyze its details, our memories of similar problems and their solutions, to come up with our current solution. All of this seems to require a conscious mind. Paradoxically, especially for extremely difficult problems, “sleeping on it” is claimed to be a viable alternative.

This thesis evaluates the effects of targeted memory reactivation during rapid eye movement sleep versus active wakefulness on problem-solving of a video game puzzle.

1.1. Sleep

The notion that sleep is not only the absence of consciousness but provides a multitude of beneficial effects for our body and mind, has been extensively researched throughout history. Fascinated by the basic need of sleep, modern scientists and their predecessors have come up with a large array of theories of why sleep is so important for us. Today, there still remain many unanswered questions, which will continue to entice further research about the enigma of sleep.

In sleep research it is paramount to scrutinize experiment protocols for possible confounding variables, which may skew the effects of sleep versus an equal length of wakefulness. Sleep is sensitive to changes of environment and thus, test-runs or “adaptation nights” in the laboratory are used to mitigate this “first night effect” on sleep quality and structure (Agnew Jr et al, 1966).

Comparison of subjective sleepiness between the wake and sleep condition is regularly used to evaluate possible sleep-deprivation or exhaustion. How different levels of sleepiness may affect performance in every individual study is difficult to assess. While it may seem easier, if the sleep group exhibits sleepiness and the wake group less so, the difference in alertness may impair the reliability and validity of the results.

This dilemma leads the way to time off-sets for the two groups, where the sleep group performs the experiment in the evening, sleeps throughout the night and continues in the morning, while the wake group begins in the morning, remains awake throughout the day and carries on the experiment in the evening. This creates the problem of how to circumvent interference through circadian effects. Circadian effects may include among others, sleepiness caused by exhaustion, drowsiness after awakening, varied levels of alertness and activity during different day phases. Therefore, subjective sleepiness and alertness need to be analyzed to search for circadian effects.

One strategy for minimizing the impact of circadian effects is to reduce the sleep interval to naps. Both groups start at the same time, while one group gets to nap for a defined length from minutes to a few hours, the other remains awake, and both continue at the same time with their experiment. The problem with naps versus regular night-time sleep, is that the inherent circadian rhythm may change sleep quality, quantity and architecture of subjects in the nap condition. Accordingly, it is difficult to extrapolate results of nap studies to sleep in general and night-time sleep in particular.

1.2. Sleep Monitoring

1.2.1. Electroencephalography

Invented by Hans Berger in 1924, electroencephalography (EEG) was up until then the most accurate and practical method to analyze brain activity, while impacting subjects minimally. It enabled novel approaches leading to major discoveries in neuroscience. Scientists continued development of applications to minimize the interference of sleep analysis via EEG and various supporting methods, aiming to get data as close to that of a natural setting as possible.

Assemblies of neurons generate electric field potentials and micro currents, which traverse through surrounding tissue and pass through electrodes placed on the scalp to an amplifier and are transformed by a visualization tool to a voltage reading. The signal from one EEG electrode is compared to reference electrodes, the difference in µV represented by a continuous line. Researchers further separate the output according to the frequency and direction of voltage switches into alpha (8-12 Hz), beta (12-30 Hz), gamma (>30 Hz), delta (0.5-4 Hz) and theta (4-8 Hz) waves (Buzsaki, 2006). However, at the time of writing there is no consensus on exact wave frequency band intervals. Additional signals are differentiated, such as spindles and k-complexes.

Since the neuronal signal strength is so small, even minor body activity can distort the EEG reading. For this reason, an EEG is usually conducted with accompanying electromyography (EMG) and electrooculography (EOG), the entirety called a polysomnography. The EMG electrodes are commonly positioned on both sides of the chin and record muscle tone and activity in the proximity. The EOG electrodes are for the most part positioned 1 cm outwards and 1 cm up- or downwards from the lateral canthus and record eye movement signals. The signals from EMG and EOG can then be used to filter the EEG signal to decrease noise and provide further information on the cognitive state. The smaller the voltage amplitude of the target signal, the more filtering needs to be used to be able to differentiate signal from noise. In addition to EMG and EOG other auxiliary tools can be used, like rib bands measuring breathing and electrocardiogram (EKG, or ECG) measuring heart activity.

1.2.2. Sleep Scoring

The profound research of the brain in various states of mind has resulted in electroencephalographically derived models of sleep not as one static state but dynamically changing sleep stages. These stages are characterized by a different composition of brain generated electric potentials, their frequencies, muscle tone and eye movements.

As several models of sleep stages emerged, the one by Rechtschaffen and Kales, while originally intended to be used as a base for more elaborate concepts, became the gold standard for decades of sleep research (Himanen & Hasan, 2000; Rechtschaffen, 1968). In their manual, Rechtschaffen and Kales described how to differentiate sleep stages (sleep scoring) in an EEG recording of a person asleep. First, they divided the entire recording into small chunks called epochs. Furthermore, they split “sleep” into six stages: Sleep Stage 0 or “Wake Stage” (W), Sleep Stage 1 (S1), Sleep Stage 2 (S2), Sleep Stage 3 (S3), Sleep Stage 4 (S4) and Rapid Eye Movement Sleep Stage (REM sleep). If the subject moved during one epoch more than 50% of the time, or the EEG output was too distorted by the movement, that epoch would be scored as movement time (MT). Epochs that show more than 50% alpha activity were considered as W. EEG frequencies increasingly shift from higher frequencies, like alpha, beta, sigma and theta waves, which are common for wakefulness, to more synchronous slower delta waves throughout S1 to S4 (Armitage, 1995; Rechtschaffen, 1968). In S1 less than half of an epoch exhibits alpha activity. In S4 delta waves make up more than 50% of the epoch (Armitage, 1995; Rechtschaffen, 1968).

REM sleep is characterized by low amplitude and high frequency waves, minimal muscle tone and jerking eye movements, which are eponymous for this stage and can only be found in REM sleep (Rechtschaffen, 1968). Even though the EEG of REM sleep looks more similar to W, S1 and S2, the consciousness of the sleeper is similarly limited as in S3 and S4. Since the EEG signals during REM sleep greatly differ from the continuous pattern from S1 to S4, the latter are also referred to as “non-REM sleep” (NREM) and REM sleep is also called “paradoxical sleep”. REM sleep may be further divided into tonic and phasic REM sleep. During phasic REM sleep apparent transient events like rapid eye movements are detectable on a large scale, whereas during tonic REM sleep they are not as pronounced but remain present on a subclinical level (Steriade et al, 1989).

Adaptations to the scoring method of Rechtschaffen and Kales have been made to streamline and modify the scoring process. One of these is provided by the American Academy of Sleep Medicine (AASM). In their own scoring manual, they refrain from distinguishing S3 and S4 from another and combine them to “slow wave sleep” (SWS) (Berry et al, 2016).

Sleep patterns change over the course of life. At the time of birth, babies do not have any SWS. The amount of SWS reaches its peak in puberty and drops increasingly from there on (Feinberg, 1989). As of 30 years of age, men and women age differently in their sleep patterns, which results in significantly less SWS, REM sleep and more S2 in men compared to women of the same age (Ehlers & Kupfer, 1997). A meta-analysis of 65 studies regarding sleep stage distribution in healthy subjects from age 5 to 102 has confirmed that in adults total sleep time, percentages of SWS and REM sleep decreased with age and the ratio of wake after sleep onset, S1 and S2 increased with age (Ohayon et al, 2004). Total sleep time decreased by about 10 minutes per decade of age. SWS percentage decreased about 2% per decade of age, while REM sleep percentage decrease was more evident after an age of 60. The ratio of wake after sleep onset, S1 and S2 was 5% higher for the group over 65 years of age compared to young adults (Ohayon et al, 2004).

Research on gender specific differences in sleep has shown that for young men versus women in their twenties there is no significant difference in sleep stage distribution (Dijk et al, 1989). Spectral analysis showed for most frequencies among all sleep stages a higher power density in the female group, for which sexually contingent anatomical differences like skull thickness may be responsible (Armitage, 1995; Dijk et al, 1989). In women ageing-related changes in sleep architecture are relatively stronger but compared to age-matched men, women have more total sleep time, SWS and less S2 (Ohayon et al, 2004).

Ever since sleep was divided into stages, research has aimed to find further characteristics of the stages and to identify individual functions.

The stages S1 and S2 show a comparably light sleep with significantly decreased activity in the thalamus and largely remaining activity in the cortical areas (Baars, 1988). In SWS and REM sleep the sleep is deeper, with reduced activity in the cortical areas, explaining why it is less likely to awake directly from SWS or REM sleep through threshold stimuli (Baars, 1988). During the lighter sleep stages S1 and S2 the brain is still able to process auditory input and initiate according motor responses (Kouider et al, 2014). Lateralized readiness potentials (LRP), which correlate with planning and conduction of motor activity were measured above the motor and pre-motor cortices. During a discriminatory auditory task with conditioned responses for either right or left index finger, LRP responses persisted from wakefulness throughout drowsiness, S1 and S2. With increasingly deeper sleep, LRP responses were more delayed, slowed and changed in aspect (Kouider et al, 2014).

Special sleep-stage and location-specific EEG-signals have been identified. In S2, k-complexes and sleep spindles (10-15 Hz) are encountered frequently. Sleep spindles are incited by GABAergic neurons in the thalamus which distribute their excitation to large parts of the neocortex (Diekelmann & Born, 2010). Sleep spindles may occur during SWS, accompanied by slow oscillations (0.8 Hz) and sharp-wave ripples. Slow oscillations are preferentially generated in the neocortex and synchronize neurons, which creates highly active “up-states” of depolarization and inhibited “down-states” of hyperpolarization. Sharp-wave ripples derive from the hippocampus and are associated with reactivation of memory traces. During SWS, blood concentration of cortisol reaches its minimum (Diekelmann & Born, 2010). Furthermore, SWS is accompanied by low levels of cholinergic activity in large parts of the brain, which sets it apart from all other sleep stages and wakefulness (Hasselmo, 1999). In rats, ponto-geniculo-occipital waves (PGO waves) and theta waves are characteristic signals in REM sleep, but their functions have yet to be revealed in humans (Diekelmann & Born, 2010). PGO waves may induce a broad reactivation of cortical memory representations during REM sleep (Lewis et al, 2018).

1.3. Learning and Memory

The findings in sleep research went hand in hand with those from other fields of neurosciences, especially learning and memory. Concepts about the process of remembering have always been part of philosophy and science. Before the dawn of cerebral non-invasive imaging technology and with advancements in neurobiology in the late twentieth century, the only objective measure able to detect memory was via remembering or retrieval of memories (Sara, 2000).

There are multiple theories on how our memory is structured and generated. The creation of memories starts with our perception, where the neurophysiology is well researched. Our sensory systems code incoming stimuli and forward them to the thalamus which acts as a filter. The thalamus relays data according to its properties to the appropriate higher cortical areas and from there it may continue to its applicable typing of memory, this being either the declarative - further divided into semantic and episodic memory -, the procedural or the emotional memory. From the thalamus, data can traverse into cortical areas and may become encoded in a specific loop in the neuronal networks, forming what we call memory. Generally, there is a distinction made between different types of memory. Short-term memory may store currently relevant data from seconds to hours, until the data becomes either integrated into long-term memory, possibly being remembered for a life-time, or forgotten.

Retrieval of memories is facilitated, when similar environmental sensations, like sounds, smells and objects, are present both at the time of the event and at the time of remembering (Tulving & Thomson, 1973). This suggests that during creation of a memory, ambiance is integrated into the “memory network” (Tulving & Thomson, 1973). Similarly, somatic contextual settings, e.g. hormonal milieus, can enable remembering after forgetting has occurred, possibly through influencing the memory system on a molecular level (Deweer & Sara, 1984; Sara, 2000).

Memories that share similar information are used to create associative models (schemas), which may be used to predict events in the outer world, allowing to plan ahead and adapt strategies to new obstacles (Lewis et al, 2018; Tse et al, 2007).

1.3.1. Memory Consolidation and Reconsolidation

Different approaches offer an explanation of how memories may transition from short-term to long-term memory. The consolidation theory states that after an event is encoded, the early memory requires strengthening through consolidation to endure and to be remembered. A possible mechanism for memory consolidation is repeated memory reactivation. Analyzing patterns of neuron activity in primate brains during tasks and succeeding resting periods, showed repeated memory reactivations in a coherent and temporal order, which may be the electrophysiological equivalent of memory consolidation (Hoffman & McNaughton, 2002).

The memory consolidation theory has its roots in the early twentieth century studies on retrograde amnesia in patients (Müller & Pilzecker, 1900; Sara, 2000). Later experiments on animals have shown that the shorter the interval between the encoding of a memory and a disruption of cognitive function, the more likely amnesia occurs (Müller & Pilzecker, 1900; Sara, 2000). Over time a retained memory is integrated stronger into the cortical network until it may resist an intervention causing amnesia.

Retrieval or updating of memories through integration of new information, incites a new consolidation process of the affected memories (Spear & Mueller, 1984). This “reconsolidation”, makes memories everchanging entities within the neural network (Spear & Mueller, 1984). Research has provided conflicting results on the degree that consolidation and reconsolidation are qualitatively similar on a molecular, temporal and spatial level.

Various animal experiments that were designed to target either the consolidation of new memories or the reconsolidation of existent memories using protein-synthesis inhibitors, have demonstrated similar amnestic results, indicating a qualitative similarity between the two processes (Nader, 2003). Contextual settings can increase vulnerability to amnestic interventions for a limited time (Misanin et al, 1968). This could be explained by similar molecular processes executed during encoding and retrieval (Mansuy et al, 1998). Reactivation of a consolidated memory results either in its reconsolidation or extinction, which in updating the memory requires protein synthesis on a qualitatively similar level (Nader, 2003). This may explain earlier findings that extinction (the unlearning of conditioned responses) based therapy of obsessive-compulsive disorder in 28 cases was more successful if the memory was recalled prior to electro-convulsive shock therapy (Rubin, 1976).

However, more recent attempts failed to recreate these results using pharmacological amnesic substances for traumatic related fear responses (Schiller & Phelps, 2011). Furthermore, animal experiments by a different research team concluded that extinction (the unlearning of conditioned responses) and reconsolidation rely on different molecular processes (Suzuki et al, 2004).

Thus, Alberini et al proposed a model in which consolidation and reconsolidation involve similar cellular chain reactions promoting long-term potentiation (LTP) in neurons that take part in a memory trace but may be primarily located in different regions of the brain (Alberini, 2005). In an attempt to explain contradictory findings on this topic, the authors suggested that less consolidated memories and more intense reactivation make memories more susceptible to amnesia-introducing procedures. Furthermore, they support the theory that reconsolidation, like consolidation, for different types of memory (these being of emotional, episodic or procedural nature) may rely on spatially distinct cortical areas. They conclude that reconsolidation is qualitatively different from consolidation in that it most likely involves modulation and not recreation of memory traces (Alberini, 2005). Therefore, reconsolidation may be seen as a misnomer and together with consolidation, they could be permutations of a larger process of encoding and retrieval of memories (Dudai, 2006).

The immediate and prolonged effects of memory reactivation during wakefulness suggest that reactivation per se may incorporate new types of information into preexisting memories (Gisquet-Verrier & Riccio, 2012). Being the first of a multi-step process of memory retrieval, reactivation renders the memory trace malleable, which enables the integration of new information and alleviates the accessibility of the memory. Multiple studies have shown that retention of original and updated memories after reactivation was already improved within a few minutes, which does not support the hypothesis that integrating new information into existing memory systems requires long processes of reconsolidation. Beyond that, recovery from amnesia or long-term forgetting after reactivation of the original memory was exhibited in similar short time frames and may persist for a long time (Gisquet-Verrier & Riccio, 2012; Spear & Riccio, 1994). The short-term effects of memory reactivation may be linked to the induced higher accessibility to the memories. At what point the facilitated retrieval deteriorates and becomes replaced by strengthening of the memory traces through reconsolidation is up to debate (Gisquet-Verrier & Riccio, 2012).

1.3.2. Memory and Sleep

During long days and nights of studying many students may wish for an easier method of integrating new information into their memory networks than actively and repeatedly revisit their text books. To them, being able to learn new information during sleep would be a dream come true. So far, research has shown that learning new information during sleep seems to be reserved for conditioning of automated responses only (Cox et al, 2014). Nevertheless, sleep scientists recommend that students improve their sleep schedule and quality to optimize their school performance, as sleep offers a multitude of beneficial effects to recently learned information (Ribeiro & Stickgold, 2014).

Scientists have discovered that sleep can improve the recollection of recently studied data. How sleep is connected to the process of learning and the mechanisms of memory is continuously being researched. Sleep appears to influence our memory process significantly, as supported by molecular correlates, like increased numbers of NMDA and AMPA receptors, to synaptic networks which reactivate and (re-) consolidate to become long-term potentiated and thus create long term memory of the data (Diekelmann & Born, 2010).

Findings suggest that encoding and retrieval of memories are most efficient during wakefulness and that preserving of memories (“memory consolidation”) is most effectively done during sleep (Diekelmann & Born, 2010). For declarative tasks, naps of only six minutes length versus an equal length of wakefulness were sufficient to significantly boost memory performance (Lahl et al, 2008). While various studies have shown that longer sleep periods yield larger improvements for declarative, procedural and emotional memory, they also suggest that the sleep period should take place at the latest on the day of encoding (Diekelmann & Born, 2010).

One argument why consolidation would be most effective during sleep is that during this “off-line” time, re-activations needed to stimulate LTP of memory traces are possible without conflicting and possibly confusing inputs from the present circulating at the same time (McClelland et al, 1995). Moreover, results have shown that SWS may strengthen declarative memories, procedural and emotional memory consolidation (Giuditta et al, 1995; Maquet, 2001; Poe et al, 2000). The highest improvements for all types of memories require both SWS and REM sleep to take place (Giuditta et al, 1995; Maquet, 2001; Poe et al, 2000). Declarative and procedural memories which are deemed to have (more) future relevance are profiting more from memory consolidation during sleep, indicating a selectivity of the sleep-dependent memory consolidation (Oudiette et al, 2013; Wilhelm et al, 2011). Furthermore, sleep enhances associative learning through promotion of item integration, gist extraction, false memories and rule extraction (Chatburn et al, 2014). However, for different tasks, different cortical representations were found, correlating to benefits of sleep for associative learning. This makes it difficult to postulate on the overall system for associative learning and specifically how sleep affects this system (Chatburn et al, 2014).

Animal experiments have demonstrated that throughout the neocortex the same neurons which are active during an experience tend to be active during the following session of rest (Hoffman & McNaughton, 2002). This rest can be quiet wakefulness or sleep (Hoffman & McNaughton, 2002). A functional magnetic resonance imaging (fMRI) study by Peigneux et al on healthy subjects showed that even throughout active wakefulness, memory reactivations from declarative and procedural tasks persist, measured through increased regional blood oxygen level-dependent responses (Peigneux et al, 2006). Memory traces may be further processed, as post-training activity persisted for 15 minutes in hippocampal areas and for up to 1 hour in cortical areas. In confirmation of previous results, declarative tasks involved hippocampus signal increase, and procedural tasks produced signal increases in cerebello-frontal and cerebello-striatal circuits, including the caudate nucleus. As to how similar in quantity and quality this is to the processing described in sleep studies remains unclear to the authors, as are the efficiency and extent of the reactivations compared to those in sleep (Peigneux et al, 2006).

There is no consensus whether dreams are manifestations of memory reactivations or root from an entirely separate process. However, dreaming or mentation of a completed virtual maze task was correlated with better performance in the succeeding run, indicating that dreams themselves may be recognized cognitive representations of memory reactivation and may improve sleep-dependent processing of memories further (Wamsley et al, 2010).

A concept about increased memory performance with sleep versus without sleep was proposed by Stickgold and Walter, called the “memory triage” (Stickgold & Walker, 2013). Their hypothesis tries to answer why memories are treated distinctively from each other, depending on specific qualities of these memories. According to their idea, what earlier was referred to as sleep-facilitated or -dependent memory consolidation is an active process that involves selectively improved retention as is, integration into existing memory schemes and abstraction (Stickgold & Walker, 2013). The selection processes use specific tags, e.g. a prescribed future relevance of the information or the emotional context when the memory was conceived, which seem to have a faster decay rate than the original memories themselves (Rauchs et al, 2011; Stickgold & Walker, 2013). This selectivity may be consciously incited and work through top-down feedback loops (running from the medial temporal, prefrontal and posterior parietal cortices) exhibited during sleep spindles (Wylie et al, 2007). According to Stickgold and Walter, the triage is formed by memory consolidation, “item integration” into preexisting networks and “multi-item generalization”. “Multi-item generalization” may take forms like rule extrapolation, insight and gist extraction. In their view, these different forms of sleep-facilitated memory processing may be closely linked to the different sleep stages, although up until conduction of their review, there was no clear evidence for this (Stickgold & Walker, 2013).

Information which is very adherent to an existing schema may bypass conventional hippocampus dependent memory consolidation and receive consolidation during REM sleep through a different faster consolidation circuit, including the medial prefrontal cortex (Durrant et al, 2015; Tse et al, 2007; van Kesteren et al, 2012). In a within-subject designed study, participants were asked to memorize new melodic tunes fitting into their culturally habituated musical schema (“tonal”), and tunes that did not fit the schema (“atonal”). Half of the tunes were encoded 24 hours prior to the retrieval task, and the other half 30 minutes before. Subjects spent the daytime out on their own and the night in the laboratory under polysomnography. The retrieval task presented a mixture of studied and new melodies and tested the confidence of recognition. Tonal melodies learned 24 hours prior were recalled significantly more than atonal melodies. Atonal melody recognition from both encoding sessions was significantly lower than that of consolidated tonal melodies and non-significantly different from unconsolidated tonal recollection. Power spectral analyses of the frequency bands showed significant correlation differences for central theta activity with tonal versus atonal melody recognition. Neither slow wave activity nor sleep spindles were in significant correlation to tonal tune recognition (Durrant et al, 2015). The results of these studies may be explained by the “SLIMM”-model (van Kesteren et al, 2012). SLIMM states that the medial prefrontal cortex inhibits the medial-temporal lobe which maintains hippocampus-dependent consolidation, if the neocortical memory trace exhibits enough schema-congruence (van Kesteren et al, 2012). Moreover, this type of schema-conformant consolidation appears to be REM sleep-related, if not dependent on it (Tse et al, 2011).

1.3.3. Synaptic Homeostasis versus System Consolidation?

Taking results from animal and human studies into account, Tononi et al developed the synaptic homeostasis hypothesis to explain one necessary basic function of sleep concerning the development and maintaining of memory (Tononi & Cirelli, 2006). They based it on the two-process model for sleep cycles by Borb and Achermann, which distinguishes the circadian part dependent on the suprachiasmatic nucleus and the homeostatic part which increases during wakefulness and decreases during sleep (Borb & Achermann, 1999). Tononi and Cirelli’s explanation for the homeostatic effect is based on synaptic potentiation (LTP), which reaches its maximum before sleep and its minimum at the end of sleep; SWS and sleep-dependent upregulation of factors linked to depotentiation and depression are the embodiment of this downscaling. SWS activity is directly influenced by the amount of LTP accumulated during the day. Since slow wave activity is generated by synchronous de- and repolarization of regional neurons, this depresses the synchronizing effect that LTP has on two specific connected neurons. According to the authors, this ensures efficiency and functionality of the brain, by increasing the difference in potentiation between relevant and less relevant memories. Downscaling under a certain threshold synaptic potentiation results in dismantling of those synapses, thus requiring regular potentiation to stay intact (Tononi & Cirelli, 2006). Support for their theory comes through findings from Huber et al, who have demonstrated that if a certain brain area is more engaged by a cognitive task, the same area will exhibit more slow wave activity, from Van der Werf et al, who found that suppression of SWS resulted in reduced encoding capacity and from Mander et al, showing that age-dependent reduction of sleep spindles predicts less successful encoding of new information

(Huber et al, 2004; Mander et al, 2013; Van Der Werf et al, 2009). It remains unclear whether synaptic homeostasis would sufficiently explain results of increased memory and procedural task performance after sleep compared to wakefulness. The authors state that their theory and sleep-dependent (re-) consolidation would not be mutually exclusive. However, the synaptic homeostasis hypothesis delivers one possible answer why memory encoding of new information is enhanced after sleep (Tononi & Cirelli, 2006). A computational model of the concepts of synaptic homeostasis showed how new memories may be incorporated into old ones via integration and assimilation (Hashmi et al, 2013; Tononi & Cirelli, 2014)

In response to the synaptic homeostasis hypothesis, Rasch and Born proposed the system consolidation theory, in which sleep plays a major role for memory retention (Rasch & Born, 2007). When a memory gets encoded, two separate memory traces are created. One is located in the short-term storage (for declarative memories including the hippocampus), the other in the long-term storage (neocortex). During sleep, the short-term memory loop running through the hippocampus reactivates repeatedly (e.g. in form of sharp-wave ripples), which induces consolidation of the long-term memory trace, the process called “training” and the result “system consolidation”. The reactivations take place preferentially in the early sleep half which contains more SWS (Rasch & Born, 2007). In the late sleep period, which contains more REM sleep, “synaptic consolidation” is achieved through LTP (Diekelmann & Born, 2010). In addition to consolidating a memory, this may also go through a qualitative transformation creating new explicit knowledge and insight as shown by Wagner et al and Gais et al (Gais et al, 2007; Wagner et al, 2004). Once a memory is redistributed to the long-term memory, continuous reactivation makes it decreasingly reliant on the hippocampal “training” loop (Rasch & Born, 2007). The authors refer to numerous studies implicating that sleep does have a significantly stronger effect on memory retention and gaining of insight than passive wakefulness, therefore not only a state of general depression as described by Tononi and Cirelli (Rasch & Born, 2007; Tononi & Cirelli, 2006). Rasch and Born underline the importance of temporally coordinated memory trace reactivations in SWS, which unlike during wakefulness is less likely to be disrupted and thus most important for memory consolidation in the long-term memory (Rasch & Born, 2007).

Peigneux et al stated in 2006 that memory reactivations during active wakefulness would serve as a method for updating existing memories with new data, rather than relaying them to the long-term memory (Peigneux et al, 2006). Studies using auditory or olfactory cues to reactivate associated memories of pre-sleep training experiences would support their theory. The more reactivations during sleep there could be incited, the stronger the consolidation and possible transformation of the memory would become (Peigneux et al, 2006). Rasch and Born suggest that despite the LTP-aversive milieu of SWS, reactivation may tag synapses for LTP during succeeding REM sleep or wakefulness, both states generating a LTP-friendly environment (Rasch & Born, 2007).

The sequential hypothesis of the function of sleep declares that REM sleep has to follow SWS sleep in its physiological pattern to optimize memory consolidation (Giuditta et al, 1995). Diekelmann and Born incorporated this hypothesis into the system consolidation theory to explain the consolidating effects of SWS in defiance to its “long-term depression”-harboring transmitter constellation (Diekelmann & Born, 2010). They proposed that reactivation during SWS tags specific synapses which receive LTP during REM sleep (or S2 or wakefulness) (Diekelmann & Born, 2010). These stages exhibit LTP-appropriate transmitter milieus which facilitate the consolidation of a memory (Rasch et al, 2009b). Additionally, they stressed that while LTP might be impeded in large parts of the brain during SWS, reactivated neurons might still go through LTP (Diekelmann & Born, 2010). Support comes from studies that have shown that increasing the cholinergic tone during SWS or decreasing during REM sleep impaired sleep-associated consolidation (Gais & Born, 2004; Rasch et al, 2009a). In the end, the synaptic homeostasis hypothesis and system consolidation theory may both contribute to the beneficial effect of sleep on memory (Diekelmann & Born, 2010).

Taking into account the multitude of studies demonstrating SWS-dependent reactivation of memory traces, the system consolidation theory was renamed to “active system consolidation theory”, highlighting the fact that sleep is actively promoting consolidation of memories, instead of just protecting memories from interferences (Diekelmann & Born, 2010; Feld & Diekelmann, 2015; Rasch & Born, 2013).

More research delivered evidence for both synaptic homeostasis hypothesis and active system consolidation, as presented by Almeido-Filho et al (Almeida-Filho et al, 2018). At birth, both REM sleep duration and concentration of synaptic plasticity related enzymes and gene expressions are very high. This is a possible explanation for the fast-paced development at that time. The authors propose that particularly in the first 12 hours after hippocampus-dependent encoding, REM sleep may be essential for “memory corticalization”. The latter is the transition from recent short-term hippocampus-dependent memories to remote hippocampus-independent long-term memories. Findings from both fMRI studies and cellular metabolism studies support their concept that REM sleep, through activation of enzymes and increased immediate-early gene expression inducing synaptic LTP (especially “Zif-268”, or “Egr1”), induces calcium-dependent neocortical plasticity. Memory corticalization may enhance creativity through consecutive memory trace restructuring in the cortical network (Almeida-Filho et al, 2018). Furthermore, REM sleep-dependent corticalization may not only strengthen but also promote forgetting, depending on which type of tagging occurred during preceding wakefulness and NREM sleep, referred to as the “synaptic embossing theory” (Almeida-Filho et al, 2018; Poe, 2017). “Zif-268” expression is especially high in cortical areas active during a prior novel experience and during REM sleep. Adapting the synaptic homeostasis hypothesis, Almeido-Filho et al state that SWS-dependent systemic downscaling is accompanied by specific upscaling of tagged networks either directly or during subsequent REM sleep. After training, REM sleep duration may be increased for up to 7 days. Among other popular theories, the synaptic homeostasis hypothesis and active system consolidation theory remain all the more relevant, as they start to become facets of a larger picture concerning molecular and system memory processes (Almeida-Filho et al, 2018).

Researchers have demonstrated that unlike in SWS, memory reactivations in REM sleep are less condensed and occur simultaneously for unrelated memory networks (Lewis et al, 2018). REM sleep reactivations may be induced through PGO waves, which in collaboration with high cortisol and acetylcholine levels and high expression of immediate-early genes facilitate activation and linking of associated schemas (Lewis et al, 2018).

1.4. Targeted Memory Reactivation and Selectivity of Sleep-Dependent Consolidation

Studies have shown that under certain circumstances retention of data can be improved by stimulating the brain with data-associated impulses during certain sleep stages. This concept is called targeted memory reactivation (TMR). Unlike remembering, which requires consciousness, TMR aims to reactivate memories subconsciously during wakefulness or during sleep. Functionally, TMR is similar to that of contextual cueing but is intentionally presented during creation of a memory and again during processing of the memory, instead of during retrieval as contextual cueing was used previously (Deweer & Sara, 1984; Sara, 2000; Tulving & Thomson, 1973). A study comparing patients with unilateral or bilateral hippocampal sclerosis to matched healthy subjects found that TMR of declarative memories only benefitted subjects with at least one intact hippocampus, adding to evidence that declarative memory consolidation and declarative memory TMR requires hippocampal function (Fuentemilla et al, 2013).

There are different options to reactivate a memory, the most popular in sleep science being odor and auditory. Odor has proven to be a highly potent contextual cue during declarative tasks and unlike auditory or visual cues did not interfere with sleep architecture and subjects were not aware of it after waking (Carskadon & Herz, 2004; Chu & Downes, 2002; Parker et al, 2001; Rasch et al, 2007). Odor might be more likely to induce TMR for declarative and emotional memories compared to sounds, because the olfactory system is not compromised during sleep through down-regulation of the thalamus (Schouten et al, 2017). However, audio stimuli may be a lot more specific to the associated memory. Furthermore, TMR should be using short stimuli durations to prevent habituation and if possible uncommon stimuli to prevent accidental reactivation of untargeted memories (Schouten et al, 2017).

In auditory sleep TMR, a sound stimulation is played during encoding of the data (learning) and again during sleep. Like odor, audio is a very strong contextual cue, which increases retention rate the largest, when it is played during encoding and retrieval of a memory (Smith & Vela, 2001). Since sleep is more vulnerable to audio than odor concerning arousals, sound stimulation during sleep needs to be carefully implemented (Carskadon & Herz, 2004).

Sound stimulation protocols vary greatly between studies. For some tasks it is possible to rely on previously learnt associations between a sound and an item, like “meow” and “cat”. In other cases, a new association needs to be induced between a sound and an item, or a category during the training session. This then enables it to reactivate the target memory upon presentation of the sound itself. The general assumption is that a better the cognitive connection between sound and target during training would result in a more effective TMR.

Given the inherent differences between odor and auditory stimulation, it is possible that they may be used to reveal distinct underlying processes of selectivity of sleep-dependent memory consolidation. Furthermore, they may provide different results for similar memory tasks, which could give insight on how different cortical areas affected by TMR interact with another.

1.4.1. Findings of Odor-based Targeted Memory Reactivation

Initiating a surge of TMR-based studies, Rasch et al used semi-continuous (30s on-30s off) odor cueing during one declarative, visuo-spatial memory task and one procedural finger-tapping sequence task, then reapplied this odor during either SWS, REM sleep or wakefulness (Rasch et al, 2007). The only group that benefitted from the odor stimulation was the SWS group and this only for the visuo-spatial memory task. No groups benefitted from odor stimulation in the finger-tapping sequence task (Rasch et al, 2007). As to why explicitly SWS consolidation of declarative tasks was affected by odor cueing, Rasch et al refer to the direct link between olfactory system and the hippocampus, the increased susceptibility of hippocampal reactivation during SWS and its importance for declarative memory consolidation (Rasch et al, 2007; Zelano & Sobel, 2005). Odor cueing during SWS prompted hippocampal memory reactivations, which was shown using fMRI, making this study a prime example for TMR during sleep (Rasch et al, 2007).

Odor-TMR during wakefulness and during SWS may have different effects on performance in a visuo-spatial two-dimensional object location task (Diekelmann et al, 2011). TMR during wakefulness can increase lability in a succeeding interference task, whereas TMR during SWS may increase stability in that task. The two contrary results are possibly connected to reactivation of different cortical regions detected in fMRI and different neurohumoral milieus as described previously. In the fMRI, TMR during wakefulness reactivated predominantly the right lateral prefrontal cortex, while TMR during SWS reactivated the left hippocampus, retrosplenial, temporal and additional medial frontal areas. This may support the system consolidation theory, in that the redistribution of memory traces from hippocampal circuits to cortical circuits gets promoted through memory reactivation in SWS, and this process might be actively initialized by TMR. The system consolidation during SWS would protect the reactivated memories, whereas during wakefulness the post-reactivation destabilization as seen in previous studies using amnesic agents dominates. Importantly, subjects in the sleep stimulation group were awakened before REM sleep was reached, which in the system consolidation theory might be linked to post-SWS reactivation reconsolidation of memories (Diekelmann et al, 2011). 90 minutes of SWS without TMR had a comparable consolidating effect on visuo-spatial memory as 40 minutes with odor-TMR, while 40 minutes of SWS without TMR were incapable of exhibiting a significant consolidating effect (Diekelmann et al, 2012). Throughout the nap, SWS odor-TMR of an interference visuo-spatial memory task did not impair the non-reactivated sleep-dependent consolidation of a target visuo-spatial memory task, suggesting that sleep consolidation is stronger than or insensitive to interference by TMR (Seibold et al, 2018).

In a study by Diekelmann et al, odor-TMR during SWS could improve explicit knowledge of an implicitly learned sequence in the Serial Reaction Time Task (SRTT) but only for men (Diekelmann et al, 2016). These results support previous results that SRTT procedural performance is unaffected by SWS-TMR, and that gender and menstrual cycle may affect memory consolidation (Cousins et al, 2014; Diekelmann et al, 2016; Genzel et al, 2012). However, odor-cueing, unlike auditory TMR, may not be selective enough to promote consolidation of the implicitly learned underlying sequence in the SRTT (Diekelmann et al, 2016).

Moreover, TMR using odor presentation during sleep may increase creativity in problem-solving measured by the “Unused Uses Task” as described by Guilford (Guilford, 1967; Ritter et al, 2012).

1.4.2. Findings of Auditory Targeted Memory Reactivation

Rudoy et al published a study in 2009 in which they used auditory TMR to enhance recall in a visuo-spatial memory task (Rudoy et al, 2009). Subjects were asked to memorize the exact location of 50 unique objects on a computer screen. Every time the subjects interacted with a specific object, an object-related short audio file would be played, e.g. “cat” would be accompanied by “meow”. After encoding, subjects took an approximately 75-minute nap during which white noise was presented at a steady sound pressure level. Half of the object sounds were then played in 5 second-intervals during SWS, while lowering the white noise accordingly to maintain the total sound pressure level. Retention was tested after the nap. The object location retrieval precision for the objects that were stimulated in SWS was significantly higher than for the others. Subjects were unaware of any sound stimulation having occurred during sleep and they were forced to guess which sounds were played during sleep. In a control group that was presented with the audio stimulation in wakefulness, no significant benefit in object location retrieval precision for stimulated objects was detected. This study demonstrated that memory processing during sleep can be highly specific and audio stimulation can target specific memory traces for reactivation, without necessarily disturbing sleep (Rudoy et al, 2009).

The addition of the explicitly stated variable future relevance of items to Rudoy et al’s study setup showed that “high-value” memories (as in having more future relevance) have a higher retention rate than “low-value” memories, but TMR can improve retrieval of low-value memories (Oudiette et al, 2013; Rudoy et al, 2009). Beyond that, TMR during a difficult cognitive task in wakefulness resulted in better retention of only the reactivated half of low-value memories and no conscious recognition of stimulated sounds in a later test. TMR during SWS resulted in a higher retention rate for all low-value items, associated with the categorization of items in low- and high-value during training (Oudiette et al, 2013). This discrepancy of wake stimulation and SWS stimulation may point at earlier findings of integrational properties of sleep-dependent consolidation which is able to interlink information that receives similar tags during encoding (Lau et al, 2011; Oudiette et al, 2013; Wagner et al, 2004). Furthermore, there was a significant correlation for REM sleep length with the number of forgotten low-level item locations, supporting the hypothesis that REM sleep promotes forgetting of insignificant memories. There was a significant correlation between delta power of slow waves with reactivated item retrieval, implying a correlation between SWS and reactivation triggered consolidation (Oudiette et al, 2013). SWS TMR resulted in significantly better recollection of items not highly memorized during training and for individuals who already had a high training recall accuracy (Creery et al, 2015). The optimal timing of SWS TMR is during the depolarization upstate of the slow-oscillation, which coincides with sharp-wave ripple and sleep spindle events associated with hippocampus-dependent memory consolidation (Batterink et al, 2016; Rasch & Born, 2013; Rudoy et al, 2009).

Auditory TMR during SWS exhibited beneficial results for consolidation of visuo-spatial memories with strong emotional components, as demonstrated by

Cairney et al (Cairney et al, 2014). The stronger the emotional component, and the more SWS sleep spindles were present during the nap, the better the retrieval performance. This corroborates findings that emotionally loaded memories are preferentially consolidated, even in the absence of REM sleep (Cairney et al, 2014).

Auditory TMR may improve procedural memory. Study participants learned new melodies on a virtual keyboard and were subjected auditory TMR replaying one of them during SWS during a 90-minute nap. Procedural accuracy was increased for the reactivated melody compared to a non-reactivated melody and to a new melody (Antony et al, 2012).

Replaying studied words from a foreign language during S2 and SWS resulted in better retrieval post-sleep for replayed words (Schreiner & Rasch, 2014). This correlated with more frontal negativity and slow waves and right frontal and left parietal oscillatory theta power for event-related potentials (ERP) during TMR (Schreiner & Rasch, 2014). These results were corroborated in a follow-up study (Schreiner et al, 2015). Evidence was found that during TMR in NREM sleep after presentation of a cue, there is a sensitive time frame in which additional stimuli may inhibit TMR-related memory gain (Schreiner et al, 2015).

A per-subject individually designed machine learning algorithm was able to detect auditory TMR-induced frequency band changes in S2 and SWS, which may provide an opportunity to also detect natural task-specific memory reactivations automatically (Belal et al, 2018). Using auditory TMR to reactivate a hidden sequence of a visuo-auditory conditioned SRTT, the algorithm was able to detect significantly more SWS reactivations than S2 reactivations, suggesting there are numerically more triggered memory reactivations during SWS. S2-reactivations were preferentially identified in the second half of the night (Belal et al, 2018).

Some approaches have failed to prove any beneficial effect of auditory TMR on sleep-dependent memory consolidation. Donohue and Spencer analyzed the effect of environmental sounds on retention rate of semantically unrelated word pairs (Donohue & Spencer, 2011). The semantic task differed qualitatively from earlier studies that used spatial learning tasks. The setup of audio stimulation was different from Rudoy et al in that only one “ocean”-sound was played at a steady level during the entire encoding interval and one “ocean” or “rain” sound was played during the entire sleep interval with the subjects’ knowledge in their own beds. The authors did not find any significant improvement in the group having “ocean”-sound stimulation during encoding and sleep versus the control group having “ocean”-sound stimulation during encoding and “rain”-sound stimulation during sleep. Both sleep groups performed significantly better than a control group that did not sleep in the incubation interval, showing that their semantic task was receptive to sleep-dependent consolidation (Donohue & Spencer, 2011). Possible explanations for the inefficiency of TMR in this setup may include the continuous stimulus presentation, the awareness of the stimulation before sleep and after waking, the lack of stimulus specificity to the target memories and interfering reactivations of unrelated episodic memories associated with the “ocean” sound (Schouten et al, 2017).

1.4.3. Induction of Forgetting Through Targeted Memory Reactivation

Sleep-associated retrieval gain of memories reactivated through TMR versus forgotten memories are significantly correlated with fast sleep spindles in the 13.5-15 Hz band in the left parietal cortex; the sleep spindle amount predicting higher retrieval for reactivated and lower retrieval for non-reactivated memories (Saletin et al, 2011). This suggests both active forgetting and active consolidation of appropriately “tagged” memories (Stickgold & Walker, 2013).

TMR may also promote active forgetting (Simon et al, 2017). In the first part of the experiment, subjects were presented a word list. Words were followed by either a sound indicating the word should be forgotten, or a sound indicating the previous word should be retained. In the second part of the experiment a visuospatial object-location task was performed, during which item specific sounds were presented. During the first half of SWS 5 item specific sounds were presented in alternation with the forget cue. Seven days later, comparison of the performance in the retrieval task of the reactivated items with 5 random non-reactivated items showed significantly lower recall of the objects, accuracy of object location placement and confidence rating. There was no correlation with specific sleep stages (Simon et al, 2017).

1.4.4. REM Sleep and the Selectivity of Sleep-Dependent Consolidation

The role of REM sleep in sleep-dependent consolidation is not clear. In the active system consolidation theory, REM sleep has the role of strengthening and weakening memories according to their SWS-dependent tagging (Diekelmann & Born, 2010). In line with this idea, Oudiette et al suggest that REM sleep may promote forgetting of memories with low future relevance, as seen in their study on auditory TMR of a visuo-spatial memory task (Oudiette et al, 2013).

Auditory TMR in the second half of sleep during phasic REM sleep (REM sleep stage with apparent transient events like rapid eye movements) versus Stage 2 versus no TMR, discovered that only the REM sleep TMR group exhibited increased retrieval and in addition generalization after being displayed pictures of faces (Sterpenich et al, 2014). The images depicted 120 negative and 120 neutral rated faces, and two neutral sounds were assigned to either negative or neutral to be played when these were displayed. Both sounds were used as reactivating stimuli during TMR. After TMR either during phasic REM sleep or S2 or no TMR, subjects were asked to rate a mixed set of old and new pictures as “remember”, “know” or “new” (Sterpenich et al, 2014). TMR was applied during phasic REM sleep because animal studies have shown that it may be involved in active memory processing (Datta, 2000; Sterpenich et al, 2014). Stage 2 TMR resulted in neither better recollection during the retrieval task, nor generalization and integration into associative networks, unlike REM sleep TMR. After REM sleep TMR, the incidence of new images especially ones connoted negatively being recalled as “remembered” or “known” was significantly increased, which supports the hypothesized function of REM sleep to generalize and abstract memories into existing or new associative networks (Cai et al, 2009; Sterpenich et al, 2014). fMRI examination demonstrated that the retrieval task increased activity in brain areas, such as hippocampus, precuneus and medial prefrontal and lateral superior prefrontal cortices connected to declarative memory tasks (Sterpenich et al, 2014). This indicates REM sleep-dependent processing of declarative memories (Sterpenich et al, 2014).

TMR may also be used to weaken social biases (Hu et al, 2015). Subjects' bias was measured using two implicit associations tests, one for gender and one for race, to establish their baseline bias. During an encoding task, subjects responded to counter-stereotypical pairings presented with a distinct sound for gender and race bias. Pre-nap bias was significantly reduced from baseline. One of these sounds was presented during a 90-minute nap during SWS with polysomnography and post-nap bias revealed a significant decrease only for the cued bias. One-week post-encoding bias was measured and revealed only for the cued bias a non-significant increase compared to baseline (Hu et al, 2015). This was predicted by time spent in SWS x REM sleep, suggesting that this type of memory consolidation requires sequential SWS and REM sleep, as proposed in the active system consolidation theory and sequential hypothesis (Diekelmann & Born, 2010; Giuditta et al, 1995; Hu et al, 2015).

Evidence supporting the sequential hypothesis surfaced that lexical competition between new fictional words and known words correlated with relative time spent in REM sleep (Tamminen et al, 2017). This suggests that TMR during nap in SWS may regulate memory processing during REM sleep, promoting item integration into existing vocabulary (Tamminen et al, 2017).

1.5. Research on Problem-Solving and Sleep

Within the field of neuroscience, problem-solving research is conducted by a variety of specializations. Different types of problems have been crafted to test various specific skills and cognitive capabilities. They range from intelligence, logic, orientation and mathematics to association, transfer and creativity. Not as much the solution, but the path to find the solution and the techniques that have evolved over generations and during our lifetime are of utmost interest in neuroscience. Sometimes a problem is solved instantaneously, sometimes it is solved after countless attempts and other times it is solved after having turned to other activities. For sleep science, problem-solving is of special interest, since anecdotal reports and sayings attribute an intrinsic problem-solving capability to sleep.

There are multiple ways to solve a problem, ranging from the application of a known algorithm to sudden insight. Earlier studies have shown that solving a problem through insight promotes an emotional reaction with increased activity in the amygdala and surprise (Bowden et al, 2005; Dougal & Schooler, 2007; Gick & Lockhart, 1995; Metcalfe, 1986). Furthermore, solving a problem through insight increases the probability of “discovery misattribution”, which is defined as falsely remembering to have known the solution in advance of solving the problem (Dougal & Schooler, 2007). These findings suggest that the experience of problem-solving may affect the emotional and episodic memory (Dougal & Schooler, 2007).

In a Number Reduction Task (NRT), which tests insight into a hidden rule, 8 hours of sleep after training doubled the number of insight occurrences within groups, compared to wakefulness (Wagner et al, 2004). Sleep may promote the extraction of explicit knowledge and gaining of insight through reorganization of memories. The reaction time improvement expected from repetitive tasks only occurred within the group of “non-solvers” but not in the group of “solvers”. “Solvers” refers to subjects discovering an intrinsic abstract rule, which provided participants with a faster way to solve the tasks than the one they were trained to do (Wagner et al, 2004). Furthermore, SWS-rich early night sleep promoted transformation of pre-sleep implicit rule knowledge to explicit knowledge, while REM-rich night sleep did not achieve this to a similar extent. A possible explanation is that REM-sleep can only stabilize implicit rule knowledge, not generate it (Yordanova et al, 2008).

Research on creative problem-solving has targeted the “incubation” effect (Gilhooly, 2016; Poincaré, 1910). Incubation starts after having encountered a problem and comprises moving to a different activity and possibly engaging in “unconscious work”, and ends either when a sudden insightful solution comes to mind or when the solution arises without sudden insight (Gilhooly, 2016; Poincaré, 1910). Two distinct experimental procedures have produced incubation effects. The “delayed incubation” takes place after subjects have unsuccessfully attempted solving the problem and the “immediate incubation” ensues when immediately after presentation of the problem, subjects are tasked with an incubation interference task (Gilhooly, 2016). Incubation research of creative problem-solving has largely focused on divergent problems, asking the subject for multiple possible novel solutions, and less on insight problems, which usually have a single solution. Three effects are hypothesized to contribute the incubation effect: conscious “intermittent work” during the interval, “beneficial forgetting” of fixated strategies from the earlier attempt and “unconscious work”. According to the review by Gilhooly on this subject, results from delayed and immediate incubation may only be explained in their entirety through “unconscious work”, perhaps in form of spreading cortical activation as proposed by Hélie and Sun (Gilhooly, 2016; Hélie & Sun, 2010).

For the Remote Associates Test (RAT) napping containing REM sleep improved association and integration of items over mere napping with SWS or quiet wakefulness (Cai et al, 2009). The RAT is designed to test creative problem-solving using 3 to 1-word associations. Three words which have a common word associated to them are presented to the subject and the subject needs to identify the context word (e.g. “chalkboard”, “classroom” and “book” are associated with “school”). Problem-solving was enhanced for naps containing SWS or REM sleep and quiet wakefulness only if there was pre-incubation exposure to the task. There was no better memory retention of the REM sleep nap group concerning the pre-incubation exposure, supporting the idea that problem-solving is not linked to better memory performance as described earlier by Dougal and Schooler (Cai et al, 2009; Dougal & Schooler, 2007). These results may indicate that RAT performance gains rely on REM sleep-dependent processing (Cai et al, 2009). Furthermore, more difficult associations of the RAT may require a broader spreading of activation across the neocortex to arrive at their solutions (as suggested by Ohlsson et al) and this may get facilitated through a night's sleep incubation between practice and testing sessions especially for difficult RAT problems (Ohlsson, 1992; Sio et al, 2013). However, some teams have not been able to replicate these results and presume that sleep may only strengthen memories of the training session, not creative problem-solving (Landmann et al, 2016). They state that creative problem-solving is uniquely different from conceptualization, rule learning or integration into existing schemas, in that it necessitates breaking down known algorithms and strategies and reassembling them in a new way. This does not get facilitated through sleep (Landmann et al, 2016; Landmann et al, 2014).

Sleep after solving logical problems may facilitate analogical problem-solving of new problems with low surface similarity (Monaghan et al, 2015). Subjects were presented with 6 problems before either sleep or wakefulness, which they either solved or were given the solution to, and instructed that these might be of future relevance, prior to incubation. Each of these training problems was paired with an analogous target problem, each pair having low surface similarity, and the paired problems were presented after incubation to the subjects. Solving the training problems themselves or being given the solution did not change the solution rate of target problems. The sleep group performed significantly better on target problems but neither recognition of the training problem's solution nor of similarity between the pairs was different from other groups. The authors ascribe the better performance of the sleep group to the structural generalization across all training problems promoted through active system consolidation (Monaghan et al, 2015).

Schonauer et al tested the effect of incubation napping or awake versus none on creative problem-solving capabilities of magic tricks and insight problems and found no sleep-related improvement (Schonauer et al, 2018). In their experiment neither sleep nor incubation increased the likelihood to solve a problem, suggesting that sleep may not promote creative problem-solving competence. There was no significant difference in ratio of analytical, algorithmic solutions to insight solutions between groups. They propose that incubation, which promotes spreading of activation, may not suffice to restructure the cortical representations of the problems giving way to new creative approaches (Schonauer et al, 2018).

Lewis et al proposed a “broader form of the information overlap to abstract framework” (BiOtA), which states that repeated memory reactivation promotes reorganization, integration and concentration of memory and schema representations in the cortex (Lewis et al, 2018). Initial hippocampus-dependent memory replays in NREM sleep train the first level of cortical representations. These are mostly accurate to the original and overlapping components between memories. The memory replays can induce integration, abstraction and gist extraction. In the succeeding REM sleep episode, many cortical memory representations are randomly reactivated by PGO-waves, which trains their next level of cortical representations. Memories that include overlapping schematic information train the same cortical representation of the overarching schemas. Through high expression of acetylcholine and immediate early genes (e.g. Zif-268), linking of activated cortical representations is facilitated, which leads to new associations. Repeated alternation of NREM sleep and REM sleep lead to incrementally more concentrated, schematic memory representations, which through receiving more total reactivation and potentiation may survive forgetting of the initial accurate memory and earlier cortical memories. Moreover, memory reactivation during REM sleep may be used to test the associated schemas, the best applicable strengthened most. Each reactivation cycle promotes further restructuring of memory representations, facilitating creative problem-solving. According to the BiOtA model, REM sleep memory reactivation helps to mitigate self-imposed constraints and create new associations, thus enabling strategy changes in analogical and creative problem-solving (Lewis et al, 2018).

In 2014 Beijamini et al conducted a study which showed that naps improved the likelihood to solve a video game problem (Beijamini et al, 2014). Using the video game Speedy Eggbert Mania® (EPSITEC, 1999) as test for problem-solving capability, subjects completed a 10-minute per level practice session (PS) until they ran out of time during one level. After a 90-minutes incubation interval spent either napping or in quiet wakefulness, a testing session (TS) was performed, where subjects were tasked to solve the level, they were unable to complete during the PS. There was a significant difference in solver rate between groups, with twice as many in the sleep group. In the sleep group all subjects who reached SWS during their nap solved the problem. No significant correlation could be found between problem-solving and REM sleep during the nap. The significant effect of SWS and lack thereof for REM sleep may be related to the problem configuration, requiring visuo-spatial and logical-reasoning skill to solve. The authors noted that subjects had been unaware of the second video-game session after their nap and that difficulty of the tested level in TS varied across subjects. Additionally, problem-solving rate did not correlate with participant-subjective expertise in video games (Beijamini et al, 2014). This study is of particular interest for this present thesis, as it uses the same game as a tool to test problem-solving.

1.6. Hypothesis

Analyzing previous research, this present study proposed that targeted memory reactivation via sound stimulation during REM sleep will increase the likelihood to solve a problem in a video game compared to a targeted memory reactivation during wakefulness. Moreover, it was hypothesized that there would be a difference in problem-solving capabilities, depending on the level subjects were confronted with first in the testing session, i.e. whether the testing session starts with an uncompleted level from the training session, followed by a similar new level (“Analogical Problem-Solving Test”, APST) or vice versa. Both levels of the testing session shared a low surface similarity which has been shown to increase the problem-solving capabilities for analogical logical problems (Monaghan et al, 2015). In accordance with previous research, it was expected that after targeted memory reactivation during REM sleep, subjects would solve the known level significantly more often and faster than after targeted memory reactivation during wakefulness (Lewis et al, 2018). Moreover, this study expected subjects starting with the analogical level to solve the problem-solving test significantly more often and faster than subjects starting with the problem-solving test itself, as they shared a low surface similarity.

2. Methods

2.1. Design and procedure

This study attempted to assess the role of targeted memory activation (TMR) during REM sleep versus wakefulness for problem-solving. To test this, one level of the video game Speedy Eggbert Mania® (EPSITEC, 1999) was defined as problem-solving test (PST) and subjects between ages 18 to 30 were invited to participate. Upon accepting they were allocated to two groups – the REM sleep stimulation group (REM Stim) and the Wake stimulation group (Wake Stim). Furthermore, both groups were split into two sub-groups, where one half started the testing session with the Problem-Solving Test (PST) and the other half started with an Analogical Problem-Solving Test (APST), which exhibited a low surface similarity to the PST. In both levels, subjects needed to use two characters in collaboration to solve the puzzle. Both sub-groups completed both levels.

Subjects who refused to participate in either the sleep experiment (REM Stim) or the wake experiment (Wake Stim), were allocated to the group of their preference. All other subjects were distributed randomly without preference. Upon joining this study, subjects were assigned a code, which was then used to pseudomize all documents and files processed by them.

Subjects of the REM Stim group who have never slept in a sleep laboratory, were required to have an Adaptational Night at least one week before the Experimental Night. The Adaptational Night included questionnaires about their subjective sleep quality and sleeping in the sleep laboratory with in-ear headphones and EEG, EOG and EMG electrodes monitoring their sleep. After the Adaptational Night the EEG was scanned for any indications of neurologic illnesses or sleep irregularities.

The study comprised a training and a testing session for each group, with an incubation interval with either sleep or wakefulness in between.

Preparation

The experiment started for the REM Stim at 20:30 and for the Wake Stim group at 9:20 in the sleep laboratory (for detailed schedule see Appendices Figure 4). During the training and testing sessions the lighting was the same for both groups. Upon arrival, the room and its content were presented to the subject and they were given a questionnaire about the past 24 hours to check if the preparation was as instructed. Questionnaires, control tasks and the video game instructions were presented in German. The DSpan task included English instructions.

Before the REM Stim group started the training session, they were prepared for polysomnography according to the procedure detailed in 2.5.

Training Session

The training session commenced at approximately 21:50 for the REM Stim group and at 9:20 for the Wake Stim group. Subjects were presented questionnaires assessing the mental state (Mental State Questionnaire (MSQ), see 2.6.1.), the mood state (Multidimensional Mood State Questionnaire Short-Form A (MDBF-A), see 2.6.1.) and the previous history with video games (Gaming Background Questionnaire (GBQ), see 2.6.1.) of the subjects. Completion took approximately 10 minutes.

Upon completion subjects completed a task designed to assess their short-term memory performance (Digital Span Task (DSpan), see 2.6.2.) and a task testing their vigilance via reaction time and accuracy (Vigilance Task (VT), see 2.6.2.) on a computer in their room. This step took approximately 10 minutes.

Subjective sleepiness was evaluated with a questionnaire (Stanford Sleepiness Scale (SSS), see 2.6.1.) and subjects were presented with the instructions to the video game Speedy Eggbert Mania® (EPSITEC, 1999). Subjects were given as much time as they needed to fully study the instructions. On average, subjects spent 5 minutes on this step.

Around 22:15 for the REM Stim group and 9:45 for the Wake Stim group, subjects were asked to insert headphones connected to the computer and the video game was started by the instructor. They were asked to complete five levels, these being the four training levels of the video game and the problem-solving test level. They were informed that they were on a ten-minute time limit for the problem-solving test level (PST). Subjects were unaware of the significance of the PST for this study.

Subjects who completed all four training levels and were unable to solve the PST continued with the study. Subjects who did not meet these criteria were dropped from the study.

Subjects continuing with the study were asked to complete a questionnaire assessing their game experience (Game Experience Questionnaire (GEQ), see 2.6.1.). Completion took approximately 5 minutes.

Incubation Interval

After the training session an incubation interval followed. It started at 22:50 for the REM Stim group and 10:20 for the Wake Stim group. Subjects were given a 10-minute break to use the lavatory or refresh.

Around 23:00 participants of the REM Stim group laid down in bed with taped in-ear headphones and the electrodes were connected to the EEG amplifier. Sound calibration of white noise ensued, which was then continuously presented throughout the night at 36 dB (see 2.4.). Subjects were informed that they might hear sounds during the night. Lights were switched off and subjects were left to sleep. The instructor remained in the observation room until the subjects fell asleep. Ninety minutes after the lights were extinguished, live scoring of the EEG feed and application of the TMR protocol started (see 2.4.). Eight hours after the lights went out, subjects were awakened, asked if they had slept well, electrodes and headphones were removed, and they were given time to shower. Subjects then completed a questionnaire asking for subjective evaluation of their sleep quality (Sleep Quality questionnaire (SF-A-R), see 2.6.1.)

The incubation interval of the Wake Stim group started around 10:20 with the same sound calibration task as the REM Stim group, sitting at the desk in front of the deactivated monitor.

White noise was presented through Windows Media Player using computer volume setting of 31 using the internal volume setting to achieve a white noise of 36 dB. Participants were informed that the white noise would continue in the background of the first 45 minutes of “The Lion King 2: Simba’s Pride”. After 45 minutes the movie was stopped, and subjects were given the opportunity to visit the lavatory. Upon return, they were instructed and completed a new complex vigilance task (Random Reaction Time Task (RRTT), see 2.6.2.), which would be accompanied by sounds (being the same stimulation protocol of the REM Stim group) played in the background. Completion of the RRTT took approximately 30 minutes.
After completing the RRTT, subjects were instructed how to behave during the interval. They were prohibited from consuming caffeine, alcohol, medication, drugs, doing strenuous activities like sports or sex, playing video games and napping. They left the building around 11:45 and were unsupervised until arrival at the sleep laboratory approximately 7 hours and 35 minutes after leaving. A questionnaire inquiring on how they spent the time outside of the sleep laboratory (Day Activity Questionnaire, see 2.6.1.) was completed at about 19:20, to confirm that subjects had adhered to protocol.

Testing Session

Testing session started at approximately 8:00 for the REM Stim group and at 19:25 for the Wake Stim group. Subjects completed the MSQ, MDBF-A, DSpan, VT and SSS a second time. This took ca. 15 minutes. Subjects received the video game instructions and after they were ready, headphones were inserted, and the video game started by the instructor at ca. 8:15 for REM Stim and 19:40 for Wake Stim group.

For the second video game session groups were split in two. Subjects were randomly selected to either start with the PST (Level 3 of World 3) or an entirely new level, the APST (Level 3 of World 4). In each group, 8 participants started with the PST (7 female, 1 male), and 8 with the APST (6 female, 2 male). Completion of both levels was attempted by all sub-groups. Subjects were instructed that there was no time limit for completion of these levels. After completion or resignation of both levels, subjects were presented the GEQ. This was ca. 8:55 for REM Stim and 20:20 for Wake Stim group. Next, recollection of sounds used in the TMR protocol was tested (Hear-No Hear Task (HNH, see 2.6.2.). Subjects continued with a questionnaire asking about how they thought, felt and talked about the video game between sessions (Rehearsal Questionnaire, see 2.6.1.).

Upon completion, subjects who did not solve levels during the testing session were shown the solution to those levels. The experiment concluded around 9:10 for the REM Stim group and at approximately 20:35 for the Wake Stim group.

2.2. Population

To qualify for this study subjects must be healthy non-smokers between 18 and 30 years of age, have no history of endocrine, sleep, neurological or psychiatric disorders, no history of drug or alcohol abuse, currently be under no medication other than the female contraception pill, have abstained from night shift work for at least 6 weeks prior to the experiment and be comfortable in German and basic English. Invitation was done via the circular mail service of the Eberhard Karls Universität Tübingen. In this study 50 subjects in total were recruited this way for the two groups “REM Stim” and “Wake Stim”. 24 were assigned to the REM Stim group and 26 to the Wake Stim group. For the 24 hours before and the time during the experiment alcohol, caffeine, drugs, medication other than the female contraception pill and napping were prohibited. In the night before the experiment participants were instructed to sleep no less than seven hours and not more than 9 hours. They were advised to eat a small meal before the experimental night for the REM Stim group and before each session for the Wake Stim group.

From the REM Stim group eight subjects were removed from the analysis because of solving the problem during the training session (3 subjects), thought of the solution before sleep (1 subject), being aware of the audio stimulation during sleep (2 subjects), not having enough REM sleep to get more than 70% of the audio stimulation protocol (1 subject) and not finishing the experiment (1

subject). From the Wake Stim group ten subjects were removed from the analysis because of solving the problem during the training session (4 subjects), hearing disturbing sounds during the audio stimulation (1 subject), not having the second video game session recorded due to software issues (1 subject), having sexual intercourse in between the two sessions (1 subject), failing to complete the training levels (1 subject), failing to meet the criteria of the Random Reaction Time Task during the audio stimulation (1 subject) and not hearing any video game audio during the training session (1 subject).
The data of one subject from the Wake Stim group was excluded only for the analysis of the Vigilance Task, because the task was taken twice in the first session. The rest of the data for the remaining 32 subjects entered the analysis. The average age of the included participants was 22.94 years (2.66) (Mean (SD)).

All subjects were paid for their participation according to the standard tariff of the Eberhard Karls Universität Tübingen and gave written consent prior to the Adaptational Night and or the experiment. The study was approved by the ethics committee of the university (IRB 623/2014BO2).

2.3. Problem-Solving Test: Using a Video Game as Research Tool

The video game Speedy Eggbert Mania® was used to test the problem-solving skills of subjects in one level in particular, this being Level 3 of World 3 (further referred to as PST). The game is comparable to the more popular game Sokoban (Beijamini et al, 2014). Both require logical reasoning, while minimally relying on declarative or procedural memory to complete the game. At any given time, every move and succession of moves can be reversed, providing the player with limitless attempts to start anew. In Speedy Eggbert Mania® the player controls the movement and actions of an egg-shaped character named "Blupi" by mouse to reach a floating balloon which will bring him to the next level. To reach this goal the player needs to command Blupi to interact with an assemblage of boxes by moving them directly or indirectly throughout a limited

3D scenario. As the player progresses through the scenarios, the complexity and variety of available objects increases (Beijamini et al, 2014).

The game features four different level styles (World 1-4), which depict different scenarios from lush jungles to volcanic craters with lava flowing around the center island, where the game action takes place. Each World has different ambient sounds that match the setting. Bubbling of lava, birds chirping, thunder, rain and other sounds accompany the player during the game. The playable character makes a distinct set of sounds, including moaning when pushing boxes, a sound played when the player asks for an impossible action and a sound played when the player commands the character to move to another place and running footsteps while moving to that spot. In some levels of these worlds, machinery is present, like cranes and hydraulic hammers, which make distinct sounds when “Blupi” interacts with them. Sounds may be steam release, motor sounds, high voltage sounds and others. When interacting with machinery, “Blupi” presses buttons on them, which is accompanied by a clicking sound.

The difficulty of the levels increases from World 1 to World 4 and from their individual Levels 1 to 4 (see Appendices Figure 5 for a schematic overview of the levels).

German instructions about how to play were handed out before starting the game. There all necessary information was provided, which subjects needed to solve any level. Importantly, it was stated how subjects could reverse all steps or restart at any given time in all levels.
The instructions were available to the subjects for the entirety of both video game sessions. Computer sound level was set to 31. Screen capture recording was started using the CamStudio Software version 2.7.2 (RendersoftSoftware, 2001), and the headphones inserted as soon as the game was launched by the instructor.

Training Levels

The training session started with four training levels before subjects encountered the PST. In these levels they had the opportunity to get accustomed to the game and its mechanics. In the first level (Level 1 World 1) “Blupi” must push a box into a mine, upon which the latter detonates and frees the path to the first balloon. In the second level (Level 1 World 2) “Blupi” needs to build a bridge using all three available boxes to reach the second balloon. In the third level (Level 1 World 3) subjects had to use “Blupi” to interact with a crane, a tool through which they could indirectly move boxes from one spot to another, for the first time. The crane has only a limited amount of actions available, which are predetermined by the current level. Once those actions are used up, the crane breaks and subjects must either complete the puzzle without it or reverse their steps. Similarly, the fourth level (Level 2 World 3) required participants to use the crane to loosen up a large clump of boxes, so they could use them to build a bridge to the goal. The training levels were necessary, so subjects were aware of the limitations of the crane, the boxes and the character and the possibility to reverse their actions.

Levels of Advice

If certain check points were reached, the instructor gave advice to the subjects which helped them to finish all four training levels. For the training levels the following procedure was used when a subject was unable to finish them in a certain time limit: After 20 minutes in level 1 of World 1, subjects were given the hint that they needed to use the box to remove the obstacle to complete the level (1 subject). After 20 minutes in level 1 of World 2, subjects were given the hint that they should try to move the boxes in a way they have not tried before (1 subject). After 10 minutes in level 1 of World 3, subjects were shown where the “Restart” option was located (10 subjects) and after 20 minutes subjects were told how to interact with the crane (1 subject).

Problem-solving Test

The key problem of the experiment was a specific level of the video game Speedy Eggbert Mania®. The solution of this level was only possible by having a new idea similar to a sudden insight or by extrapolating the known mechanics and transferring them to the new puzzle. For this study, both paths were considered to be characteristic for problem-solving. Theoretically, it is possible that the solution is found by accident, however none of the solvers reported that they have done so.

The training session ended with the PST (Level 3 World 3), in which subjects only had 10 minutes to complete the puzzle before the instructor would interrupt and abort the game. In this level, subjects could access two “Blupis” at the same time and to solve the puzzle, both needed to reach one of two blue balloons. The solution to this puzzle is multi-staged with the key point being that subjects must use one of the characters to pick up the other character with the crane. Once subjects had this figured out, the rest of the solution was not different from the training levels. The level included a box, which could never be used to reach the goal but served as a distractor. Upon interruption after the 10-minute mark, screen recording was stopped, and subjects were informed that they would have another chance at solving this level in the second session.

Video Game Testing Session

Subjects were told that unlike in the first session, there was no time limit this time, and as soon as they finished their starting level, they were supposed to play the other level. This was level 3 of World 4 for those who started with level 3 of World 3 and vice versa. Subjects who were able to solve the PST in the second session are “solvers”, those who failed “non-solvers”.

The APST (Level 3 World 4) features two “Blupis” as well, which in order to both reach the balloon must be used in coordination with one another by the player. However, this level does not require the player to operate a tool on another character, even though it is technically possible. Subjects were not tempted to try this, since once both characters were on the same side, no interaction with objects was necessary to complete the puzzle.

For the testing session the following procedure was used, if a subject was unable to solve one or both levels. If a subject was playing for 40 minutes in a level, they were asked by the instructor whether they wanted to give up (which at this point all did), and if applicable play the second level (level 3 of World 3 (4 subjects), level 3 of World 4 (1 subject)). If before the 40-minute time mark a subject asked, if they could give up the current level, they were told that they still had time to complete the level or could give up, if they did not want to continue (level 3 of World 3 (13 subjects), level 3 of World 4 (1 subject)).

2.4. Auditory Targeted Memory Reactivation during REM Sleep or Wakefulness

Both groups received the same auditory targeted memory reactivation protocol. It consisted of a constant chain of 22 one-second sound tracks, starting and finishing with one of two cues. The cues were bell sounds, which were not encountered during any other part of the experiment, until the Hear-No Hear task. The enveloped 20 sounds were taken directly from the PST level. These audio snippets were from an audio recording of the solution to the puzzle in the shortest possible way. Sounds of bubbling lava, steam sounds by the crane, running footsteps, “Blupi” moaning when pushing buttons, mechanic and high-voltage sounds of the crane moving, “Blupi” moaning when pushing boxes and “Blupi” celebrating to have reached the balloon that takes him to the next level. The audio chain was repeated for 10 times and ended with the finish cue of the last chain after around 22 minutes.

Before any TMR occurred, a sound calibration task was performed, whereby computer sound level was adjusted to 1 and using an E-Prime audio calibration protocol subjects were presented with white noise. If the subjects could not hear the white noise at the lowest computer volume setting, it was increased by increments of 1 and the E-Prime task repeated until they could hear the white noise. In the REM Stim group, after the sound calibration, computer volume was set to a value between 4 and 10 and the white noise was then played by Windows Media Player adapted internal volume settings for the entire night, creating 36 dB white noise. As soon as the REM sleep stage was detected, the audio stimulation protocol was started and stopped whenever the sleep stage changed, a motor or EEG arousal occurred. For a successful stimulation 70% needed to be completed within the REM sleep stage. The audio stimulation protocol run via E-Prime stimulated at a volume between 47.55 dB and 60.12 dB on top of the white noise played at 36 dB.

As the participants of the Wake Stim group were instructed about the Random Reaction Time Task (RRTT), they were informed that the task would be accompanied by sounds (being the same stimulation protocol of the REM Stim group) played in the background. Subjects were reminded that it was of utmost importance to perform well in the RRTT. Throughout the RRTT, sound stimulation was played with computer sound level 6 to 7, accompanied with white noise at varying internal volume settings in Windows Media Player with a sound pressure level of 36 dB. Stimulation was presented only during the RRTT runs, not in the 30 second breaks in between at 54.79 to 56.40 dB.

2.5. Sleep Recording and Staging

For the REM Stim group 16 electrodes in total were used to monitor the subjects' sleep. Nine EEG electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4), two reference electrodes on the mastoids, two EOG electrodes (caudolateral of the left and craniolateral of the right eye), two EMG electrodes (above the mental foramen) and one ground electrode in the center of the forehead were applied according to standard procedure using the 10/20 positioning system (Jasper, 1958). It was ensured that all impedances were less than 5 kΩ, using a manual impedance measurement device (Mini-Imp by TEMEC Instruments B.V.). Before the sleep interval, impedances were checked via BrainVision software (BrainProducts, 2000) to be below 5 kΩ for every electrode.

Total number of EEG channels was 13. The sampling rate was set at 200 Hz with sampling intervals of 5 ms. The EEG amplifier used was the BrainVision BrainAmp. Before lights were turned off, white noise was started and applied via headphones. Scoring was done live using the system of Rechtschaffen and Kales (Rechtschaffen, 1968). Sleep stages S3 and S4 were scored as SWS as in the AASM guidelines for 30-second epochs (Berry et al, 2016). Eight hours after the subjects were left to sleep, the white noise was stopped, they were awakened by the instructor. Post-experiment, all polysomnography data was processed in BrainVision Analyzer® (BrainProducts, 2015) to obtain better data visualization for sleep scoring. Processing ensued according to criteria of the Rechtschaffen & Kales manual (Rechtschaffen, 1968). The two EOG channels were interpolated and together with EMG, C3 and C4 EEG channels used for scoring. If C3 and C4 both malfunctioned during longer periods of sleep, all EEG channels were enabled for scoring. Data of EEG and interpolated EOG channels was filtered by applying a low cutoff of 1 Hz and a high cutoff of 35 Hz. EMG data was filtered with 0.03 Hz as low cutoff and 90 Hz as high cutoff. A notch filter of 50 Hz was enabled for all channels. No cutting of the polysomnographic data was performed.

Offline rescoring was performed without knowledge of when stimulation had occurred by two independent persons manually using the unpublished, non-commercial sleep scoring software SchlafAus Version 1.5.0.1 (Gais, 2000). According to the procedure described above, epoch-by-epoch visual-stage scoring was performed by two persons trained at better than 80 % agreement. The sleep latency was defined as the time until the first S1-epoch that was followed by a S2-epoch.

2.6. Control variables

This study used questionnaires, cognitive tasks, sound calibration tasks and sleep monitoring to extensively search for any confounding variables that might conceal or alter the association between TMR and the solution of the posed problem.

2.6.1. Questionnaires

All questionnaires were presented to the subjects in their German versions.

Subject Data Questionnaire

This custom-built questionnaire (Institute for Medical Psychology and Behavioral Neurobiology, Tübingen, unpublished) was used to precisely determine the population of participants. Subjects were asked about their age, gender, vision aids, smoking habits, right- or left-handedness and occupation or specialization. Furthermore, the state of the subjects that day was assessed, allowing free text answers for health, medication or drugs, their last alcoholic or caffeinated beverage, abnormal stress and night shift during the past six weeks. To analyze their sleeping habits, questions regarding their regular as well as their last bedtime, their amount of sleep, their wake-up time and day time sleep were presented. To determine possible effects of being accustomed to the setting, subjects were asked whether they had participated in any sleep associated studies prior to joining ours.

Mental State Questionnaire (MSQ)

In this custom-built questionnaire (Institute for Medical Psychology and Behavioral Neurobiology, Tübingen, unpublished), subjects were asked to rate how activated, strained, tired, motivated and concentrated they were on a 5-level Likert-type scale, where the very left equaled not at all and the very right equaled very much. This was used to check whether the current mood of the subjects affected their performance in the experiment.

Abbreviated Multidimensional Mood State Questionnaire (MDBF-A)

Subjects answered a short form of the German version of the Multidimensional Mood Questionnaire (Steyer et al, 1994). The participants expressed how content, rested, restless, bad, worn-out, composed, tired, great, uneasy, energetic, uncomfortable and relaxed they felt on a scale from 1 to 5, where 1 equaled not at all and 5 very much. These items were then processed according to the scoring protocol to generate values of the individual spectrums of good-bad, awake-tired and calm-nervous. This resulted with one value for each spectrum ranging from 4 to 20, where the high end of the spectrum represented positive values “good mood”, “alert” and “calm”, 12 being neutral and 4 represented “bad mood”, “tired” and “nervous”.

Gaming Background Questionnaire (GBQ)

This questionnaire, custom-built for this study by Felipe Beijamini (Institute for Medical Psychology and Behavioral Neurobiology, Tübingen, unpublished), aimed at discovering the prior experiences subjects had with video games. Subjects were asked about having played a video game before, starting age, frequency, weekly amount and their top three video game genres for a list of 24 items (action, fighting, first person shooters, role-playing games, massive multiplayer online role-playing games, flight simulators, race simulators, sports games, military games, space simulators, strategy games, strategic war games, real-time strategy games, god simulators, economic simulation/build-up strategy games, adventure games, arcade games, maze games, music games, pinball, platformers, puzzle games, third-person shooters and survival games). Subjects were obligated to fill out their top three, even if they have never played any of these genres. In this case, they were asked to rank by sympathy towards any of the genres. For analysis top 1 picks received 3 points, top 2 picks 2 points and top 3 picks 1 point. All non-picked genres were given 0 points.

Stanford Sleepiness Scale (SSS)

This questionnaire (Hoddes et al, 1972; Hoddes et al, 1973) examined the sleepiness of participants in the training and testing session before they started their video game session. On a scale of 1 to X (being the eighth level) they were asked to rate their sleepiness. Each item had a subjective statement associated, ranging from “I feel activated, vitalized, attentive and wide awake” to “Sleeping”.

Game Experience Questionnaire Core Module and Post Game Module (GEQ)

The GEQ (IJsselsteijn et al, 2013) allowed participants to evaluate their experience during the video game. They were asked to rate 50 subjective statements with 0-4, where 0 equaled not at all and 4 equaled absolutely. All items were processed according to the scoring protocol to generate values for the overarching attributes of “competence”, “sensory and imaginative immersion”, “flow”, “tension/annoyance”, “challenge”, “negative affect”, “positive affect”, “positive experience”, “negative experience”, “tiredness” and “returning to reality” (IJsselsteijn et al, 2013). All item values associated to the same attribute were then averaged to result in the final value of each attribute ranging from 0 to 4.

Sleep Quality Questionnaire (SF-A-R)

The SF-A-R (Görtelmeyer, 1985) returns the subjective assessment of the subjects' sleep by giving them ample possibilities to characterize it, while still providing some rating scales which can be statistically analyzed. It included questions about the time to fall asleep, image intrusions, muscle twitching, waking up during the sleep interval, dreaming, sweating, post-sleep headache and exhaustion from the prior day. Subjects of the REM Stim group were given the possibility to assess their sleep quality by rating their sleep from 1 being "very much" to 5 being "not at all" concerning how even, deep, well, relaxed, undisturbed, smooth and ample it was. They assessed their pre-sleep mood by how carefree, exhausted, in need of sleep, overstrained, even-tempered, calm, tired and relaxed they had felt on a scale from 1 being "very much" to 5 being "not at all". Participants rated their post-sleep mood by how even-tempered, drowsy, energetic, eager, alerted, refreshed, well-rested and relaxed they felt.

Day Activities Questionnaire

This questionnaire, specifically designed for this study by Felipe Beijamini and Susanne Diekelmann (Institute for Medical Psychology and Behavioral Neurobiology, Tübingen, unpublished), was completed by the Wake Stim group at the end of their incubation interval. It was specifically designed to confirm that subjects adhered to the study protocol during their time away from the laboratory. They were to answer whether during their absence from the sleep laboratory they had consumed alcoholic or caffeinated beverages, napped, performed sports or similar strenuous activities or played any video games. Additionally, they could recount in short form what their activities during the early and late afternoon had been.

Rehearsal Questionnaire

This questionnaire, specifically drafted for this study by Felipe Beijamini and Susanne Diekelmann (Institute for Medical Psychology and Behavioral Neurobiology, Tübingen, unpublished), helped to determine how subjects have actively reflected their first session video game experience until their second session. It was inquired whether they thought about the game or talked to somebody about the game. Additionally, subjects could specify how much on a scale from 1 to 5 (with 1 being not at all and 5 being very much) they thought about the game generally, by excitement or frustration, its solution, their frustration, any previously undiscovered abilities of the character, or a hidden solution, their feelings, their mistakes or whether they did not think at all about the game during this time frame.

2.6.2. Cognitive Tasks

Digit Span Task (DSpan)

The Digit Span Task (Mueller, 2011b) required to remember a non-repeating sequence of three to ten non-repeating digits (0-9). It was operated through PEBL Version 0.14, a GPL-licensed psychology software for coding and conducting experiments (Mueller; PEBL, 2010). Short-term memory performance was tested. Subjects who did not manage to repeat a five-digit sequence successfully would have been excluded from the experiment (0 subjects). Subjects who skipped the instructions and failed to repeat the five-digit sequence could repeat the task and were included in the experiment, if they could repeat the five-digit sequence. The test data of the DSpan Task was then omitted for the statistical analysis (1 subject).

Vigilance Task (VT)

The Vigilance task used by this study, derives from the Visual Reaction Time task by Dinges and Powell (Dinges & Powell, 1985) and tested the alertness of subjects as an objective control task. For five minutes subjects reacted to a red dot appearing on the left or right side of the monitor with two corresponding keys X or M as fast as possible. Subjects were asked to aim for a reaction time faster than 500 ms. If the wrong key was hit the message “False” appeared on screen. Time between appearances of the sign was 2, 4, 6, 8 or 10 seconds in a random order. Instruction was given to keep the left and right index finger always on top of the keys. Reaction times of more than 1000 ms were excluded from the analysis. This task was run via E-Prime version 2.0.10.242. E-Prime is a software which provides the means to code and design a behavioral experiment. It is distributed by Psychology Software Tools (Schneider et al, 2002).

Random Reaction Time Task

Using the PEBL software, the integrated variation of the four-choice response time task (Mueller, 2011a) was customized, to ensure the Wake Stim group would not be paying attention to the sound stimulation presented during this task via in-ear headphones.
It featured a white crosshair appearing on the four quadrants of their screen. Each quadrant had a key assigned to it, these being “F”, “J”, “V” and “N”. The task consisted of 5 runs with 500 crosses each. Between runs, 30-second pauses were given, during which subjects had time to see a summary of their performance of their last run with average accuracy and reaction time. During the task there was no indication whether the right or wrong key was pressed. The cross would remain on screen until the first key press was detected. 200 ms later the cross would reappear again in any quadrant. Subjects were instructed to remain below 500 ms average reaction time and above 80% accuracy in each run, or they would fail the task and the experiment would be terminated. They were recommended to aim for less than 450 ms average reaction time and more than 85% accuracy.

Hear-No Hear Task (HNH)

Via an E-Prime executable, which was specifically designed for this study by Felipe Beijamini, 33 sounds were presented through headphones to the subject, who needed to choose or guess, whether they remembered the sound from the interval between video game sessions, or not. From the 33 sounds 31 were taken out of the video game. 20 of them had been presented during the stimulation and 11 distractors had not been. The remaining two sounds were not related to the video game but cues of start and end of one audio stimulation cycle. This task helped to show whether subjects were aware of the stimulation or not. The distractors and cue sounds helped to differentiate between memory of video game sounds and audio stimulation.

2.7. Statistical Analysis

The study setup provided a vast number of variables, which were analyzed thoroughly via SPSS 23.0.0.2 64-bit version (IBM, 2015) using the following methods.

Problem-Solving Test Performance

The solving speed in seconds of the PST between solvers of REM Stim and Wake Stim groups and between PST solvers starting with the PST and subjects starting with the APST were compared using a univariate 2 x 2 ANOVA with condition (REM Stim versus Wake Stim) and balancing (PST first or APST first) as between-subject factors. The solving speed in seconds of the APST in the testing session (Analogical Problem Solving Test, APST) between APST-solvers of REM Stim and Wake Stim groups and between APST-solvers starting with the PST and subjects starting with the APST were compared using a univariate 2 x 2 ANOVA with condition (REM Stim versus Wake Stim) and balancing (PST first or APST first) as between-subject factors.

The rate of solvers versus non-solvers was compared between REM Stim and Wake Stim groups with a chi-square test. Furthermore, a three-way cross-tab chi-square statistic was used, with condition (REM Stim versus Wake Stim) as control variable, and balancing (PST first or APST first) and PST solving as variables.

To test if the procedure for helping subjects during the video game training session according to the specific check points presented in 2.5 predicted a higher ratio of solving the PST, chi-square tests were performed on all individual help given by the operator and whether the PST was solved or not. Furthermore, a four-way cross-tab chi-square statistic was performed, with balancing as control variable 1, condition as control variable 2, with the individual help procedures and PST solving as variables, This analysis assessed whether the advice procedure affected subjects differently, depending on whether they were subject to a different protocol (condition) and whether they had started with the PST or not in the testing session (balancing).

Video Game Training Level Performance

To assess whether a good performance in the training session predicted problem-solving of the PST, the training level performance index (TLPI) was calculated, comparing the individual time to solve (TTS) to the mean solving time of each of the four training levels (TTS1-TTS4).

$$TLPI_x = \frac{1}{\left(\left(\frac{TTS1_x}{Mean(TTS1)}\right) + \left(\frac{TTS2_x}{Mean(TTS2)}\right) + \left(\frac{TTS3_x}{Mean(TTS3)}\right) + \left(\frac{TTS4_x}{Mean(TTS4)}\right)\right)}$$

Comparison of the TLPI between “solvers” and “non-solvers” (PST solving) of REM Stim and Wake Stim (condition) ensued by using a univariate ANOVA with condition and PST solving as between-subject variables.

Hear-No Hear Task

Analysis of the data from the HNH-task for bias of the corrected recognition accuracy of stimulation game sounds (“CorrRecSGSound”) was performed. CorrRecSGSound was calculated by subtracting the false alarm rate (“1-$AccDist_x$”) from the recognition accuracy of stimulation game sounds (“AccGS).

$$CorrRecSGSound_x = (AccGS_x - (1 - AccDist_x)$$

The corrected recognition accuracy of stimulation game sounds was analyzed with a univariate ANOVA with condition (REM Stim versus Wake Stim) and “solving” (solvers versus non-solvers) as between-subject factors (see exact description 2.3) from all groups. Accuracy for non-game stimulation sounds was not examined, since there were no non-game sound distractors presented during the HNH-task.

Sleep Scoring

Sleep stage length and number of arousals were compared between the solvers and non-solvers in the REM Stim group with an independent t-test. The same comparison with another independent t-test ensued between subjects who had participated in a sleep study prior to this one and those who had not. This was to check whether adaptation to the setting of sleep experiments in general lead to a more normal sleep pattern.

Subject Data Questionnaire

From the data from the Subject Data Questionnaire, a chi-square test was performed, analyzing the gender distribution and prior participation in a sleep study between the REM Stim and Wake Stim group to check for bias. Data was examined for a possible bias for age, usual amount of sleep and amount of sleep last night between the REM Stim and Wake Stim group with an independent t-test.

Mental State Questionnaire (MSQ)

To test for significant mental state differences between REM Stim versus Wake Stim groups as well as morning versus evening sessions, two repeated measures multivariate analyses of variance (MANOVA) tests on the data generated by the questionnaire were run. A 2 x 2 MANOVA with Condition (REM Stim versus Wake Stim) as between-subject factor and Run (training versus testing session) and a 2 x 2 MANOVA with Condition as between-subject factor and Time (morning versus evening session) as within-subject factor were conducted. Dependent variables were “Activated”, “Strained”, “Tired”, “Motivated” and “Concentrated”.

Abbreviated Multidimensional Mood State Questionnaire (MDBF-A)

Examining possible significant between-group differences of subject mood states for REM Stim vs Wake stim groups and morning versus evening sessions, two repeated measures MANOVA tests on the scored MDBF-A questionnaires were performed. A 2 x 2 MANOVA with Condition (REM Stim versus Wake Stim) as between-subject factor and Run (training versus testing session) and a 2 x 2 MANOVA with Condition as between-subject factor and Time (morning versus evening session) as within-subject factor were conducted. Dependent variables were “Good mood – Bad mood”, “Alert – Tired”, and “Calm – Nervous”.

Gaming Background Questionnaire (GBQ)

Balancing of habitual gamers and no-gamers between groups was checked. No-gamers were removed from the analysis of this questionnaire. Starting age to play video games provided by the GBQ between REM Stim and Wake Stim groups was analyzed with an independent t-test. The video game genre preferences, frequency of playing and amount of playing of REM Stim and Wake Stim groups was analyzed using a Mann-Whitney U test (MWU). Furthermore, a correlation of TLPI with video gaming starting age was tested with Pearson’s r. A correlation of TLPI with frequency and with amount of playing per week was tested using Spearman’s r.

Stanford Sleepiness Scale (SSS)

The possible bias between the REM Stim and Wake Stim group concerning the pre-test sleepiness taken from the SSS questionnaire was tested with a repeated measures ANOVA. A 2 x 2 ANOVA with Condition (REM Stim versus Wake Stim) as between-subject factor and Run (training versus testing session) and a 2 x 2 ANOVA with Condition as between-subject factor and Time (morning versus evening session) as within-subject factor were conducted.

Game Experience Questionnaire Core Module and Post Game Module (GEQ)

A 2 x 2 x 2 MANOVA with Condition (REM Stim versus Wake Stim) and Solving (PST solvers versus non-solvers) as between-subject factors and Run (training versus testing session) as within-subject factor was conducted. Dependent variables were “Competence”, “Sensory and Imaginative Immersion”, “Flow”, “Tension/Annoyance”, “Challenge”, “Negative Affect”, “Positive Affect”, “Positive Experience”, “Negative Experience”, “Tired” and “Returning to Reality”.

There was no test for circadian differences between morning and evening sessions performed, because GEQ scores are sensitive to having successful or unsuccessful experiences in the video game, which would overlay any circadian effects that might be suspected.

Sleep Quality Questionnaire (SF-A-R)

Two analyses of the data generated by this questionnaire were performed, one for between-group differences between solvers versus non-solvers and one for subjects with prior sleep-study experience versus first-timers of the REM Stim group. A chi-square test was used to determine whether subjects remembered having sudden image flashes before falling asleep. Moreover, a Mann-Whitney U test was run, comparing whether subjects fell asleep immediately, whether they remembered dreaming, the amounts of muscle twitching, awakenings and sweating while asleep, how much head ache they had in the morning and how exhausting the evening session was. For the subjective assessed length of the four longest awakenings, if applicable, and the sleep quality variables, as well as the pre-sleep and post-sleep mood rated by the subjects themselves in several qualities, an independent t-test was used for analysis. The subjective assessment of the time delay until sleep was correlated to the sleep onset as scored in polysomnography using Spearman's correlation r_S.

Day Activities Questionnaire

No statistical evaluation of data from the Day Activities Questionnaire was performed, as its purpose was to corroborate that subjects conformed to study protocol during their time away from the laboratory.

Rehearsal Questionnaire

The data of the Rehearsal Questionnaire concerning whether subjects had thought about the game after playing and whether they had talked to anyone about the game was analyzed using a three-way chi-square test. Condition (REM Stim versus Wake Stim) was set as control variable and thinking and talking about the game were compared to PST solving.

Additionally, a 2 x 2 MANOVA with Condition (REM Stim versus Wake Stim) and Solving (PST solvers versus non-solvers) as between-subject factors was conducted to analyze how much subjects thought about the game generally, by excitement or frustration, its solution, their frustration, any by them yet undiscovered abilities of the character, or a hidden solution, their feelings, their mistakes or whether they did not think at all about the game during this time window.

Digit Span Task (DSpan)

From the data gathered by the DSpan task using two ANOVA tests, possible bias was checked in REM Stim versus Wake Stim groups and morning versus evening session concerning the pre-video game session memory span. A 2 x 2 MANOVA with Condition (REM Stim versus Wake Stim) as between-subject factor and Run (training versus testing session) and a 2 x 2 MANOVA with Condition as between-subject factor and Time (morning versus evening session) as within-subject factor were conducted. Repeated measure was “Memory Span”.

Vigilance Task (VT)

Data from the VT was tested using two ANOVA tests, to assess possible bias in REM Stim versus Wake Stim groups and morning versus evening session concerning the pre-video game mean reaction time. A 2 x 2 MANOVA with Condition (REM Stim versus Wake Stim) as between-subject factor and Run (training versus testing session) and a 2 x 2 MANOVA with Condition as between-subject factor and Time (morning versus evening session) as within-subject factor were conducted. Repeated measure was “Mean Reaction Time”.

Random Reaction Time Task

Performance differences in the Wake Stim group between solvers and non-solvers concerning their mean reaction time and mean accuracy during the RRTT were tested by using an independent t-test.

3. Results

3.1. Analysis of the Problem-Solving Test (PST)

A chi-square test was performed to compare solving rate between Wake Stim and REM Stim groups (Figure 1). There were no differences in solving rate between conditions (Pearson chi-square $\chi^2(1, N = 32) = 1.13$, $p = 0.29$).

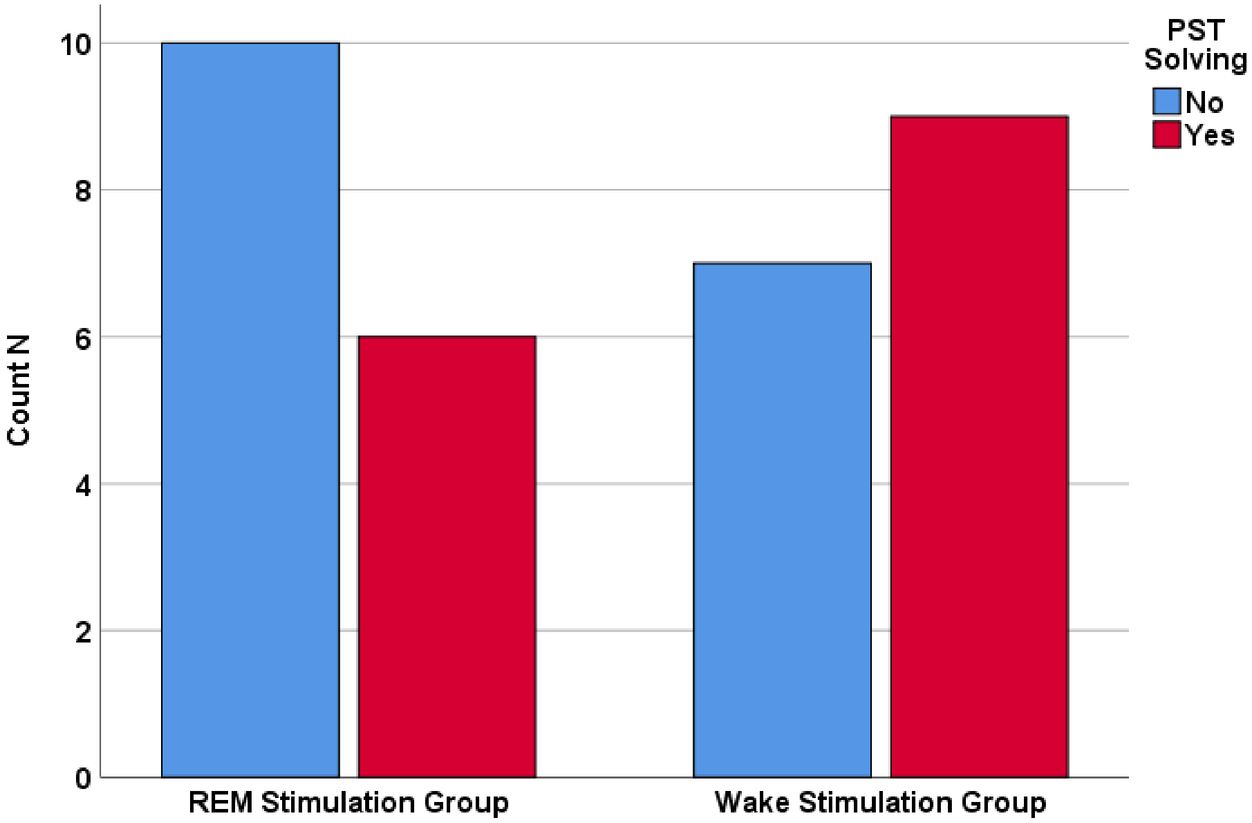

Figure 1: PST problem-solving rate between groups with either REM sleep TMR or active wakefulness TMR

PST Solving: Whether or not subjects solved the Problem-Solving Test (PST).

A three-way cross-tab chi-square statistic with condition (REM Stim versus Wake Stim) as control variable, and balancing (PST first or APST first) and PST solving as variables was performed, whether subjects in REM Stim group or

Wake Stim group had a higher rate of solving, if they started with the APST first (Figure 2). In total for both groups there was no significant effect for balancing on solving rate (Balancing*Solving, Pearson chi-square $\chi^2(1, N = 32) = 0.13$, $p = 0.72$). In the REM Stim group, subjects starting with the APST solved significantly (indicated in figures and tables with "*" after p-value) more often than those starting with the PST (Balancing*Solving, Pearson chi-square $\chi^2(1, N = 16) = 4.27$, $p = 0.04$). In the Wake Stim group there was no effect for balancing on solving (Balancing*Solving, Pearson chi-square $\chi^2(1, N = 16) = 2.29$, $p = 0.13$).

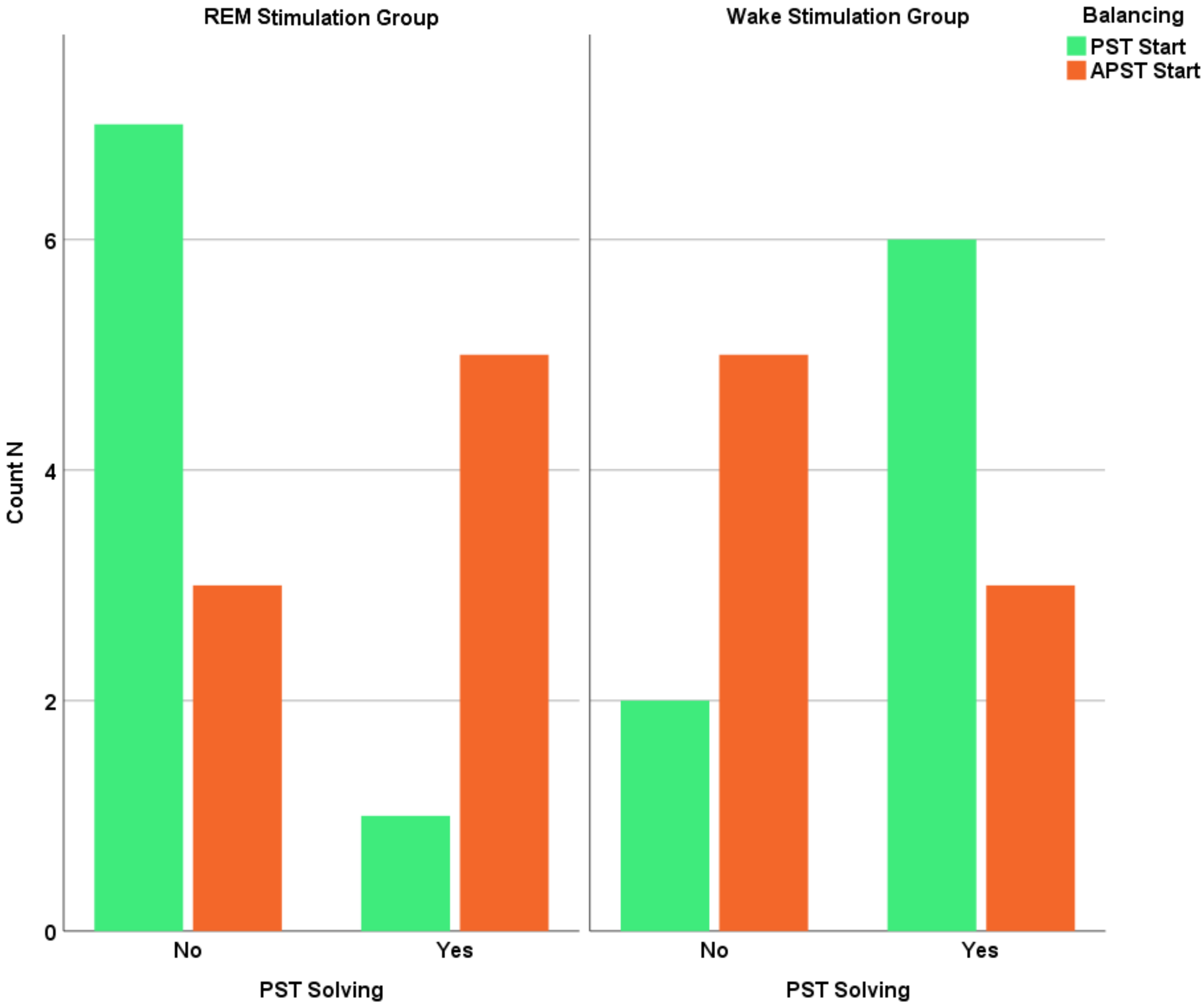

Figure 2: PST problem-solving rate between groups with either REM sleep TMR or active wakefulness TMR, separated by testing session level sequence

PST Solving: Whether or not subjects solved the Problem-Solving Test (PST).
PST Start: Subgroup starting with the PST in the testing session.
APST Start: Subgroup starting with the Analogical Problem-Solving Test (APST) in the testing session.

A chi-square test was performed to assess whether for all subjects any of the helping procedures in the training session affected the solving ratio of the PST.

No significant effect from any advice procedure on PST solving rate was found (all $p \geq 0.32$).

To analyze if there was a different impact from the helping procedures during training session on the solving rate dependent on condition and balancing, a four-way cross-tab chi-square statistic was performed. Balancing was used as control variable 1, condition as control variable 2, and the individual help procedures tested with PST solving were set as variables. All but one advice procedure did not test significantly with PST solving (all $p > 0.24$).

The only advice procedure exhibiting a significant effect on the solving rate of the PST depending on the balancing, in total for both groups or any of the individual groups, was advice given on how to restart the level 3 after 10 minutes of game time ("Restart Advice"; Table 1).

REM Stim group PST starters were unlikely to solve the PST if they had not received Restart Advice in the training session (Table 1). REM Stim group APST starters did not solve more often if Restart Advice was given in the training session. In total REM Stim group subjects were unlikely to find the solution, if they had not received Restart Advice in the training session.
Wake Stim group PST starters' solving rate was independent of Restart Advice in the training session. Wake Stim group APST starters' solving rate was independent of Restart Advice in the training session. In the entire Wake Stim group there was no effect for Restart Advice in the training session on solving rate of the PST.
Across both REM and Wake Stim groups, PST starters were more likely to find the solution, if they received Restart Advice during the training session. Across both REM and Wake Stim groups, APST starters' solving rate was independent of receiving Restart Advice during the training session. Across both REM and Wake Stim groups and both level sequences, solving rate was independent of having received Restart Advice in the training session (Table 1).

Table 1: Counts and statistical analysis of the impact by the helping procedure “Restart Advice”

Condition[1]	Balancing[2]	Restart Advice[3]	PST Solving[4]		Four-Way Cross-Tab Chi-square Statistic		
			No	Yes	Value	df	p
REM Stim	PST Start[5]	No	7	0	8.00	1	0.01*
		Yes	0	1			
	APST Start[6]	No	3	3	1.60	1	0.21
		Yes	0	2			
	Total	No	10	3	6.15	1	0.01*
		Yes	0	3			
Wake Stim	PST Start	No	1	3	0	1	1
		Yes	1	3			
	APST Start	No	2	3	2.88	1	0.09
		Yes	3	0			
	Total	No	3	6	0.91	1	0.34
		Yes	4	3			
Both	PST Start	No	8	3	3.88	1	0.05*
		Yes	1	4			
	APST Start	No	5	6	0.29	1	0.59
		Yes	3	2			
	Total	No	13	9	1.00	1	0.32
		Yes	4	6			

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Balancing refers to Testing session started with PST or APST Start

[3] In training level 3, if subjects did not solve the level in 10 minutes, they were shown where the restart option was located.

[4] Whether or not subjects solved the Problem-Solving Test (PST).

[5] Subgroup starting with the PST in the testing session.

[6] Subgroup starting with the Analogical Problem-Solving Test (APST) in the testing session.

PST solving speed of REM Stim PST solvers ranged from 368 s to 2201 s with a mean of 1117.83 s (685.52 s). PST solving speed of the REM Stim PST solver starting with the PST in the testing session (PST start, only one subject) was 368 s. PST solving speed of REM Stim PST solvers starting with the APST in the testing session (APST start) ranged from 468 s to 2201 s with a mean of 1267.80 s (647.11 s).

PST solving speed of Wake Stim PST solvers ranged from 491 s to 2280 s with a mean of 1143.33 s (652.20 s). PST solving speed of Wake Stim PST solvers with PST start ranged from 521 s to 2280 s with a mean of 1310.00 s (741.10 s). PST solving speed of Wake Stim PST solvers with APST start ranged from 491 s to 1015 s with a mean of 810.00 s (279.98 s).

A univariate 2 x 2 ANOVA with condition (REM Stim versus Wake Stim) and balancing (PST first or APST first) as between-subject factors was conducted to check whether between solvers, solving speed of the PST differed between conditions and balancing (Figure 3). It revealed no differences between REM Stim group and Wake Stim group solvers (Condition, Pillai's trace F(1,11) = 0.33, p = 0.58) and no differences between PST-starter solvers and APST first solvers (Balancing, Pillai's trace F(1,11) = 0.23, p = 0.64). There was no effect on solving speed of the PST for solvers found between conditions and starting level (Condition*Balancing, Pillai's trace F(1,11) = 2.77, p = 0.12).

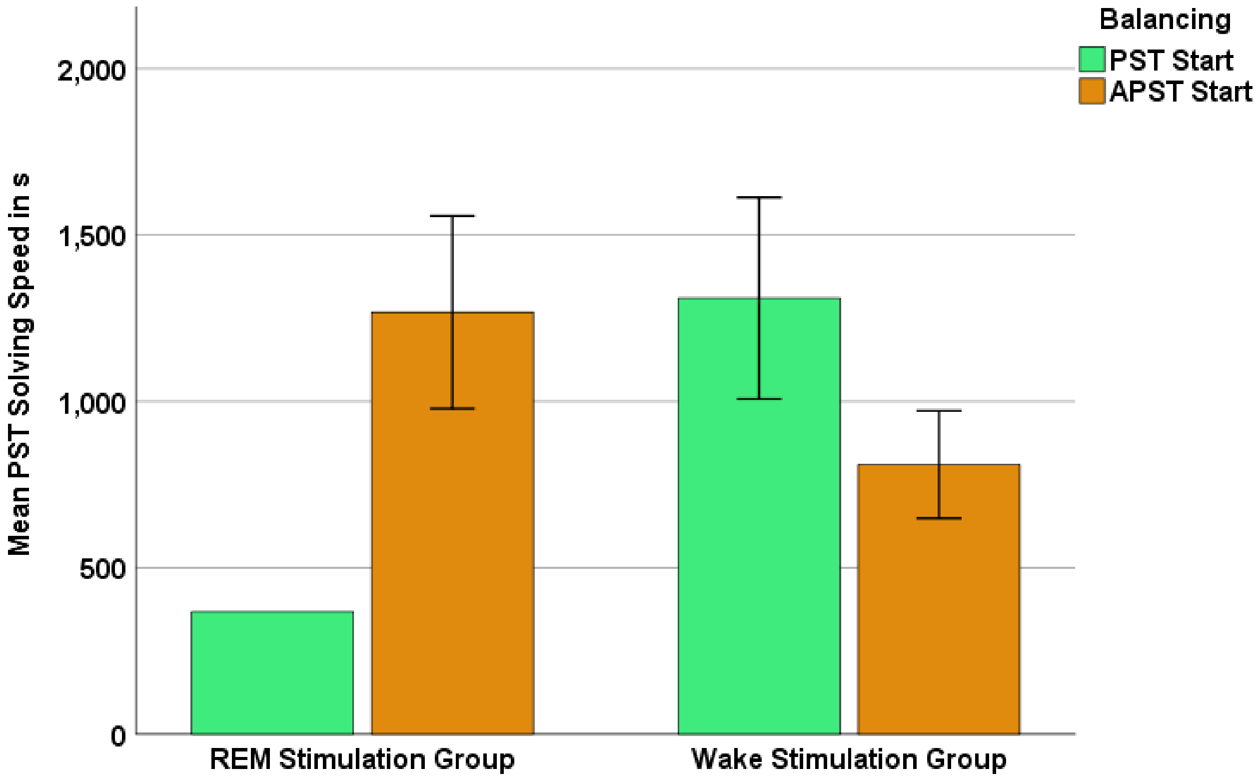

Figure 3: Mean PST problem-solving speed between groups with either REM sleep TMR or active wakefulness TMR, separated by testing session level sequence

Solvers: Subjects who solved the Problem-Solving Test (PST).
PST Start: Subgroup starting with the PST in the testing session.
APST Start: Subgroup starting with the Analogical Problem-Solving Test (APST) in the testing session.
Error Bars: ± 1 standard error (SE)*
* Note: REM Stimulation Group Solvers with PST start have no standard error bar indicator, since only one subject of this subgroup solved the PST.

Analogical Problem-Solving Test (APST) solving speed of REM Stim APST solvers ranged from 300 s to 1356 s with a mean of 628.75 s (354.19 s). APST solving speed of REM Stim APST solvers with PST start ranged from 313 s to 1356 s with a mean of 781.63 s (445.52 s). APST solving speed of REM Stim

APST solvers with APST start ranged from 300 s to 690 s with a mean of 475.88 s (130.08 s).

APST solving speed of Wake Stim APST solvers ranged from 273 s to 930 s with a mean of 589.14 s (176.90 s). APST solving speed of Wake Stim APST solvers with PST start ranged from 273 s to 808 s with a mean of 564.43 s (176.84 s). APST solving speed of Wake Stim APST solvers with APST start ranged from 436 s to 930 s with a mean of 613.86 s (187.36 s).

The solving speed of the APST between APST-solvers of REM Stim and Wake Stim groups and between APST-solvers starting with the PST and subjects starting with the APST were compared using a univariate 2 x 2 ANOVA with condition (REM Stim versus Wake Stim) and balancing (PST first or APST first) as between-subject factors. It revealed no significant differences in APST solving times dependent on condition (Pillai's trace F(1, 26) = 0.16, p = 0.69), balancing (Pillai's trace F(1, 26) = 1.67, p = 0.21) or both (Condition*Balancing, Pillai's trace F(1, 26) = 3.21, p = 0.09).

3.2. Analysis of Video Game Training Level Performance

A 2 x 2 x 2 ANOVA with Condition, Balancing and PST solving (Solving) as between-subject variables revealed no difference between conditions on the training level performance index (TLPI, see 2.7; Table 2; Condition, Pillai's trace F(1,24) = 0.12, p = 0.73). Solvers did not differ significantly in the TLPI from non-solvers (Table 2; Solving, Pillai's trace F(1, 24) = 2.70, p = 0.11). TLPI varied significantly between level sequence subgroups (Balancing, Pillai's trace F(1, 24) = 7.23, p = 0.01). There was no significant interaction between Condition and Balancing (Condition*Balancing, Pillai's trace F(1, 24) = 0.50, p = 0.49), Balancing and Solving (Balancing*Solving, Pillai's trace F(1, 24) = 0.07, p = 0.79) or Condition, Balancing and PST Solving (Condition*Balancing*Solving, Pillai's trace F(1, 24) = 0.02, p = 0.89). There was a significant interaction for Condition and Solving on the TLPI (Condition*Solving, Pillai's trace F(1, 24) = 6.65, p = 0.02).

Table 2: Descriptive Statistics of Training Level Performance Index (TLPI)

Condition[1]	Balancing[2]	PST Solving[3]	Count N	TLPI Mean (SD)
REM Stim	PST Start[4]	Non-Solvers	7	0.24 (0.12)
		Solvers	1	0.22 (0)
		Total	8	0.24 (0.11)
	APST Start[5]	Non-Solvers	3	0.41 (0.18)
		Solvers	5	0.35 (0.10)
		Total	8	0.37 (0.13)
	Total	Non-Solvers	10	0.29 (0.15)
		Solvers	6	0.33 (0.10)
		Total	16	0.31 (0.13)
Wake Stim	PST Start	Non-Solvers	2	0.15 (0.05)
		Solvers	6	0.34 (0.08)
		Total	8	0.30 (0.11)
	APST Start	Non-Solvers	5	0.25 (0.08)
		Solvers	3	0.42 (0.04)
		Total	8	0.31 (0.11)
	Total	Non-Solvers	7	0.22 (0.08)
		Solvers	9	0.37 (0.08)
		Total	16	0.30 (0.11)
Both	PST Start	Non-Solvers	9	0.22 (0.11)
		Solvers	7	0.33 (0.09)
		Total	16	0.27 (0.11)
	APST Start	Non-Solvers	8	0.31 (0.14)
		Solvers	8	0.38 (0.09)
		Total	16	0.34 (0.12)
	Total	Non-Solvers	17	0.26 (0.13)
		Solvers	15	0.35 (0.09)
		Total	32	0.31 (0.12)

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Balancing refers to Testing session started with PST or APST Start

[3] Whether or not subjects solved the Problem-Solving Test (PST).

[4] Subgroup starting with the PST in the testing session.

[5] Subgroup starting with the Analogical Problem-Solving Test (APST) in the testing session.

Independent t-tests were used to further analyze the significant interaction between Condition and PST Solving on the TLPI.

Independent t-tests revealed that REM Stim non-solvers and solvers did not differ in TLPI (t(14) = -0.51, p = 0.62). TLPI was significantly higher for solvers than non-solvers of the Wake Stim group (t(14) = -3.78, p < 0.01). Wake Stim mean TLPI for solvers was 0.37 (0.08) and 0.22 (0.08) for non-solvers. Solvers and non-solvers between conditions did not differ in TLPI (Solvers, t(13) = -0.85, p = 0.41; Non-Solvers, t(15) = 0.25, p = 1.19).

3.3. Analysis of the Hear-No Hear task (HNH)

A univariate ANOVA of the corrected recognition of game sounds (see 2.7) revealed no differences between REM Stim and Wake Stim groups (main effect Condition, Pillai’s trace F(1, 28) = 2.76, p = 0.11), no differences between solvers and non-solvers in both groups (main effect Solving, Pillai’s trace F(1, 28) = 1.30, p = 0.26) and no differences between solvers and non-solvers in between groups (interaction Condition*Solving, Pillai’s trace F(1, 28) = 0.29, p = 0.60). Non-solvers mean corrected recognition of game sounds was 0.23 (0.28) (Mean (SD)) for REM Stim and 0.37 (0.36) for Wake Stim. Solvers mean corrected recognition of game sounds was 0.03 (0.17) for REM Stim and 0.29 (0.44) for Wake Stim.

3.4. Analyses of the Sleep Quality Questionnaire (SF-A-R) and Polysomnography

SF-A-R

A chi-square test showed no significant difference between solvers and non-solvers for sudden image flashes during falling asleep ($\chi^2(2, N = 16) = 1.37$, $p = 0.50$). A Mann-Whitney U test was conducted to analyze how fast subjects felt they could fall asleep, whether they noticed muscle twitching, awakenings and sweating during the night, how well they remembered dreaming and how much headache and exhaustion from the prior day they felt in the morning. Of these parameters, none revealed significant differences between solvers and non-solvers (all $p \geq 0.17$), except that non-solvers felt they could fall asleep faster (non-solvers: Mdn = 3 (after 20 min), solvers: Mdn = 3.5 (4 = after 40 min); $U = 12.50$, $p = 0.04$). An independent t-test was performed to test whether solvers and non-solvers noticed a different length of the four longest awakenings, if applicable, and whether they rated their sleep, pre-sleep or post-sleep mood differently, when presented a variety of attributes as described in 2.4.1. The independent t-test revealed that solvers assessed their post-sleep mood significantly more balanced than non-solvers ($t(14) = -2.26$, $p = 0.04$). Mean values for balanced were 1.80 (0.42) for non-solvers and 2.33 (0.52) for solvers. No other variables differed between solvers and non-solvers according to the independent t-test (all $p \geq 0.06$).

Analysis of subjects with prior sleep-study experience in sleep-studies versus first-timers was performed. A chi-square test showed no significant difference between subjects with prior sleep-study experience and first-timers for sudden image flashes during falling asleep ($\chi^2(2, N = 16) = 0.69$, $p = 0.71$). A Mann-Whitney U test was conducted to analyze how fast subjects felt they could fall asleep, whether they noticed muscle twitching, awakenings and sweating during the night, how well they remembered dreaming and how much headache and exhaustion from the prior day they felt in the morning. Of these parameters, none revealed significant differences between subjects with prior sleep-study experience and first-timers (all $p \geq 0.22$).

An independent t-test was performed to test whether subjects with prior sleep-study experience and first-timers noticed a different length of the four longest awakenings, if applicable, and whether they rated their sleep in the laboratory differently, when presented a variety of attributes as described in 2.4.1. The independent t-test revealed no significant differences between subjects with prior sleep-study experience and first-timers (all $p \geq 0.07$).

Polysomnography

An independent t-test revealed no differences between solvers and non-solvers in the REM Stim group for either total sleep time, or time spent in S1, in S2, in SWS, in REM sleep, awake after sleep started or in movement time (Table 3). Furthermore, there were no significant differences between solvers and non-solvers in epochs with movement artifacts, time until sleep (S1 epoch with following S2 epoch), time until SWS and time until REM sleep (Table 3).

Table 3: Descriptive statistics and independent t-tests of polysomnography analysis split between solvers and non-solvers of REM Stim group

Dependent Variable	Descriptive Statistics		Independent t-tests		
	Condition[1]				
	Non-solvers[2] N = 10 Mean (SD)	Solvers[3] N = 6 Mean (SD)	t	df	p
Total sleep[4] (min)	462.95 (11.73)	456.00 (13.71)	1.08	14	0.30
Total S1 (min)	26.70 (15.16)	31.41 (11.66)	-0.65	14	0.53
Total S2 (min)	260.30 (26.02)	261.83 (31.06)	-0.11	14	0.92
Total SWS (min)	68.15 (29.90)	64.83 (27.81)	0.22	14	0.83
Total REM sleep (min)	90.90 (23.90)	73.00 (19.96)	1.54	14	0.15
Total Wakefulness (min)	14.85 (20.71)	23.25 (20.27)	-0.79	14	0.44
Sleep onset[5] (min)	16.90 (11.21)	25.83 (14.38)	-1.39	14	0.19
SWS onset (min)	22.45 (25.84)	24.75 (10.03)	-0.21	14	0.84
REM sleep onset (min)	110.90 (49.29)	134.58 (76.44)	-0.76	14	0.46
Movement time (min)	2.05 (1.28)	1.67 (0.82)	0.65	14	0.52
Epochs with movement artifacts (N)	60.00 (16.07)	64.50 (19.38)	-0.50	14	0.62

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Non-Solvers being subjects who did not solve the PST.

[3] Solvers being subjects who solved the PST.

[4] Total sleep being the time the subject spent asleep after bedtime until the defined wake-up time after 8 hours.

[5] Sleep onset being the time from bedtime until sleep.

Range for time until sleep was 3.5 minutes to 40.5 minutes with a mean of 20.25 (12.82) (Mean (SD)). Range for total sleep time was 442.5 minutes to 477.5 minutes with a mean of 460.34 (12.54) minutes. Range for time spent awake after sleep was 0 minutes to 55 minutes with a mean of 18.00 (20.30) minutes.

Performance of another independent t-test ensued, to search for differences in sleep between subjects in the REM Stim group that had prior experience with sleep studies and those that had not. From the mentioned parameters above, no significant differences were revealed (all $p > 0.12$), except that the subjects with prior sleep-study experience spent more time in movement time during sleep. Mean movement time was 1.40 (0.70) (Mean (SD)) for first-timers and 2.75 (1.21) for subjects with prior sleep study experience ($t(14) = -2.85$, $p = 0.01$).

Spearman's Correlation showed that the subjective assessment of the subject for the time it took to fall asleep correlated positively with the analysis of the polysomnography for time until sleep (Spearman Correlation $r_s = 0.78$, $p < 0.01$) and negatively with the total sleep time (Spearman Correlation $r_s = -0.76$, $p < 0.01$). Furthermore, a negative correlation was found with time spent in SWS (Spearman Correlation $r_s = -0.62$, $p = 0.01$).

3.5. Comparison of Group Populations, the Subject Data Questionnaire and the GBQ

Independent t-tests revealed that age did not differ between groups (Table 4). Usual amount of night sleep was not significantly different between groups. Amount of sleep in the night prior to the experiment did not differ between groups (Table 4).

Table 4: Means and statistical analysis of age, usual amount of night sleep and amount of sleep in the night prior to the experiment between REM Stim and Wake Stim groups

Dependent Variable	Descriptive Statistics		Independent t-tests		
	Condition[1]	Mean (SD)	t	df	p
Age (years)	REM Stim	22.69 (2.89)	-0.53	30	0.60
	Wake Stim	23.19 (2.48)			
Usual amount of night sleep (hours)	REM Stim	8.03 (0.50)	0.89	30	0.38
	Wake Stim	7.88 (0.50)			
Night sleep before experiment (hours)	REM Stim	8.03 (0.42)	1.45	30	0.16
	Wake Stim	7.78 (0.55)			

[1] Condition refers to Rem Stim and Wake Stim groups.

A chi-square test of independence showed that REM Stim and Wake Stim groups did not differ significantly regarding gender distribution, in having prior experience with sleep studies or in having previously played video games (Table 5).

Table 5: Descriptive statistics and statistical analysis of gender distribution, prior experience with sleep studies and having previously played video games between groups

Dependent Variable	Descriptive Statistics			Chi-square Statistic		
	Condition	Category	N	Value	df	p
Gender	REM Stim	Female	13	0.00	1	1
		Male	3			
	Wake Stim	Female	13			
		Male	3			
Prior sleep study experience	REM Stim	No	10	0.58	1	0.45
		Yes	6			
	Wake Stim	No	12			
		Yes	4			
Previously played video games	REM Stim	No	2	0.24	1	0.63
		Yes	14			
	Wake Stim	No	3			
		Yes	13			

[1] Condition refers to Rem Stim and Wake Stim groups.

Two subjects from REM Stim and three subjects from Wake Stim groups were omitted from analysis of the GBQ, because they declared not to have played video games before. An independent t-test showed no differences between conditions for the age that subjects started to play video games (REM Stim 10.36 (3.47) (Mean (SD)); Wake Stim 12.50 (2.97); t(25) = -1.72, p = 0.10)). A Mann-Whitney U test revealed no difference between REM Stim and Wake Stim groups in frequency (REM Stim: Mdn = 2 (twice a month), Wake Stim: Mdn = 2; U = 89, p = 0.90) or duration of video game sessions (REM Stim: Mdn = 1 (less than 3 hours per week), Wake Stim: Mdn = 1; U = 89, p = 0.88). Moreover, there was no difference in video game genre preferences between conditions (all p ≥ 0.06).

A correlation of TLPI with video gaming starting age was tested using Pearson's r. A correlation of TLPI with frequency and with amount of playing per week was tested using Spearman's r. No significant correlation with TLPI was found (all $p \geq 0.06$).

3.6. Analyses of Mental State, Multidimensional Mood State Short-Form A (MDBF-A) and Stanford Sleepiness Scale (SSS)-Questionnaires

Analysis of the Mental State Questionnaire (MSQ)

A repeated measures 2 x 2 MANOVA showed no significant effect on mental state for REM Stim versus Wake Stim (Condition, Pillai's trace $F(5, 26) = 0.10$, $p = 0.99$) and no significant effect for training (Run 1) versus testing session (Run 2) (Table 6; Run, Pillai's trace $F(5,26) = 1.06$, $p = 0.40$). However, mental state in the sessions was significantly different between groups for “strained”, “tired” and “motivated” (Table 6; Run*Condition, Pillai's trace $F(5, 26) = 4.65$, $p < 0.01$).

Table 6: Descriptive statistics and repeated measures 2 x 2 MANOVA of the Mental State Questionnaire

Scales		Condition[1]		Interaction Run*Condition	
		REM Stim N = 16 Mean (SD)	Wake Stim N = 16 Mean (SD)	Univariate F	p
Activated	Run 1[2]	2.94 (1.00)	3.25 (0.58)	1.67	0.21
	Run 2[3]	3.44 (0.96)	3.25 (1.07)		
Strained	Run 1	1.44 (0.63)	1.81 (0.83)	6.90	0.01*
	Run 2	1.62 (0.89)	1.31 (0.48)		
Tired	Run 1	3.19 (0.66)	2.63 (1.09)	7.64	0.01*
	Run 2	2.19 (0.75)	2.75 (1.07)		
Motivated	Run 1	3.31 (1.08)	3.88 (0.62)	8.69	0.01*
	Run 2	4.00 (0.63)	3.50 (1.03)		
Concentrated	Run 1	3.25 (0.58)	3.44 (0.73)	3.56	0.07
	Run 2	3.69 (0.60)	3.38 (0.81)		

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Run 1 being training session.

[3] Run 2 being testing session.

These three variables were then analyzed using dependent and independent t-tests, accordingly. Independent t-tests revealed no significant difference for “strained”, “tired” and “motivated” between groups in either session (all $p \geq 0.08$).

Dependent t-tests showed that in the testing session the REM Stim was significantly less tired than in the training session and more motivated (Table 7). Dependent t-tests of the Wake Stim group revealed that they were less strained in the testing session than in the training session (Table 7).

Table 7: Significant dependent t-tests of “strained”, “tired” and “motivated” and variable means with standard deviations of REM Stim and Wake Stim

Dependent Variable	Descriptive Statistics			Dependent t-tests		
	Condition[1]	Session	Mean (SD)	t	df	p
Strained	Wake Stim	Run 1[2]	1.81 (0.83)	2.24	15	0.04*
		Run 2[3]	1.31 (0.48)			
Tired	REM Stim	Run 1	3.19 (0.66)	3.87	15	<0.01*
		Run 2	2.19 (0.75)			
Motivated	REM Stim	Run 1	3.31 (1.01)	-2.71	15	0.02*
		Run 2	4.00 (0.63)			

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Run 1 being training session.

[3] Run 2 being testing session.

To check for possible circadian effects on the mental state, a repeated measures 2 x 2 MANOVA was performed, comparing evening (Time 1) with morning (Time 2) session. Mental state did not diverge between groups (Condition, Pillai’s trace F(5, 26) = 0.10, p = 0.99) but was significantly different in morning versus evening session (Time, Pillai’s trace F(5, 26) = 4.65, p < 0.01). Subjects in the evening session were less strained (Pillai’s trace F(5, 26) = 6.90, p = 0.01), more tired (Pillai’s trace F(5, 26) = 7.64, p = 0.01) and less motivated (Pillai’s trace F(5, 26) = 8.69, p = 0.01). There was no difference in morning and evening sessions between groups (Condition*Time, Pillai’s trace F(5, 26) = 1.06, p = 0.40).

Analysis of the Multidimensional Mood State Questionnaire Short-Form A (MDBF-A)

A repeated measures 2 x 2 MANOVA showed no significant effect on mood state for REM Stim versus Wake Stim (Table 8; Condition, Pillai’s trace F(3, 28) = 1.22, p = 0.32). Subjects were in a less good mood in the testing session

(Run, Pillai’s trace F(3, 28) = 4.57, p = 0.01). Mood state in the sessions was significantly different between groups for ”Good-Bad” (GB) and “Alert-Tired” (AT) (Table 8; Run*Condition, Pillai’s trace F(3, 28) = 12.89, p < 0.01).

Table 8: Descriptive statistics and repeated measures 2 x 2 MANOVA of the Multidimensional Mood State Questionnaire Short-Form A

Scales		Condition[1]			Main Effect Run		Interaction Run*Condition	
		REM Stim N = 16 Mean (SD)	Wake Stim N = 16 Mean (SD)	Both N = 32 Mean (SD)	Univariate F	p	Univariate F	p
Good-Bad	Run 1[2]	18.19 (1.52)	18.25 (1.73)	18.22 (1.60)	8.05	0.01*	6.65	0.02*
	Run 2[3]	18.13 (1.31)	16.94 (2.27)	17.53 (1.92)				
Alert-Tired	Run 1	12.87 (2.50)	15.56 (2.92)	14.22 (3.00)	0.98	0.33	24.39	<0.01*
	Run 2	15.88 (2.47)	13.56 (3.60)	14.72 (3.26)				
Calm-Nervous	Run 1	17.94 (1.39)	16.88 (1.71)	17.41 (1.62)	0.07	0.79	1.16	0.29
	Run 2	17.75 (1.34)	17.19 (1.76)	17.47 (1.57)				

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Run 1 being training session.

[3] Run 2 being testing session.

Because of the significant interaction, GB and AT were analyzed using dependent and independent t-tests, accordingly. Independent t-tests revealed no difference for GB between groups (all p > 0.08) and that REM Stim was less alert in training session (t(30) = -2.80, p = 0.01) and more alert in testing session than Wake Stim group (t(30) = 2.12, p = 0.04).

Dependent t-tests of the REM Stim group showed that they were more alert in the testing session (t(15) = -3.59, p < 0.01). Dependent t-tests of the Wake Stim group revealed that in the training session they were in better mood (t(15) = 3.52, p < 0.01) and more alert (t(15) = 3.51, p < 0.01).

To check for possible circadian effects on the mood state, a repeated measures 2 x 2 MANOVA was performed, comparing evening (Time 1) with morning (Time 2) session. Mood state did not diverge between groups (Condition, Pillai's trace F(3, 28) = 1.22, p = 0.32) but was significantly different in morning versus evening session (Time, Pillai's trace F(3,28) = 12.89, p < 0.01). Subjects in the evening session were in a less good mood (Pillai's trace F(3, 28) = 6.65, p = 0.02) and less alert (Pillai's trace F(3, 28) = 24.39, p < 0.01). There was a significant difference in morning and evening sessions between groups (Time*Condition, Pillai's trace F(3, 28) = 4.57, p = 0.01), with groups being in a differently good mood in between sessions (Pillai's trace F(3, 28) = 8.05, p = 0.01). Because of the significant interaction, GB was analyzed using dependent and independent t-tests, accordingly. Independent t-tests revealed no significant difference for GB between groups in either session (all p ≥ 0.08).

Dependent t-tests of the REM Stim group showed no difference of good mood between sessions. Dependent t-tests of the Wake Stim group revealed that in the morning session they were in better mood (t(15) = -3.52, p < 0.01).

Analysis of the Stanford Sleepiness Scale (SSS)

A repeated measures 2 x 2 ANOVA showed no significant effect on sleepiness for REM Stim versus Wake Stim (Condition, Pillai's trace F(1, 30) = 0.58, p = 0.45) and training versus testing (Table 9; Run, Pillai's trace F(1, 30) = 0.96, p =

0.34). A significant effect for sleepiness in sessions between groups was found (Table 9; Run*Condition, Pillai's trace F(1, 30) = 16.92, p < 0.01).

Table 9: Descriptive statistics and repeated measures 2 x 2 ANOVA of Stanford Sleepiness Scale

Scales		Condition[1]		Interaction Run*Condition	
		REM Stim N = 16 Mean (SD)	Wake Stim N = 16 Mean (SD)	Univariate F	p
Sleepiness	Run 1[2]	3.00 (0.82)	2.5 (0.63)	16.92	< 0.01*
	Run 2[3]	2.19 (0.54)	3.00 (0.89)		

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Run 1 being training session.

[3] Run 2 being testing session.

Because of the significant interaction, sleepiness was analyzed using dependent and independent t-tests, accordingly. Independent t-tests revealed no significant difference for sleepiness between training sessions (t(30) = 1.94, p = 0.06), but REM Stim was significantly less tired in the testing session than Wake Stim (t(30) = -3.11, p < 0.01).

Dependent t-tests of the REM Stim group showed that they were sleepier in the training session (t(15) = 3.57, p < 0.01). Dependent t-tests of the Wake Stim group revealed that they were more tired in the testing session (t(15) = -2.24, p = 0.04).

To check for possible circadian effects on sleepiness, a repeated measures 2 x 2 ANOVA was performed, comparing evening (Time 1) with morning (Time 2) session. Sleepiness did not diverge between groups (Condition, Pillai's trace F(1, 30) = 0.58, p = 0.45) but was significantly different in morning versus evening session, subjects in the evening session being more sleepy (Time, Pillai's trace F(1, 30) = 16.92, $p < 0.01$). There was no significant difference sleepiness during morning and evening sessions between groups (Time*Condition, Pillai's trace F(1, 30) = 0.96, p = 0.34).

3.7. Analysis of the Game Experience Questionnaire (GEQ)

A repeated measures 2 x 2 x 2 MANOVA of game experience with condition (REM Stim versus Wake Stim) and PST solving as between-subjects' effects was performed (descriptive statistics see Appendices Table 13).

Between-Subjects Effects

There was no association between condition and game experience (Condition, Pillai's trace F(11, 18) = 0.47, p = 0.90). Game experience in both sessions was different between solvers and non-solvers (Solving, Pillai's trace F(11, 18) = 2.43, p = 0.05). Solvers rated themselves higher in "competence" (Pillai's trace F(11, 18) = 13.23, $p < 0.01$), "positive affect" (Pillai's trace F(11, 18) = 15.05, $p < 0.01$) and "positive experience" (Pillai's trace F(11, 18) = 8.23, p = 0.01). Solvers scored lower in "tension/annoyance" (Pillai's trace F(11, 18) = 6.67, p = 0.02) and "tired" (Pillai's trace F(11, 18) = 6.24, p = 0.02). The other game experience qualities showed no significant differences between solvers and non-solvers (all $p > 0.05$).

Depending on the condition, solving the PST had a significant effect on game experience concerning "competence", "positive affect" and "positive experience" (Condition*Solving, Pillai's trace F(11, 18) = 5.90, p = 0.02). Further testing of these three qualities was performed using independent t-tests, accordingly (for descriptive statistics see Appendices Table 13).

Independent t-tests revealed that in the testing session subjects of the REM Stim group did not rate differently in any of these three qualities, whether they were solvers or non-solvers (all $p \geq 0.22$). Solvers of the Wake Stim group exhibited higher "competence" (Run 1, t(14) = - 5.40, $p < 0.01$; Run 2, t(14) = - 7.37, $p < 0.01$), "positive affect" (Run 1, t(14) = - 3.84, $p < 0.01$; Run 2, t(14) = - 8.15, $p < 0.01$) and "positive experience" (Run 1, t(14) = - 2.58, p = 0.02; Run 2,

$t(9.78) = -7.09$, $p < 0.01$) in training and testing sessions than non-solvers of Wake Stim. REM Stim non-solvers had a higher level of “positive affect” ($t(12.49) = 2.26$, $p = 0.04$) and “positive experience” ($t(15) = 2.20$, $p = 0.04$) in the testing session than Wake Stim non-solvers. “Competence” was comparable in all sessions between non-solvers and “positive affect” and “positive experience” did not differ in the training session between non-solvers (all $p > 0.05$). Wake Stim solvers had higher training level “competence” ($t(13) = -2.50$, $p = 0.03$) and “positive experience” ($t(13) = -2.38$, $p = 0.03$) than REM Stim solvers, while no difference was found for “positive affect” (all $p > 0.05$). Solvers did not differ in the testing session game experience (all $p > 0.09$).

Within-Subjects Effects

Game experience was significantly different between training and testing sessions (Run, Pillai’s trace $F(11, 18) = 3.78$, $p = 0.01$), with subjects in the testing session exhibiting lower assessments for “flow” (Pillai’s trace $F(11, 18) = 4.22$, $p = 0.05$) and higher “tension/annoyance” (Pillai’s trace $F(11, 18) = 8.20$, $p = 0.01$) and “negative affect” (Pillai’s trace $F(11, 18) = 7.07$, $p = 0.01$).

There was no dependency of session and condition on game experience (Run*Condition, Pillai’s trace $F(11, 18) = 2.04$, $p = 0.09$) nor of session and condition and PST solving on game experience (Run*Condition*Solving, Pillai’s trace $F(11, 18) = 0.69$, $p = 0.73$).

There was a significant impact on game experience by PST solving depending on session (Run*Solving, Pillai’s trace $F(11, 18) = 2.54$, $p = 0.04$). In both sessions solvers rated higher in “competence” (Pillai’s trace $F(11, 18) = 4.30$, $p = 0.05$). Only in the testing session did solvers rate higher in “positive affect” (Pillai’s trace $F(11, 18) = 10.05$, $p < 0.01$) and “positive experience” (Pillai’s trace $F(11, 18) = 6.79$, $p = 0.02$). Only in the testing session did solvers rate lower in “tension/annoyance” (Pillai’s trace $F(11, 18) = 4.94$, $p = 0.03$), “negative affect” (Pillai’s trace $F(11, 18) = 10.94$, $p < 0.01$), “negative experience” (Pillai’s trace $F(11, 18) = 9.09$, $p = 0.01$) and “tired” (Pillai’s trace $F(11, 18) = 10.93$, $p < 0.01$).

Further analysis of the interaction effect seen for these variables was conducted accordingly via independent and dependent t-tests.

Independent t-tests indicated that in both sessions solvers rated higher in “competence” than non-solvers (Run 1, $t(30) = -2.08$, $p = 0.05$; Run 2, $t(30) = -4.13$, $p < 0.01$). For the other qualities there were no differences between solvers and non-solvers in the training session (all $p > 0.05$). In the testing session solvers rated lower in “tension/annoyance” (Run 2, $t(30) = 3.22$, $p < 0.01$), “negative affect” (Run 2, $t(30) = 3.13$, $p < 0.01$), “negative experience” (Run 2, $t(26.93) = 2.73$, $p < 0.01$) and “tired” (Run 2, $t(22.87) = 3.23$, $p < 0.01$). In the testing session solvers rated higher in “positive affect” (Run 2, $t(30) = -4.61$, $p < 0.01$) and “positive experience” (Run 2, $t(30) = -2.98$, $p = 0.01$).

Dependent t-tests showed that non-solvers exhibited higher “tension/ annoyance” ($t(16) = -3.66$, $p < 0.01$), “negative affect” ($t(16) = -4.78$, $p < 0.01$) and “negative experience” ($t(16) = -3.56$, $p < 0.01$) in the testing session compared to the training session. They exhibited lower “positive affect” ($t(16) = 2.74$, $p = 0.01$) in the testing session than in the training session. Other qualities of game experience for non-solvers did not change between sessions (all $p \geq 0.15$).

Dependent t-tests indicated that solvers rated higher in “positive experience” ($t(14) = -2.48$, $p = 0.03$) in the testing session than in the training session. Apart from this, there was no significant change of game experience for solvers between sessions (all $p \geq 0.06$).

3.8. Analysis of Rehearsal Questionnaire

The three-way chi-square crosstab statistic, with condition as control variable and thinking about the game versus PST solving as variables, found no effect of having thought about the game for PST solving in either condition (REM Stim: Pearson Chi-Square $\chi^2(2, N = 16) = 2.23$, $p = 0.33$. Wake Stim: Pearson Chi-Square $\chi^2(1, N = 16) = 1.37$, $p = 0.24$. Both conditions: Pearson Chi-Square $\chi^2(2, N = 32) = 3.38$, $p = 0.19$.).

The three-way chi-square crosstab statistic, with condition as control variable and talking about the game versus PST solving as variables, found no effect of having talked to anyone about the game for PST solving in either condition

(REM Stim: Pearson Chi-Square χ²(1, N = 16) = 0.15, p = 0.70. Wake Stim: Pearson Chi-Square χ²(1, N = 16) = 0.04, p = 0.84. Both conditions: Pearson Chi-Square χ²(1, N = 32) = 0.38, p = 0.54.).

A 2 x 2 MANOVA with PST solving and condition as between-subject factors found significant differences between REM Stim and Wake Stim groups (Table 10; Condition, Pillai's trace F(11, 18) = 2.52, p = 0.04). The Wake Stim group thought more about how funny the game was than the REM Stim group (Table 10). No other variables were different between conditions (all p ≥ 0.08). There was no difference between solvers and non-solvers (Solving, Pillai's trace F(11, 18) = 1.19, p = 0.36). Subjects did not differ in their thinking and emotional attitude dependent on PST solving between conditions (Condition*Solving, Pillai's trace F(11, 18) = 0.40, p = 0.94).

Table 10: Descriptive Statistics and 2 x 2 MANOVA of the Rehearsal Questionnaire

Scales	Condition[1]	PST Solving[2]			Main effect Condition	
		Non-Solvers[3] Mean (SD)	Solvers[4] Mean (SD)	Both Mean (SD)	Univariate F	p
Thinking about the game	REM Stim	2.9 (1.37)	3.5 (0.84)	3.13 (1.2)	2.33	0.14
	Wake Stim	2.29 (0.76)	2.89 (1.17)	2.63 (1.02)		
	Both	2.65 (1.17)	3.13 (1.06)	2.88 (1.13)		
Thinking about solving	REM Stim	2.8 (1.4)	4.17 (1.17)	3.31 (1.45)	0.67	0.42
	Wake Stim	2.71 (1.7)	3.44 (1.13)	3.13 (1.41)		
	Both	2.76 (1.48)	3.73 (1.16)	3.22 (1.41)		
Thinking game was funny	REM Stim	1.7 (1.06)	1 (0)	1.44 (0.89)	4.28	0.05*
	Wake Stim	2.29 (1.7)	2.22 (1.3)	2.25 (1.44)		
	Both	1.94 (1.34)	1.73 (1.16)	1.84 (1.25)		
Thinking	REM Stim	2.8 (1.55)	2.17 (1.17)	2.56 (1.41)	0.08	0.78

about frustration after game	Wake Stim	3.14 (1.68)	2.11 (1.17)	2.56 (1.46)		
	Both	2.94 (1.56)	2.13 (1.13)	2.56 (1.41)		
Thinking about “Blupi” abilities	REM Stim	2.6 (1.9)	2.67 (1.63)	2.63 (1.75)	1.96	0.17
	Wake Stim	1.86 (1.07)	1.89 (1.17)	1.88 (1.09)		
	Both	2.29 (1.61)	2.2 (1.37)	2.25 (1.48)		
Thinking about hidden solution	REM Stim	3.6 (1.71)	4 (1.55)	3.75 (1.61)	1.25	0.27
	Wake Stim	3.43 (1.99)	2.78 (1.64)	3.06 (1.77)		
	Both	3.53 (1.77)	3.27 (1.67)	3.41 (1.7)		
Thinking about feelings during game	REM Stim	1.6 (0.84)	1.67 (0.82)	1.63 (0.81)	3.38	0.08
	Wake Stim	1.29 (0.49)	1.11 (0.33)	1.19 (0.4)		
	Both	1.47 (0.72)	1.33 (0.62)	1.41 (0.67)		
Thinking about game because of frustration	REM Stim	1.7 (1.06)	2.33 (1.21)	1.94 (1.12)	0.64	0.43
	Wake Stim	1.86 (1.21)	1.56 (0.88)	1.69 (1.01)		
	Both	1.76 (1.09)	1.87 (1.06)	1.81 (1.06)		
Thinking about game because of excitement	REM Stim	1.4 (0.52)	1.5 (0.55)	1.44 (0.51)	0.00	0.96
	Wake Stim	1.43 (0.79)	1.44 (1.01)	1.44 (0.89)		
	Both	1.41 (0.62)	1.47 (0.83)	1.44 (0.72)		
Thinking about own mistakes during	REM Stim	3 (1.83)	4 (1.1)	3.38 (1.63)	2.34	0.14
	Wake Stim	2.29 (1.6)	3 (1.41)	2.69 (1.49)		
	Both	2.71 (1.72)	3.4 (1.35)	3.03 (1.58)		

playing						
Not thinking about game	REM Stim	2.3 (1.77)	1.5 (1.22)	2 (1.59)	0.57	0.46
	Wake Stim	2.43 (1.62)	2.22 (1.48)	2.31 (1.49)		
	Both	2.35 (1.66)	1.93 (1.39)	2.16 (1.53)		

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] PST Solving represents whether or not subjects solved the Problem-Solving Test (PST).

[3] Non-Solvers being subjects who did not solve the PST.

[4] Solvers being subjects who solved the PST.

3.9. Analyses of Digital Span Task (DSpan) and Vigilance Task (VT)

Analysis of the Digital Span Task (Dspan)

A repeated measures 2 x 2 ANOVA of the memory span revealed that the REM Stim group had a significantly longer memory span (Table 11; Condition, Pillai’s trace F(1, 29) = 11.63, $p < 0.01$) and no difference between training and testing sessions (Table 11; Run, Pillai’s trace F(1, 29) = 2.02, $p = 0.17$). No significant difference in memory span between groups and sessions was found (Table 11; Run*Condition, Pillai’s trace F(1, 29) = 0.37, $p = 0.55$).

Table 11: Descriptive statistics and repeated measures 2 x 2 ANOVA of the Digital Span Task

Scales		Condition[1]		Main effect Condition	
		REM Stim N = 15 Mean (SD)	Wake Stim N = 16 Mean (SD)	Univariate F	p
Memory span	Run 1[2]	7.73 (1.62)	6.3 (1.00)	11.63	< 0.01*
	Run 2[3]	7.93 (1.49)	6.75 (0.93)		

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Run 1 being training session.

[3] Run 2 being testing session.

To check for possible circadian effects on digit sequence memory span, a repeated measures 2 x 2 ANOVA was performed, comparing evening (Time 1) with morning (Time 2) session. Memory span was better in the REM Stim group (Condition, Pillai’s trace F(1, 29) = 11.63, $p < 0.01$). There was no significant difference between memory span performance in evening versus morning session (Time, Pillai’s trace F(1, 29) = 0.37, p = 0.55). There was no significant difference in sleepiness during morning and evening sessions between groups (Time*Condition, Pillai’s trace F(1, 29) = 2.02, p = 0.17).

Analysis of the Vigilance Task (VT)

A repeated measures 2 x 2 ANOVA of the mean reaction time in the vigilance task revealed no difference between groups (Table 12; Condition, Pillai’s trace F(1, 29) = 0.40, p = 0.53) and no difference between training and testing sessions (Run, Pillai’s trace Pillai’s trace F(1, 29) = 2.16, p = 0.15). No significant difference in mean reaction time between groups and sessions was found (Run*Condition, Pillai’s trace F(1, 29) = 0.34, p = 0.56).

Table 12: Descriptive statistics of the Vigilance Task

Scales		Condition[1]	
		REM Stim N = 16 Mean (SD)	Wake Stim N = 15 Mean (SD)
Mean reaction time (ms)	Run 1[2]	449.91 (43.23)	446.35 (31.95)
	Run 2[3]	444.57 (40.79)	433.93 (19.82)

[1] Condition refers to Rem Stim and Wake Stim groups.

[2] Run 1 being training session.

[3] Run 2 being testing session.

To check for possible circadian effects on mean reaction time in the vigilance task, a repeated measures ANOVA was performed, comparing evening (Time1) with morning (Time2) session. There was no difference in mean reaction time in the vigilance task between groups (Condition, Pillai's trace F(1, 29) = 0.40, p = 0.53) and no difference between evening and morning sessions (Time, Pillai's trace Pillai's trace F(1, 29) = 0.34, p = 0.56). No significant difference in mean reaction time between groups and sessions was found (Time*Condition, Pillai's trace F(1, 29) = 2.16, p = 0.15).

3.10. Analysis of the Random Reaction Time Task (RRTT)

Mean accuracy and mean reaction time in the RRTT were compared between solvers and non-solvers in Wake Stim group to check whether there was a difference in the reaction task performance between them. An independent t-test revealed no differences in performance between solvers and non-solvers in the Wake Stim group (Mean accuracy in % t(14) = -1.60, p = 0.13. Mean reaction time in ms t(14) = -0.90, p = 0.38). Mean accuracy was 90.61 % (3.23 %) for non-solvers and 92.87 % (2.42 %) for solvers. Mean reaction time was 422.19 ms (28.87 ms) for non-solvers and 410.02 ms (25.00 ms) for solvers.

4. Discussion

4.1. REM Sleep TMR Not Superior to Active Wakefulness TMR for Problem-Solving

In contrast to this study’s starting hypothesis, the results have shown no significant beneficial effect of TMR during REM sleep versus TMR during active wakefulness on either likelihood or speed of problem-solving of a video game level. As of writing, this study is the first one to assess the effect of REM sleep TMR versus active wakefulness TMR on problem-solving of a video game level. However, various studies have covered partial aspects of this study’s approach.

Other findings suggest that sleep promotes memory consolidation of declarative, procedural and emotional memories (Diekelmann & Born, 2010). Sleep also enhances associative learning (Chatburn et al, 2014). Evidence has accumulated that REM sleep may be important for optimal cognitive functionality in several ways. REM sleep seems to improve memory consolidation of novel events, and procedural and emotional memory, with an even stronger effect, if both SWS and REM sleep take place during consolidation sleep (Giuditta et al, 1995; Maquet, 2001; Poe et al, 2000). Furthermore, schema-adherent information is suspected to receive a special, faster type of consolidation during REM sleep (Durrant et al, 2015; Tse et al, 2007; van Kesteren et al, 2012). The active system consolidation theory connects REM sleep to reactivation and LTP of SWS-reactivation tagged synaptic correlates of memories (Almeida-Filho et al, 2018; Diekelmann & Born, 2010; Diekelmann et al, 2011; Gais & Born, 2004; Rasch & Born, 2007; Rasch et al, 2009b). Moreover, REM sleep is attributed a role in corticalization of hippocampus-dependent memories (Almeida-Filho et al, 2018). REM sleep consolidation is proposed to be specific to tags like those of future relevance, in that forgetting of items with no future relevance may be facilitated by REM sleep (Oudiette et al, 2013). Activation and linking of associated schemas may be facilitated by the special milieu of REM sleep (Lewis et al, 2018).

The video game this study used requires minimal declarative and procedural memory and is not known to broad parts of the subject sample’s culture, so it is not to be expected that special consolidation or linking of associated schemas affected problem-solving. Subjects were made aware that they had a second attempt at the PST, which could have induced preferential consolidation of related memories. Subjects in the REM Stim group did not perform better in the PST, even though they had post-training night sleep, which in the studies mentioned provided the strongest improvements in memory tasks (Diekelmann & Born, 2010). This study did not find a sleep-associated improvement in problem-solving.

Additionally, TMR was applied during either REM sleep or during active wakefulness, depending on the condition. As during SWS, auditory TMR is viable in REM sleep, too, because both are characterized a higher threshold for stimuli-induced awakenings and slowed wakening (Baars, 1988). If it is ensured that the stimulation does not incite arousals, sleep architecture should remain largely unaffected. This may be achieved through continuous presentation of white noise throughout the night with repeated brief sound stimulations in the target interval, while a steady sound pressure level is kept (Rudoy et al, 2009; Sterpenich et al, 2014).
This study used similar audio stimulation protocols as used in previous studies. The data suggests that sleep was not impaired for subjects in the REM sleep TMR (REM Stim) condition.

Research concerning the effect of REM sleep TMR provided mixed results so far. Some showed benefits for declarative memory (Sterpenich et al, 2014). Others did not show any benefit for declarative or for procedural tasks (Rasch et al, 2007). Integration, generalization and abstraction of memories into existing or new associative networks may be facilitated during REM sleep (Cai et al, 2009; Sterpenich et al, 2014).

Results differ when TMR is applied during sleep or wakefulness. Memory task performance in the wakefulness-TMR group appeared subpar to that of sleep-TMR groups (Diekelmann et al, 2011; Oudiette et al, 2013). In this study there was no indication that REM Stim performed better in the target task than Wake Stim.

So far, most audio stimulation protocols for TMR have been simpler, consisting of one short sound per item. This study used a more complex audio stimulation protocol, in that sounds taken from the PST-level were used to attempt reactivation of PST-memories, to further facilitate problem-solving processes during the incubation interval. However, sounds were not exclusive to the PST, as two of the training levels have similar ambient sounds and “Blupi” sounds are the same for all the levels. Specifically, the “victory sound” of “Blupi” reaching the balloon was only encountered in the practice levels, and not during PST training. The sequence of the sounds presented during stimulation represented parts of the audio of the PST solution. It is unlikely that this exact sequence triggered preferentially PST-related memories, since subjects could play in any sequence during training or testing session and thus may have encountered the sounds in different sequences than that of TMR.

While the positive effect of sleep on memory performance is largely accepted by the scientific community, sleep’s role in problem-solving remains a matter of debate. As proposed by the BiOtA model, REM sleep memory reactivation may help to reduce self-imposed constraints and induce new associations, which could then enable strategy changes in analogical and creative problem-solving (Lewis et al, 2018). Yet, some research teams found no effect or benefits associated to sleep on creative problem-solving (Landmann et al, 2016; Landmann et al, 2014). For the Remote Associates Test (RAT), results suggest that sleep promotes higher performance increases for difficult than for easier RAT problems, if compared to an equal time in wakefulness (Ohlsson, 1992; Sio et al, 2013). Furthermore, more time in REM sleep may be linked to this improvement in problem-solving (Cai et al, 2009). Several studies have shown that a better memory performance may not result in better problem-solving capability in the RAT (Cai et al, 2009; Dougal & Schooler, 2007).

So far, one study has used the same video game to analyze sleep’s effect on problem-solving ability. In their study, Beijamini et al found only a significant effect for time spent in SWS during a post-training nap, not for REM sleep on problem-solving capability of levels from Speedy Eggbert Mania® (Beijamini et al, 2014; EPSITEC, 1999). The researchers proposed that the video game

problems might require visuo-spatial and logical reasoning skill to solve. Previous video game expertise did not affect the solving rate (Beijamini et al, 2014).
This present study cannot corroborate these findings. In REM Stim, solvers did not have more SWS than non-solvers. Study designs varied, as Beijamini et al's study used napping in favor of night-sleep and defined individual subject-specific levels, instead of one level as PST (Beijamini et al, 2014). Moreover, subjects were not aware of the testing session, so future relevance of their training session was unclear to them before incubation (Beijamini et al, 2014). This was different in this study, where subjects were informed that they would have a second attempt at the PST in the testing session. As demonstrated in other studies, the knowledge of a future relevance of an item increases the memory consolidation of this item, possibly at the expense of other items (Oudiette et al, 2013; Wilhelm et al, 2011).

Previous studies indicate that for logical problems, sleep after solving a training set of problems has shown to facilitate solving of new analogical problems with low surface similarity to another (Monaghan et al, 2015). All training levels solved during the training session shared a variable amount of aspects with the PST. The key problem of the PST, being the interaction between two “Blupis” through use of the crane, was not one of these shared aspects. Possibly, there was not enough surface similarity with the PST to facilitate solution of the PST after sleep.

Therefore, improvements in problem-solving by sleep may be either attributed to memory consolidation effects or other problem-solving facilitating sleep effects or both. Understanding what features of a problem task decide the type of cognitive processing during wakefulness may be required to gain insight into the selectivity of sleep-dependent treatment of these problem-solving tests. Further research on which types of problem tasks benefit from memory consolidation and which improvements in problem-solving cannot be attributed solely to memory consolidation needs to be conducted to unmask further sleep-encouraged processes aiding problem-solving.

The results of this study suggest that the combination of night sleep and REM sleep TMR does not improve problem-solving skill in a video game puzzle compared to active wakefulness TMR with daytime wakefulness. It is unclear, whether a short incubation interval spent either asleep or awake as used in nap studies produces a greater difference in problem-solving. The implemented TMR protocol may have been unsuited to initiate sleep-dependent processing of problem-solving related information of the PST.

It is possible that for this PST, REM sleep TMR was detrimental to problem-solving, perhaps by interfering with corticalization and restructuring processes active during REM sleep (Almeida-Filho et al, 2018). Comparison to performance of a non-TMR sleep group is needed to explore this possibility. Additionally, a SWS-TMR control experiment may clarify if the TMR protocol is not suited explicitly for REM sleep stimulation. Perhaps subjects during active wakefulness profited more from TMR than during REM sleep, leveling sleep-dependent benefits for problem-solving. A wake control group without TMR may help to assess this possibility. At last, the format of this problem-solving test may be exempted from sleep-dependent problem-solving improvement or the PST. Perhaps it was too difficult and too dependent on the virtual application of problem-solving skills. Support comes from the fact that subjects with better performance in the training levels, were more likely to solve the PST. Other problem-solving tests should be tested to see whether REM sleep TMR may improve performance in these tasks over active wakefulness TMR.

Alternative protocols testing problem-solving with a within-subject approach may lead to more conclusive results for the effect of TMR on problem-solving during wakefulness or various sleep stages. A within-subject design may also help to assess whether TMR during the mentioned conditions disrupts sleep, preventing sleep-associated gain in problem-solving, as suggested above.

4.2. Facilitation of Problem-Solving Through Analogical Task Only in REM Stim Group

This study did not confirm the hypothesis that subjects starting with a new analogical level, based on similar concepts as the PST, would be more likely and faster to solve the PST. This study found no effect of starting level on solving or speed of solving. However, if conditions are evaluated separately, REM Stim APST starters solved significantly more often than REM Stim PST-starters but not faster. There was no difference in solving rate and speed between level sequence for subgroups of Wake Stim.

Sleep after solving a training set of logical problems has shown to facilitate solving of new analogical problems with low surface similarity to another (Monaghan et al, 2015). Training levels may not have shared enough surface similarity to the PST to facilitate its solution. However, surface similarity to the alternative starting level of the testing session (hereafter noted as Analogical Problem-Solving Test, APST) may have been high enough. All subjects from the REM Stim group solved the APST, while two subjects from the Wake Stim group did not. These two also failed to solve the PST. One of these subjects started with the APST the other did not. An improvement in APST performance for REM Stim subjects through the analogical problem-solving facilitation as described by Monaghan et al is possible (Monaghan et al, 2015).

It may be proposed that in addition to sleep-dependent facilitation of low surface similarity problems, REM Stim subjects benefitted from further video game “reactivations” through the APST before attempting the PST a second time. Since no benefits for level sequence was demonstrated in Wake Stim, the APST start in REM Stim may be either sleep or REM sleep TMR dependent. These improvements cannot be achieved similarly through wakefulness with TMR. If there was such a benefit for the REM Stim group, the question why REM Stim did not perform better overall in the PST than Wake Stim remains unresolved.

Sleep TMR has been shown to be able to both selectively strengthen and promote forgetting of reactivated memories compared to wakefulness (Saletin et al, 2011; Simon et al, 2017; Stickgold & Walker, 2013). In this specific case, this can be ruled out, as subjects were not informed until the testing session of having to play the APST, nor about their testing session level sequence. Thus, it is unlikely that any differential sleep-facilitated consolidation may explain the stark contrast between level sequence subgroups of the REM Stim group compared to the Wake Stim group.

The synaptic homeostasis hypothesis explains better cognitive performance after sleeping through a process that involves downscaling of synaptic weights and emphasizing relative differences between synaptic strengths (Tononi & Cirelli, 2006). This may explain why REM Stim benefitted more from the APST start for the PST than Wake Stim: REM Stim subjects would be more receptive. However, this theory cannot account for the lack of overall better PST performance in the REM Stim group.

It is unlikely that a “training effect” in the testing session was present. The additional testing session video game playing did not improve performance continuously over time, with the best performance at the end of the testing session. If this had been the case, APST starters would have performed better in the PST with a higher solving rate or faster solving time. This was only the case for REM Stim APST starters compared to REM Stim PST starters and only in solving rate, not solving time. Furthermore, PST starters would have performed better in the APST with higher solving rate or faster solving time. However, APST solving times were comparable between PST and APST starters for subjects who solved the APST. Since only two subjects were unable to solve the APST and both were part of Wake Stim, the sample size of this study is too small to disprove this possibility for solving rate. This study should be replicated using a larger sample size to analyze this possibility further.

Overall, the findings of this study that REM Stim PST starters were unlikely to solve the PST compared to Wake Stim PST starters cannot be explained through any of the currently proposed theories. Additional processes that have selectively impaired REM Stim PST-starters’ performance compared to other subgroups could account for overall similar PST performance across groups.

This contrasts with the sleep-associated improvements many studies found for sleep condition groups in various experimental settings (Almeida-Filho et al, 2018). Additional research on this field is required to examine sleep- and REM sleep-TMR associated problem-solving improvements depending on having played a new (and or analogical) level compared to subjects receiving active wakefulness TMR.

4.3. Possible Confounding Variables

Since there was no measurable gain in problem-solving ability through the combination of REM TMR and sleeping versus wake TMR and wakefulness, other factors must be considered that determined whether a subject solved or did not solve the PST.

4.3.1. Sample Differences Between Conditions

There were no inherent differences between samples in age, gender distribution, usual amount of sleep or sleep in the night prior to the experiment. Furthermore, there were no significant differences between groups in their video game habits and preferences.

Consequently, the subject samples between conditions in this study did not differ in any of the obvious factors that were able to confound results. However, of the other control variables several yielded significant differences between conditions.

Basic Cognitive Tests

REM Stim showed a significantly longer memory span in the DSpan task than Wake Stim. Moreover, memory span was similar between training and testing, and morning and evening sessions. Even though a bias in digital memory span towards REM Stim could be identified, REM Stim and Wake Stim performed similarly in the PST. This suggests that the PST may not be sensitive to the differences in memory span between the two conditions. Moreover, the DSpan task did not exhibit a significant training effect, since both sessions' performances were comparable. Vigilance was comparable between groups with no significant differences between sessions. There was no training effect or bias between conditions identified. Vigilance and memory span appear unlikely to have confounded the results of the PST. The lack of training effects in these tasks is one reason for their prevalence in cognitive research.

Video Game Ability

Video game ability was assessed through the training level performance index (TLPI, see 2.7). A higher index indicates a faster solving speed of the training levels according to this study's sample. Thus, the TLPI does not reflect testing session performance in solving speed or rate.

Video game ability was comparable between conditions and between PST solvers and non-solvers. A significantly higher video game ability was identified for subjects starting with the Analogical Problem-Solving Test (APST) and for Wake Stim solvers. Moreover, the analysis suggests that TLPI does not correlate with earlier video game playing starting age, or frequency or amount of playing per week. This supports earlier findings that video game expertise does not yield better results in Speedy Eggbert Mania® (Beijamini et al, 2014; EPSITEC, 1999).

The TLPI delivers one possible explanation for what determined PST solving in the Wake Stim group. Wake Stim subjects who performed better during the training session were more likely to solve. Additionally, APST starters had a higher TLPI than PST starters, which was true for all solvers and non-solvers alike. This may have exerted a confounding effect on PST-solving assessment between subgroups and inflated the effect described in 4.2, namely that REM Stim APST starters were more likely to solve than REM Stim PST starters.

Ergo, the specific skill for the video game of interest is a possible confounding variable. Future studies should check for skill levels of their subjects in the problem task, when assuming impact of experimental interventions on problem-solving.

4.3.2. Mental State, Mood State, Sleepiness and Circadian Effects

To reveal possible confounding effects deriving from mental state, mood state and sleepiness, test results were compared between training and testing sessions. Additionally, these tests were analyzed according to the time of day they were conducted at to discover possible circadian effects.

Mental State

Mental state was not different between conditions and comparable between training and testing session across conditions. It was significantly different between groups depending on the session. While there was no difference found between groups, analyses of the individual groups showed that REM Stim was less tired and more motivated. Moreover, Wake Stim was less strained in the testing session than in the training session.

Subjects who are more tired or strained or less motivated in their training session may perform worse, which may increase time spent in training levels, negatively affecting their TLPI. Since only the REM Stim group was more tired and less motivated and only the Wake Stim group was more strained in the training session, these effects may have negated each other. Alternatively, these effects have not been strong enough to significantly affect problem-solving between groups or have been offset by the higher motivation and less tiredness or less strain in the testing session. Future studies should test whether conditions differ in mental state specifically before any problem-solving tests to assess possible confounding effects.

Mood State

Both conditions exhibited a similar mood state. Generally, subjects were in a less good mood in their testing session than in their training session. Mood state changed depending on condition and session. REM Stim was less alert in the training session and more alert in the testing session than Wake Stim. In-group analysis demonstrated that REM Stim was less alert and Wake Stim was in a better mood and more alert in their training session than in their testing session.

PST performance may have been affected by mood state differences in the training and testing sessions. It remains unclear whether lower alertness in the training impaired problem-solving greater than lower alertness during the testing session. Therefore, a possible confounding effect on problem-solving must be considered. Future studies should assess the mood state of their subjects when studying problem-solving.

Sleepiness

Sleepiness was similar between conditions and between sessions. Comparison of conditions between sessions revealed a difference in sleepiness. Training session sleepiness was comparable between conditions, but REM Stim was significantly less sleepy in the testing session than Wake Stim. In-group analysis revealed that REM Stim was sleepier and Wake Stim was less sleepy in their training session than in the testing session.

These results show that REM Stim may have benefitted from less sleepiness in their testing session compared to Wake Stim. However, difference in sleepiness was small (REM Stim testing 2.19 ± 0.54. Wake Stim testing 3.00 ± 0.89. testing $t(30) = 2.12$, $p < 0.01$). It is unlikely that different sleepiness levels alone have confounded results of the PST but may have attributed together with other candidate variables.

Circadian Effects Between Conditions

Time of day analysis revealed no different mental state between conditions. Analysis showed a circadian effect on mental state, being morning session subjects were more strained, more motivated and less tired than in the evening session. Comparing groups between sessions found no significant effect. Difference in mental state between conditions in the training and testing sessions may be partially explained through circadian effects.

Circadian analysis indicated that mood state was not different between conditions. Mood state was affected by time of day, in that subjects were in a less good mood and less alert in the evening. Mood state varied between conditions between sessions. No difference between conditions was found and individual group analysis of REM Stim revealed no difference between time of day. However, Wake Stim was in a better mood in the morning session than in the evening session.

Analysis of circadian effects showed no difference in sleepiness between conditions at the same time. Time of day significantly impacted sleepiness with subjects exhibiting higher levels of sleepiness in the evening than in the morning. No difference in sleepiness was found comparing conditions between morning and evening sessions.

Altogether, groups did not vary in mental state, mood state and sleepiness. Between session group differences can be partially explained through circadian effects. In the training session REM Stim may have been handicapped by less alertness compared to Wake Stim.

In the testing session REM Stim may have benefitted from more alertness and less sleepiness than Wake Stim.

It remains unclear how in-group differences between sessions in mental state, mood state and sleepiness that may be attributed to circadian effects have impacted problem-solving in this study. Whether it promotes higher chances in problem-solving, if training or testing is done during the morning or evening, should be examined further.

4.3.3. Sleep quality in REM Stim

For the most part, subjective sleep quality parameters were comparable between solvers and non-solvers of the PST. Interestingly, solvers claimed to have taken longer to fall asleep and felt more balanced after sleep than non-solvers. Objective sleep parameters gained through polysomnography revealed no significant differences between solvers and non-solvers. The comparison of sleep study experts and first-timers revealed no differences in their subjective sleep quality. Apart from sleep study experts exhibiting more movement time during sleep, polysomnography between sleep study experts and first-timers was comparable.

To assess the meaningfulness of the subjective assessment of sleep latency, a correlation with polysomnographic values was tested. Although the subjective sense of time was exaggerated compared to what polysomnography revealed, a positive correlation was found. The longer subjects thought they needed to fall asleep, the longer the sleep onset and the shorter the time spent in SWS and the total sleep time were.

The contradiction that solvers both stated they took longer to fall asleep and nevertheless felt more balanced after sleep compared to non-solvers is difficult to assess. If solvers' falling asleep was impaired and they still felt more balanced the next morning, it may be assumed that their sleep was more replenishing than that of non-solvers or that they generally exhibit higher levels of feeling balanced in the morning or overall.

It seems peculiar that subjects claiming to have had a harder time to fall asleep, performed better in the PST, when sleep has been implicated to have a beneficial effect on many cognitive functions (Almeida-Filho et al, 2018; Diekelmann & Born, 2010; Sara, 2000; Stickgold & Walker, 2013; Tononi & Cirelli, 2006). This study adds to the conflicting results of research on sleep and problem-solving. The present results support earlier findings that sleep may not have a big role in creative problem-solving and insight (Landmann et al, 2016; Schonauer et al, 2018). However, it is unclear how much creativity contributes to or how much insight is needed for solving this study's PST. Other teams have found strong indications for improvements in problem-solving by sleep versus wakefulness (Beijamini et al, 2014; Cai et al, 2009; Monaghan et al, 2015; Sio et al, 2013; Wagner et al, 2004). This inconsistency may be explained by differences between nap and night-sleep studies and differences between problem tasks. It may be necessary to differentiate between these factors to clarify what does and what does not improve problem-solving. More research will be required to make comparisons between similar studies conclusive on this topic.

4.3.4. Stimulation Awareness

RRTT Performance

Solvers performed similarly to non-solvers in the RRTT. This contradicts that solvers payed more attention to the TMR than non-solvers, which could have increased their likelihood of successfully solving the PST. Overall Wake Stim subjects performed very well in the RRTT which makes it unlikely that they could concentrate on the TMR in addition to the RRTT. However, it cannot be ruled out that TMR was processed consciously in addition to subconscious mechanisms in the Wake Stim group, increasing their PST solving rate compared to REM Stim group.

As is already standard practice, TMR recollection tasks should be used, to investigate whether large discrepancies in TMR recognition are present between sleep groups and wakefulness control groups. This could reveal a possible confounding effect on testing performance.

HNH Performance

Stimulation sound recognition varied between individuals, but no significant difference was found between solvers and non-solvers. Correct recognition of TMR sounds did not increase the likelihood of successfully solving the PST.

By using this study's specific TMR protocol, this experiment attempted to increase the effectiveness on problem-solving compared to simply replaying random sounds from the video game. The subconscious of the subjects was targeted, aiming to instigate a learning cycle of the sound pattern. Hypothetically, this might subconsciously lead the subject to the correct solution during the incubation interval or testing session.

As discussed in 4.1, albeit the special TMR protocol, solving rates were not higher when compared to those from previous studies using no TMR (Beijamini et al, 2014). The effectiveness of TMR for this type of study should be further researched.

4.3.5. Auxiliary Possibly Confounding Variables

Different TMR Onset Between Conditions

The latency of TMR during the incubation interval was different between REM Stim and Wake Stim groups. REM Stim subjects received TMR not earlier than 90 minutes after falling asleep, because live scoring was started at that time and REM sleep episodes usually occur later in sleep (Rechtschaffen, 1968). TMR was presented to Wake Stim subjects approximately 50 minutes to one hour after the incubation interval video footage was started. This discrepancy between TMR onset may have affected results of TMR between groups. Research teams should aim to keep TMR latency the same between groups, since research has shown that memories may change over time, starting as soon as the memory is created (Gisquet-Verrier & Riccio, 2012; Sara, 2000).

Training Advice

From the entire training session advice procedure, only the advice given how to restart a level had a significant impact on solving the PST. Further analysis showed that this affected only the PST starters of the REM Stim group. In this specific population there was an effect of Restart Advice on problem-solving probability. It is important to note that only one subject from the PST starter subgroup of REM Stim solved the PST and that subject received Restart Advice. Furthermore, Restart Advice was necessary for subjects to complete the training session. Even though subjects were given instruction on how to play the video game including how to restart a level, multiple subjects would not use this feature, even though they were at an impasse. While this study aimed to keep observer intrusions to a minimum, this helping procedure was deemed necessary.

This study should be created using a larger sample size to confirm whether Restart Advice is not only coincidentally associated with problem-solving in this study’s results.

Game Experience

Game experience was similar across conditions but different between solvers and non-solvers. Solvers generally had a more positive game experience and evaluated themselves more competent at the game. This was the case even after the training session, indicating a possible factor that determined who solved the PST. Overall, non-solvers had a more negative game experience, especially concerning emotional aspects. The differences in game experience related to the PST performance was expected. Solvers' game experience improved after solving and non-solvers' game experience worsened after unsuccessfully aborting the video game. In this study, the game experience in the testing session was more negative, related to the larger change in game experience in non-solvers. However, Wake Stim non-solvers rated their experience even worse than REM Stim non-solvers. Possibly this is related to the findings of the mood state and sleepiness analysis (see 4.3.2), where Wake Stim subjects tended to be in a worse mood and more tired before the testing session. Wake Stim solvers in the training session rated themselves more competent and showed higher positive affection to the game than REM Stim solvers. Again, this fits the findings of the mood state analysis (see 4.3.2), where Wake Stim subjects were in a better mood and more alert before their training session.

To evaluate the importance of game experience on problem-solving, comparing the training session experience is essential, since testing session experience is very susceptible to subjective fulfillment through solving and frustration through non-fulfillment through not being able to solve the PST, as seen in 3.7. Moreover, subjects who were not able to solve during the testing session played for a longer time than solvers, which may have further increased their fatigue and listlessness towards the game.

The training session comparison shows that subjects in the wake condition who felt more positively about the game were more likely to solve the PST. Interestingly, this correlation is significant, unlike the correlation to the objective training session performance in form of the TLPI. As to why the REM Stim group did not show similar tendencies is not clear. Self-assessment may be an important contributor to problem-solving and should be further researched in related studies.

Possible reasons why Wake Stim solvers and non-solvers differed more in their game experience may include additional circadian effects and differences in character personality traits (see 4.3.2). As mentioned in 2.7, this study refrained from running additional analyses for circadian effects for the GEQ, because the impact solving or non-solving have on the game experience. This would impair an identification of real circadian effects. In general, researchers should ask their subjects about their type of experience when conducting research on video games or problem-solving, as it could be shown here that game experience relates to better problem-solving performance. Perhaps additional motivation in form of a bonus for successful completion of the PST could increase the future relevance of the game and improve performance (Wilhelm et al, 2011). Future studies should aim to make the problem-solving as rewarding as possible, to ensure best performances of their subjects.

Rehearsal

Thinking or talking about the game during the incubation interval did not affect the likelihood of successfully solving the PST. The only measurable significant difference in reflection of and affection by the game during the incubation interval was that REM Stim thought more about how funny they rated the game.

The Rehearsal Questionnaire was designed to help assessment on whether subjects rehearsed the video game during the incubation interval, while either awake going about their daily business or in bed, trying to sleep. As could be shown here, subjects of this study did not benefit from rehearsal for their PST performance. However, having enjoyed the game and thinking about how funny it was, was different between REM Stim and Wake Stim groups, with Wake Stim subjects remembering the game funnier than REM Stim subjects. Together with the game experience analysis, this supports the idea that Wake Stim subjects felt differently about the game than REM Stim subjects.

A possibility for PST solving in REM Stim subjects was that they thought about the solution while lying awake and thinking about the game before falling asleep. The analysis of the Rehearsal Questionnaire does not support this idea. Furthermore, subjects were asked after completion of the video game testing session when they had thought about the solution. If subjects said that it occurred to them before sleep, they were dropped from the study. This happened in one case.

Altogether, rehearsal should be analyzed when assessing performance increases in problem-solving over a longer incubation interval, especially if the environment of the subjects is not controlled during this time, as was the case in this study. While a possible confounding effect for rehearsal on problem-solving could not be found in this study, it cannot be ruled out for future studies.

4.4. Study Design Difficulties and Limitations

This study produced a high rate of failed experiments caused by difficulties within the design itself and technical difficulties. Only 32 of 50 experiments were successful, delaying the schedule significantly. Of the 18 failed experiments 8 were REM Stim and 10 were Wake Stim group subjects.

A single-blind approach was used, meaning that the experimenter always knew whether TMR or no TMR was applied. Subjects were only aware of being part of a wakefulness or sleep group. Subjects interested in the study that did not want to be in Wake Stim were allowed to participate in REM Stim and vice versa. This could have led to sample differences between conditions. In general, studies using double-blind (observers unknowing of subject group) or triple-blind (observers and separate evaluation committee oblivious to subject group) designs help to avoid observer bias. Higher observer expectation may increase subject performance, e.g. through subconscious differences in observer behavior (Rosenthal & Jacobson, 1968).

Checkpoints

This study implemented a strict set of rules on when an experiment should be discontinued. Solving the PST in the training session lead to exclusion of the subject for this study and accounted for three failed experiments in REM Stim and four in Wake Stim. One subject in REM Stim reported to have figured out the PST solution before falling asleep, leading to exclusion of the study. For these subjects, no improvement on problem-solving would have been measurable using the described study design. In Wake Stim one subject was excluded, because of not adhering to the instructions given for the incubation interval. The instructions prohibited activities that may incite changes in hormonal balance (e.g. sexual intercourse, sports, stress, medication), modulate the wakefulness condition (sleeping, caffeine, alcohol) and conflict with neuronal representation and processing of the video game training session (playing other video games).

The incubation interval instructions for Wake Stim aimed to keep the incubation interval between REM Stim and Wake Stim as similar as possible. However, it interfered with a normal day activity of the subjects, as those would have likely engaged in some of the prohibited activities. Perhaps this may be one reason, why subjects in the Wake Stim group were in a less good mood in the evening, as described in the mood state analysis (see 4.3.2). If the instructions had been more lenient, blood hormone analysis would have been required to prove that the daily activities of the Wake Stim group did not affect their hormone levels at the time of the testing session. However, they would not account for the incubation interval itself, during which the processing of the experiment experience has taken place. Another option would have been to keep the subjects in the sleep laboratory for the entire incubation interval, where monitoring of their activities and perhaps regular blood sampling would have been possible. Whether this method would have resulted in the Wake Stim subjects being of a better mood in the testing session is debatable.

Technical Difficulties

Two subjects from Wake Stim were removed from the study because of technical difficulties concerning audio. The audio setup for the Wake Stim group required correct connection of the audio cable to one of two computers. During the video game sessions, audio was played through the computer used by the subjects. During the RRTT, white noise and TMR was presented using a separate computer. Sleep laboratories were shared among different research teams using different audio setups, which further increased the likelihood for mistakes in this study. One subject from Wake Stim was excluded because of a screen recording software error during the training session. CamStudio required a specific setup to correctly capture the on-screen footage on the computer used by this study (RendersoftSoftware, 2001). For unknown reasons, these settings would reset to default, causing loss of video footage. Video game footage was required for this study, because initially analysis of in-game behavior was planned. Later, this proved to be out of the scope of this study, as the planned scoring procedure for in-game behavior was too subjective and no other applicable methods were found. Future studies should prefer simple setups to decrease technical errors and using only validated tools.

Polysomnography

Absolute awareness of having received stimulation during sleep in REM Stim occurred in two cases and these were excluded. Comparison of their performance with those of the other REM Stim or Wake Stim subjects was not possible. The polysomnography used in this study adhered to the standards described in 2.3. During the sleep interval, live scoring was impeded by missing and distorted electrode signals. In the cases of the mentioned two subjects being awake during REM sleep stimulation, polysomnography data was not sufficiently intact to enable correct assessment of sleep stage and application of TMR was faulty. This study used sixteen electrodes in total, one ground electrode placed on forehead, nine of them placed over cortical regions and two each used for EMG, EOG and reference. This allowed to compensate for malfunctioning of multiple electrodes and achieve adequate live scoring. Electrode malfunctioning was a common occurrence in this study. Sweating and moving of subjects throughout the night most likely accounted for the dislocation and malfunctioning of electrodes, especially those placed frontally, occipitally and as EMG electrodes on the chin. While temperature-control at 24 °C was implemented in all sleep laboratories, subjects used their own sleep outfit and may have varied in their heat tolerance while asleep. In some cases, even extensive amounts of tape were not able to prevent electrode malfunctioning throughout the night. Furthermore, thick, long or curly hair of some subjects impaired installation and persistence of electrodes. Offline scoring was performed as described in 2.3. and necessary to correctly score especially difficult epochs. If signals were too disrupted, the epoch was scored as Movement Time. More durable equipment may reduce the number of faulty TMR applications and consequently reduce the incidence of failed experiments.

Rapid Eye Movement Sleep Targeted Memory Reactivation

For REM Stim experiments, the stimulation stretched over multiple REM sleep episodes possibly prolongated by the difficult live scoring conditions. Number and length of REM sleep episodes and total amount of REM sleep varied between subjects. 15 REM Stim subjects received the entire TMR protocol. One subject received above 70% and could thus be included in the study. Another subject only received less than 70%, excluding him or her from this study. Variance of REM sleep between subjects has been documented in many studies. A meta-analysis of some of these conducted by Ohayon et al demonstrated that even among healthy subjects of similar age, sleep stage percentages, length and total amount have a high variance (Ohayon et al, 2004). TMR protocols should be designed not only to include sufficient repetitions but also be short enough to be presented to a similar extent to all subjects. Moreover, it is still unclear how TMR during multiple sleep stage episodes compares to TMR during only one sleep stage episode. More research on this question is needed, to determine comparability of studies using different TMR protocols.

Stress

The protocol was very strenuous on both observer and subjects of the study. One REM Stim subject quit the experiment, having lost motivation. One Wake Stim subject was unable to solve the training levels and another one failed the RRTT during TMR. These subjects had to be removed from the study. While having a multitude of tests and questionnaires helps to detect confounding variables, it also produces more stress for the subjects. Those more susceptible to stress may underperform, introducing further possible confounders. This should be kept in mind, when designing a study protocol.

Evaluation of Problem-Solving

This study used an all-or-none rating for the problem-solving of the PST (solving or not solving). The time-to-solve variable was only applicable to subjects who solved. There was no continuous variable to assess problem-solving of the PST for subjects who did not solve. In some cases, improvements in problem-solving between conditions may have not been high enough to lead to solution of the PST. A tool that provides a continuous variable for problem-solving ability is needed to reveal this “subclinical” increase in problem-solving. The tool may focus on behavior, analyzing which methods or strategies subjects use to solve the problem, the creativity of their approach, whether they have used it before and how fast they execute new strategies. Other options may be to use divergent problems as done by Gilhooly et al or to award points for correct steps to solve the problem as implemented by Monaghan et al (Gilhooly, 2016; Monaghan et al, 2015). However, a continuous variable for problem-solving may not predict solving of insight problems, since the mechanism of insight problems is unknown and thus not measurable (Bowden et al, 2005; Gick & Lockhart, 1995; Hélie & Sun, 2010; Ohlsson, 1992). The scoring procedure of problem-solving needs to be applicable explicitly to the used problem-solving test and there may not be a single best option for problem-solving studies in general.

Effect of Targeted Memory Reactivation on EEG

This study did not monitor EEG signal responses to TMR stimulation in Wake Stim. Therefore, a comparison of the TMR-induced cortical responses between REM sleep and wakefulness was not possible. Analyzing the effect of TMR on REM Stim subjects’ EEG was beyond the scope of this study. Other research teams using TMR should consider using EEG monitoring of all their groups to allow to discover whether responses to TMR are different between sleep stages and wakefulness and whether such a difference is connected to a difference in problem-solving performance.

Gender Distribution

Due to the low numbers of male subjects interested in taking part in this study, no 50-50 gender distribution between conditions could be achieved. Male subjects were balanced among conditions, since results suggest males play video games more often than females (Király et al, 2017). Evidence has accumulated that in women the menstrual cycle may affect sleep-dependent memory consolidation and perhaps impair effectiveness of SWS TMR compared to men (Cousins et al, 2014; Diekelmann et al, 2016; Genzel et al, 2012). This study did not check for menstrual cycle phase or sexual hormone level in female subjects. A confounding effect of hormonal cycle is possible. In future studies, menstrual cycle phase or sexual hormone levels should be tested to validate this possibility. Furthermore, research teams conducting studies about video games should verify that gender distribution is equal among conditions or to first use a male-only approach and later compare findings to mixed or female-only conditions.

Summary

Anecdotal references and sayings attribute a beneficial effect of sleep on solving problems, especially if these are difficult. Currently scientific results are split. Some sleep research teams found beneficial effects on problem-solving, particularly for difficult problems (Sio et al, 2013). Other teams could not corroborate this (Landmann et al, 2016). Moreover, results indicate that sleeping after solving analogical problems facilitates the solution of logical problems after wakening (Monaghan et al, 2015).

Sleep is a heterogenous process of distinguishable sleep stages (Rechtschaffen, 1968). Although studies keep providing new evidence for models and theories that postulate how subconscious sleep-facilitated improvements in learning, memory and problem-solving occur, there are no definitive answers yet (Almeida-Filho et al, 2018). As a possible equivalent for memory consolidation, neuronal activity during a task is replayed in a coherent and temporal order in a succeeding rest period (Hoffman & McNaughton, 2002). The reactivations may help to incorporate new types of information into preexisting memories (Gisquet-Verrier & Riccio, 2012).

The reactivation of specific memory loops can be triggered in subjects, even when asleep (Rasch et al, 2007). This “targeted memory reactivation” (TMR) at large has produced increases in sleep-dependent memory processing, utilizing either olfactory or auditory stimuli as triggers (Schouten et al, 2017). Evidence has emerged that the rapid eye movement sleep stage (REM sleep) may be directly involved with the selectivity of sleep-dependent memory consolidation (Oudiette et al, 2013; Stickgold & Walker, 2013). REM sleep memory reactivations may reduce self-imposed constraints, thereby facilitating creative and analogical problem-solving (Lewis et al, 2018).

This present study used auditory targeted memory reactivation (TMR) of problem-associated memories to facilitate the solution of a specific video game level (Problem-Solving Test, PST). Furthermore, this study used a second video game level with an analogical solution strategy (Analogical Problem-Solving Test, APST), which had been shown to increase the solving rate of logical

problems (Monaghan et al, 2015). In the present study 32 subjects participated and were allocated to the REM sleep TMR group (REM Stim) and to the active wakefulness TMR group (Wake Stim). After the video game training session (including an attempt at the Problem-Solving Test), REM Stim subjects slept overnight in the sleep laboratory and auditory TMR was applied during REM sleep. After a 45-minute break, Wake Stim subjects received auditory TMR while working on a vigilance task and pursued their regular day schedule outside the laboratory, to return in the evening for further testing. During the testing session half of each group started with the Problem-Solving Test (PST) and the other half with the Analogical Problem-Solving Test (APST) and all attempted to complete both levels.

This study found no beneficial effect for REM sleep TMR over active wakefulness TMR on solving rate or speed of the PST. The theory that REM sleep memory reactivations facilitate problem-solving was not confirmed (Lewis et al, 2018). A beneficial effect of sleep for problem-solving as described by other authors was not found (Beijamini et al, 2014; Sio et al, 2013). PST solving was facilitated by prior APST solving only for REM Stim subjects. APST solving rate was higher in the REM Stim group. These results support that sleep improves analogical problem-solving (Monaghan et al, 2015). Possible confounding effects were mental and mood state, sleepiness and subjective video game experience. Apart from the latter, these effects seem to be partly related to the circadian rhythm (Borb & Achermann, 1999).

Future studies should try to replicate these results with control conditions of slow wave sleep TMR and no TMR sleep and wake groups. Additionally, larger sample sizes should be used, to further assess the overall importance of sleep and TMR for problem-solving. Enhancing sleep procedures to optimize cognitive capabilities remain an interesting prospect for further research.

Zusammenfassung

Anekdoten und Redewendungen weisen Schlaf einen positiven Effekt insbesondere auf das Lösen von schwierigen Problemen zu. Derzeit ist der Forschungsstand uneins. Manche Studien fanden Belege für verbessertes Lösen vor allem schwieriger Probleme durch Schlaf (Sio et al, 2013). Andere fanden keinen Effekt (Landmann et al, 2016). Durch Schlafen nach dem Lösen analoger Probleme verbessere sich das Problemlösen danach (Monaghan et al, 2015).

Schlaf ist ein heterogener Prozess unterscheidbarer Schlafstadien (Rechtschaffen, 1968). Obwohl Belege für Erklärungsmodelle der positiven Effekte von Schlaf auf Lernen, Gedächtnis und Problemlösung gefunden wurden, fehlen bisher die abschließenden Beweise (Almeida-Filho et al, 2018). Als mögliches Korrelat der Gedächtniskonsolidierung wiederholen sich kongruente neuronale Aktivierungen während einer Tätigkeit auch in den folgenden Ruhephasen (Hoffman & McNaughton, 2002). Diese Reaktivierungen können die Integration neuer Informationen in frühere Erinnerungen ermöglichen (Gisquet-Verrier & Riccio, 2012).

Selbst während des Schlafes lassen sich Reaktivierungen bestimmter Erinnerungen triggern (Rasch et al, 2007). Mit olfaktorischen oder auditorischen Stimuli kann diese „Gezielte Erinnerungsreaktivierung“ (TMR) Effekte von Schlaf auf diese Erinnerungen verstärken (Schouten et al, 2017). Ein Zusammenhang des Rapid Eye Movement Schlafes (REM Schlaf) mit der Selektivität der schlafabhängigen Gedächtniskonsolidierung wurde beschrieben (Oudiette et al, 2013; Stickgold & Walker, 2013). Gedächtnisreaktivierungen im REM Schlaf können selbstauferlegte Einschränkungen abschwächen und damit kreatives und analoges Problemlösen fördern (Lewis et al, 2018).

Die vorliegende Studie verwendete eine auditorische „Gezielte Erinnerungsreaktivierung“ (TMR) von Problem-assoziierten Erinnerungen um die Lösung eines speziellen Videospiellevels (Problem-Solving Test, PST) zu erleichtern. Ein weiteres Level mit einer analogen Lösungsstrategie (Analogical Problem-Solving Test, APST) wurde eingesetzt, welches Konzept in anderen

Studien die Lösungsrate von Problemen erhöhte (Monaghan et al, 2015). An dieser Studie nahmen 32 Probanden teil und wurden der REM Schlaf TMR Gruppe (REM Stim) und der Gruppe mit TMR während aktiven Wachseins (Wake Stim) zugeteilt. Nach einer Trainingseinheit (inklusive eines Versuches am Problem-Solving Test) schlief die REM Stim Gruppe über Nacht im Schlaflabor und erhielt TMR während des REM Schlafes. Wake Stim Probanden hingegen erhielten nach einer 45-minütigen Pause die TMR während eines Vigilanztestes und gingen ihren täglichen Aktivitäten außerhalb des Labors nach, um abends für weitere Tests zurückzukehren. In der Testeinheit startete die Hälfte jeder Gruppe mit dem Problem-Solving Test (PST) und die andere Hälfte mit dem Analogical Problem-Solving Test (APST) und alle versuchten beide Level zu lösen.

Diese Studie fand keine verbesserte Lösungsrate oder -geschwindigkeit des PST durch REM Schlaf TMR im Vergleich zu der TMR während des aktiven Wachseins. Die Theorie, dass Gedächtnisreaktivierungen im REM Schlaf Problemlösen erleichtern, wurde nicht bestätigt. (Lewis et al, 2018). Beschriebene Verbesserungen des Problemlösens durch Schlaf konnten nicht bestätigt werden (Beijamini et al, 2014; Sio et al, 2013). Nur in der REM Stim Gruppe war PST-Lösungsrate höher nach APST-Lösung. Die Lösungsrate des APST selbst war höher in der REM Stim Gruppe. Dies könnte ein Beleg für ein verbessertes Lösen analoger Probleme nach dem Schlafen sein (Monaghan et al, 2015). Mögliche konfundierende Faktoren waren geistige und emotionale Verfassung, Schläfrigkeit und subjektives Erleben des Videospiels. Außer letzterem lassen sich diese teilweise durch die zirkadiane Rhythmik erklären (Borb & Achermann, 1999).

Zukünftige Studien sollten versuchen diese Ergebnisse mit größeren Stichproben zu replizieren. Kontrollgruppen mit „Slow Wave“ Schlaf TMR, sowie Schlaf- und Wachgruppen ohne TMR sollten zusätzlich untersucht werden, um die Bedeutung von Schlaf und TMR auf Problemlösen im Gesamten einzuschätzen. Die Möglichkeiten einer Optimierung kognitiver Fähigkeiten durch additive Prozeduren während des Schlafes bleiben eine interessante Idee.

Bibliography

Agnew Jr, H., Webb, W. B. & Williams, R. L. (1966) The First Night Effect: An Eeg Study of Sleep. *Psychophysiology*, 2(3), 263-266.

Alberini, C. M. (2005) Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? *Trends Neurosci*, 28(1), 51-6.

Almeida-Filho, D. G., Queiroz, C. M. & Ribeiro, S. (2018) Memory corticalization triggered by REM sleep: mechanisms of cellular and systems consolidation. *Cellular and Molecular Life Sciences*, 1-26.

Antony, J. W., Gobel, E. W., O'hare, J. K., Reber, P. J. & Paller, K. A. (2012) Cued memory reactivation during sleep influences skill learning. *Nature neuroscience*, 15(8), 1114.

Armitage, R. (1995) The distribution of EEG frequencies in REM and NREM sleep stages in healthy young adults. *Sleep*, 18(5), 334-341.

Baars, B. (1988) A Cognitive Theory of Consciousness Cambridge Univ. Press, Cambridge, UK.

Batterink, L. J., Creery, J. D. & Paller, K. A. (2016) Phase of Spontaneous Slow Oscillations during Sleep Influences Memory-Related Processing of Auditory Cues. *J Neurosci*, 36(4), 1401-9.

Beijamini, F., Pereira, S. I., Cini, F. A. & Louzada, F. M. (2014) After being challenged by a video game problem, sleep increases the chance to solve it. *PLoS One*, 9(1), e84342.

Belal, S., Cousins, J., El-Deredy, W., Parkes, L., Schneider, J., Tsujimura, H., Zoumpoulaki, A., Perapoch, M., Santamaria, L. & Lewis, P. (2018) Identification of memory reactivation during sleep by EEG classification. *Neuroimage*, 176, 203-214.

Berry, R. B., Brooks, R., Gamaldo, C. E., Harding, S. M., Lloyd, R. M., Marcus, C. L. & Vaughn, B. V. (2016) *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications: version 2.3*American Academy of Sleep Medicine.

Borb, A. A. & Achermann, P. (1999) Sleep homeostasis and models of sleep regulation. *Journal of biological rhythms*, 14(6), 559-570.

Bowden, E. M., Jung-Beeman, M., Fleck, J. & Kounios, J. (2005) New approaches to demystifying insight. *Trends in cognitive sciences*, 9(7), 322-328.

BrainProducts (2000) BrainVision Recorder Version 1.20.0701.

BrainProducts (2015) BrainVision Analyzer 2 Version 2.1.1.

Buzsaki, G. (2006) *Rhythms of the Brain*Oxford University Press.

Cai, D. J., Mednick, S. A., Harrison, E. M., Kanady, J. C. & Mednick, S. C. (2009) REM, not incubation, improves creativity by priming associative networks. *Proceedings of the National Academy of Sciences*, 106(25), 10130-10134.

Cairney, S. A., Durrant, S. J., Hulleman, J. & Lewis, P. A. (2014) Targeted memory reactivation during slow wave sleep facilitates emotional memory consolidation. *Sleep*, 37(4), 701-7, 707A.

Carskadon, M. A. & Herz, R. S. (2004) Minimal olfactory perception during sleep: why odor alarms will not work for humans. *Sleep*, 27(3), 402-405.

Chatburn, A., Lushington, K. & Kohler, M. J. (2014) Complex associative memory processing and sleep: a systematic review and meta-analysis of

behavioural evidence and underlying EEG mechanisms. *Neuroscience & Biobehavioral Reviews*, 47, 646-655.
Chu, S. & Downes, J. J. (2002) Proust nose best: Odors are better cues of autobiographical memory. *Memory & cognition*, 30(4), 511-518.
Cousins, J. N., El-Deredy, W., Parkes, L. M., Hennies, N. & Lewis, P. A. (2014) Cued memory reactivation during slow-wave sleep promotes explicit knowledge of a motor sequence. *Journal of Neuroscience*, 34(48), 15870-15876.
Cox, R., Korjoukov, I., de Boer, M. & Talamini, L. M. (2014) Sound asleep: processing and retention of slow oscillation phase-targeted stimuli. *PLoS One*, 9(7), e101567.
Creery, J. D., Oudiette, D., Antony, J. W. & Paller, K. A. (2015) Targeted Memory Reactivation during Sleep Depends on Prior Learning. *Sleep*, 38(5), 755-63.
Datta, S. (2000) Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. *Journal of Neuroscience*, 20(22), 8607-8613.
Deweer, B. & Sara, S. J. (1984) Background stimuli as a reminder after spontaneous forgetting: Role of duration of cuing and cuing-test interval. *Animal Learning & Behavior*, 12(2), 238-247.
Diekelmann, S., Biggel, S., Rasch, B. & Born, J. (2012) Offline consolidation of memory varies with time in slow wave sleep and can be accelerated by cuing memory reactivations. *Neurobiology of learning and memory*, 98(2), 103-111.
Diekelmann, S. & Born, J. (2010) The memory function of sleep. *Nat Rev Neurosci*, 11(2), 114-26.
Diekelmann, S., Born, J. & Rasch, B. (2016) Increasing Explicit Sequence Knowledge by Odor Cueing during Sleep in Men but not Women. *Front Behav Neurosci*, 10, 74.
Diekelmann, S., Büchel, C., Born, J. & Rasch, B. (2011) Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nature neuroscience*, 14(3), 381.
Dijk, D. J., Beersma, D. G. & Bloem, G. M. (1989) Sex differences in the sleep EEG of young adults: visual scoring and spectral analysis. *Sleep*, 12(6), 500-507.
Dinges, D. F. & Powell, J. W. (1985) Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior research methods, instruments, & computers*, 17(6), 652-655.
Donohue, K. C. & Spencer, R. M. (2011) Continuous re-exposure to environmental sound cues during sleep does not improve memory for semantically unrelated word pairs. *Journal of cognitive education and psychology: JCEP*, 10(2), 167.
Dougal, S. & Schooler, J. W. (2007) Discovery misattribution: when solving is confused with remembering. *Journal of Experimental Psychology: General*, 136(4), 577.
Dudai, Y. (2006) Reconsolidation: the advantage of being refocused. *Curr Opin Neurobiol*, 16(2), 174-8.
Durrant, S. J., Cairney, S. A., McDermott, C. & Lewis, P. A. (2015) Schema-conformant memories are preferentially consolidated during REM sleep. *Neurobiol Learn Mem*, 122, 41-50.

Ehlers, C. & Kupfer, D. (1997) Slow-wave sleep: do young adult men and women age differently? *Journal of sleep research*, 6(3), 211-215.
EPSITEC, e. (1999) Speedy Eggbert Mania.
Feinberg, I. (1989) Effects of maturation and aging on slow wave sleep in man. *Slow Wave Sleep. Physiological, Phathophysiological, and Functional Aspects*, 31-48.
Feld, G. B. & Diekelmann, S. (2015) Sleep smart-optimizing sleep for declarative learning and memory. *Front Psychol*, 6, 622.
Fuentemilla, L., Miró, J., Ripollés, P., Vilà-Balló, A., Juncadella, M., Castañer, S., Salord, N., Monasterio, C., Falip, M. & Rodríguez-Fornells, A. (2013) Hippocampus-dependent strengthening of targeted memories via reactivation during sleep in humans. *Current Biology*, 23(18), 1769-1775.
Gais, S., Albouy, G., Boly, M., Dang-Vu, T. T., Darsaud, A., Desseilles, M., Rauchs, G., Schabus, M., Sterpenich, V. & Vandewalle, G. (2007) Sleep transforms the cerebral trace of declarative memories. *Proceedings of the National Academy of Sciences*, 104(47), 18778-18783.
Gais, S. & Born, J. (2004) Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proceedings of the National Academy of Sciences*, 101(7), 2140-2144.
Genzel, L., Kiefer, T., Renner, L., Wehrle, R., Kluge, M., Grözinger, M., Steiger, A. & Dresler, M. (2012) Sex and modulatory menstrual cycle effects on sleep related memory consolidation. *Psychoneuroendocrinology*, 37(7), 987-998.
Gick, M. L. & Lockhart, R. S. (1995) Cognitive and affective components of insight.
Gilhooly, K. J. (2016) Incubation and intuition in creative problem solving. *Frontiers in psychology*, 7, 1076.
Gisquet-Verrier, P. & Riccio, D. C. (2012) Memory reactivation effects independent of reconsolidation. *Learn Mem*, 19(9), 401-9.
Giuditta, A., Ambrosini, M. V., Montagnese, P., Mandile, P., Cotugno, M., Zucconi, G. G. & Vescia, S. (1995) The sequential hypothesis of the function of sleep. *Behavioural brain research*, 69(1-2), 157-166.
Görtelmeyer, R. (1985) On the development of a standardized sleep inventory for the assessment of sleep. *Methods of sleep research*, 93-98.
Guilford, J. P. (1967) The nature of human intelligence.
Hashmi, A., Nere, A. T. & Tononi, G. (2013) Sleep-dependent synaptic down-selection (II): single-neuron level benefits for matching, selectivity, and specificity. *Frontiers in neurology*, 4, 148.
Hasselmo, M. E. (1999) Neuromodulation: acetylcholine and memory consolidation. *Trends in cognitive sciences*, 3(9), 351-359.
Hélie, S. & Sun, R. (2010) Incubation, insight, and creative problem solving: a unified theory and a connectionist model. *Psychological review*, 117(3), 994.
Himanen, S.-L. & Hasan, J. (2000) Limitations of rechtschaffen and kales. *Sleep medicine reviews*, 4(2), 149-167.
Hoddes, E., Zarcone, V. & Dement, W. (1972) Cross-validation of the Stanford sleepiness scale. *Sleep Research*, 1, 91.
Hoddes, E., Zarcone, V., Smythe, H., Phillips, R. & Dement, W. (1973) Quantification of sleepiness: a new approach. *Psychophysiology*, 10(4), 431-436.

Hoffman, K. L. & McNaughton, B. L. (2002) Coordinated Reactivation of Distributed Memory Traces in Primate Neocortex. *Science*, 297(5589), 2070-2073.

Hu, X., Antony, J. W., Creery, J. D., Vargas, I. M., Bodenhausen, G. V. & Paller, K. A. (2015) Unlearning implicit social biases during sleep. *Science*, 348(6238), 1013-1015.

Huber, R., Ghilardi, M. F., Massimini, M. & Tononi, G. (2004) Local sleep and learning. *Nature*, 430(6995), 78.

IJsselsteijn, W. A., de Kort, Y. A. W. & Poels, K. (2013) *The Game Experience Questionnaire*Human Technology, I.

Jasper, H. (1958) The international “10–20” system of the International Federation. *Electroencephalography and Clinical Neurophysiology*, 10, 371-375.

Király, O., Sleczka, P., Pontes, H. M., Urbán, R., Griffiths, M. D. & Demetrovics, Z. (2017) Validation of the ten-item internet gaming disorder test (IGDT-10) and evaluation of the nine DSM-5 internet gaming disorder criteria. *Addictive Behaviors*, 64, 253-260.

Kouider, S., Andrillon, T., Barbosa, L. S., Goupil, L. & Bekinschtein, T. A. (2014) Inducing task-relevant responses to speech in the sleeping brain. *Curr Biol*, 24(18), 2208-2214.

Lahl, O., Wispel, C., Willigens, B. & Pietrowsky, R. (2008) An ultra short episode of sleep is sufficient to promote declarative memory performance. *Journal of sleep research*, 17(1), 3-10.

Landmann, N., Kuhn, M., Maier, J.-G., Feige, B., Spiegelhalder, K., Riemann, D. & Nissen, C. (2016) Sleep strengthens but does not reorganize memory traces in a verbal creativity task. *Sleep*, 39(3), 705-713.

Landmann, N., Kuhn, M., Piosczyk, H., Feige, B., Baglioni, C., Spiegelhalder, K., Frase, L., Riemann, D., Sterr, A. & Nissen, C. (2014) The reorganisation of memory during sleep. *Sleep medicine reviews*, 18(6), 531-541.

Lau, H., Alger, S. E. & Fishbein, W. (2011) Relational memory: a daytime nap facilitates the abstraction of general concepts. *PloS one*, 6(11), e27139.

Lewis, P. A., Knoblich, G. & Poe, G. (2018) How Memory Replay in Sleep Boosts Creative Problem-Solving. *Trends in cognitive sciences*, 22(6), 491-503.

Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Ancoli-Israel, S., Jagust, W. J. & Walker, M. P. (2013) Impaired prefrontal sleep spindle regulation of hippocampal-dependent learning in older adults. *Cerebral Cortex*, 24(12), 3301-3309.

Mansuy, I. M., Winder, D. G., Moallem, T. M., Osman, M., Mayford, M., Hawkins, R. D. & Kandel, E. R. (1998) Inducible and reversible gene expression with the rtTA system for the study of memory. *Neuron*, 21(2), 257-265.

Maquet, P. (2001) The role of sleep in learning and memory. *science*, 294(5544), 1048-1052.

McClelland, J. L., McNaughton, B. L. & O'reilly, R. C. (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological review*, 102(3), 419.

Metcalfe, J. (1986) Premonitions of insight predict impending error. *Journal of experimental psychology: Learning, memory, and cognition*, 12(4), 623.

Misanin, J. R., Miller, R. R. & Lewis, D. J. (1968) Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science*, 160(3827), 554-555.

Monaghan, P., Sio, U. N., Lau, S. W., Woo, H. K., Linkenauger, S. A. & Ormerod, T. C. (2015) Sleep promotes analogical transfer in problem solving. *Cognition*, 143, 25-30.

Mueller, S. The PEBL Manual programming and usage guide for the Psychology Experiment Building Language PEBL Version 0.14.[Online]. ISBN 978-0-557-65817-6.

Mueller, S. (2011a) PEBL's Four-choice response time task.

Mueller, S. (2011b) The PEBL digit span test.

Müller, G. E. & Pilzecker, A. (1900) *Experimentelle Beiträge zur Lehre vom Gedächtnis*, *1*. Z. Psychol. Ergänzungsband: JA Barth.

Nader, K. (2003) Memory traces unbound. *Trends in neurosciences*, 26(2), 65-72.

Ohayon, M. M., Carskadon, M. A., Guilleminault, C. & Vitiello, M. V. (2004) Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*, 27(7), 1255-1273.

Ohlsson, S. (1992) Information-processing explanations of insight and related phenomena. *Advances in the psychology of thinking*, 1, 1-44.

Oudiette, D., Antony, J. W., Creery, J. D. & Paller, K. A. (2013) The role of memory reactivation during wakefulness and sleep in determining which memories endure. *J Neurosci*, 33(15), 6672-8.

Parker, A., Ngu, H. & Cassaday, H. J. (2001) Odour and Proustian memory: reduction of context-dependent forgetting and multiple forms of memory. *Applied Cognitive Psychology: The Official Journal of the Society for Applied Research in Memory and Cognition*, 15(2), 159-171.

PEBL, P. (2010) The Psychology Experiment Building Language. PEBL.

Peigneux, P., Orban, P., Balteau, E., Degueldre, C., Luxen, A., Laureys, S. & Maquet, P. (2006) Offline persistence of memory-related cerebral activity during active wakefulness. *PLoS Biol*, 4(4), e100.

Poe, G. R. (2017) Sleep is for forgetting. *Journal of Neuroscience*, 37(3), 464-473.

Poe, G. R., Nitz, D. A., McNaughton, B. L. & Barnes, C. A. (2000) Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain research*, 855(1), 176-180.

Poincaré, H. (1910) Mathematical creation. *The Monist*, 321-335.

Rasch, B. & Born, J. (2007) Maintaining memories by reactivation. *Curr Opin Neurobiol*, 17(6), 698-703.

Rasch, B. & Born, J. (2013) About sleep's role in memory. *Physiological reviews*, 93(2), 681-766.

Rasch, B., Büchel, C., Gais, S. & Born, J. (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*, 315(5817), 1426-1429.

Rasch, B., Gais, S. & Born, J. (2009a) Impaired off-line consolidation of motor memories after combined blockade of cholinergic receptors during REM sleep-rich sleep. *Neuropsychopharmacology*, 34(7), 1843.

Rasch, B., Pommer, J., Diekelmann, S. & Born, J. (2009b) Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. *Nature neuroscience*, 12(4), 396.

Rauchs, G., Feyers, D., Landeau, B., Bastin, C., Luxen, A., Maquet, P. & Collette, F. (2011) Sleep contributes to the strengthening of some memories over others, depending on hippocampal activity at learning. *Journal of Neuroscience*, 31(7), 2563-2568.

Rechtschaffen, A. (1968) A manual for standardized terminology, techniques and scoring system for sleep stages in human subjects. *Brain information service*.

RendersoftSoftware (2001) CamStudio 2.7.2.

Ribeiro, S. & Stickgold, R. (2014) Sleep and school education. *Trends in Neuroscience and Education*, 3(1), 18-23.

Ritter, S. M., Strick, M., Bos, M. W., Van Baaren, R. B. & Dijksterhuis, A. (2012) Good morning creativity: task reactivation during sleep enhances beneficial effect of sleep on creative performance. *Journal of sleep research*, 21(6), 643-647.

Rosenthal, R. & Jacobson, L. (1968) Pygmalion in the classroom. *The urban review*, 3(1), 16-20.

Rubin, R. D. (1976) Clinical use of retrograde amnesia produced by electroconvulsive shock: a conditioning hypothesis. *Canadian Psychiatric Association Journal*, 21(2), 87-90.

Rudoy, J. D., Voss, J. L., Westerberg, C. E. & Paller, K. A. (2009) Strengthening individual memories by reactivating them during sleep. *Science*, 326(5956), 1079-1079.

Saletin, J. M., Goldstein, A. N. & Walker, M. P. (2011) The role of sleep in directed forgetting and remembering of human memories. *Cerebral Cortex*, 21(11), 2534-2541.

Sara, S. J. (2000) Retrieval and reconsolidation: toward a neurobiology of remembering. *Learning & Memory*, 7(2), 73-84.

Schiller, D. & Phelps, E. A. (2011) Does reconsolidation occur in humans? *Frontiers in behavioral neuroscience*, 5, 24.

Schneider, W., Eschman, A. & Zuccolotto, A. (2002) *E-Prime reference guide*, 2.0.10.242 edition. Psychology Software Tools, Incorporated.

Schonauer, M., Brodt, S., Pohlchen, D., Bressmer, A., Danek, A. H. & Gais, S. (2018) Sleep Does Not Promote Solving Classical Insight Problems and Magic Tricks. *Front Hum Neurosci*, 12, 72.

Schouten, D. I., Pereira, S. I., Tops, M. & Louzada, F. M. (2017) State of the art on targeted memory reactivation: sleep your way to enhanced cognition. *Sleep Medicine Reviews*, 32, 123-131.

Schreiner, T., Lehmann, M. & Rasch, B. (2015) Auditory feedback blocks memory benefits of cueing during sleep. *Nature communications*, 6, 8729.

Schreiner, T. & Rasch, B. (2014) Boosting vocabulary learning by verbal cueing during sleep. *Cerebral Cortex*, 25(11), 4169-4179.

Seibold, M., Rasch, B., Born, J. & Diekelmann, S. (2018) Reactivation of interference during sleep does not impair ongoing memory consolidation. *Memory*, 26(3), 377-384.

Simon, K. C., Gomez, R. & Nadel, L. (2017) 0234 LOSING MEMORIES WITH TARGETED MEMORY REACTIVATION. *Sleep*, 40(suppl_1), A86-A86.

Sio, U. N., Monaghan, P. & Ormerod, T. (2013) Sleep on it, but only if it is difficult: effects of sleep on problem solving. *Memory & cognition*, 41(2), 159-166.

Smith, S. M. & Vela, E. (2001) Environmental context-dependent memory: A review and meta-analysis. *Psychonomic bulletin & review*, 8(2), 203-220.

Spear, N. E. & Mueller, C. W. (1984) Consolidation as a function of retrieval, in Weingartner, H. & Parker, E. (eds), *Memory consolidation*. New York: Psychology Press, 123-160.

Spear, N. E. & Riccio, D. C. (1994) *Memory: Phenomena and principles*Allyn & Bacon.

Steriade, M., Paré, D., Bouhassira, D., Deschenes, M. & Oakson, G. (1989) Phasic activation of lateral geniculate and perigeniculate thalamic neurons during sleep with ponto-geniculo-occipital waves. *Journal of Neuroscience*, 9(7), 2215-2229.

Sterpenich, V., Schmidt, C., Albouy, G., Matarazzo, L., Vanhaudenhuyse, A., Boveroux, P., Degueldre, C., Leclercq, Y., Balteau, E., Collette, F., Luxen, A., Phillips, C. & Maquet, P. (2014) Memory reactivation during rapid eye movement sleep promotes its generalization and integration in cortical stores. *Sleep*, 37(6), 1061-75, 1075A-1075B.

Steyer, R., Schwenkmezger, P., Notz, P. & Eid, M. (1994) Testtheoretische Analysen des Mehrdimensionalen Befindlichkeitsfragebogen (MDBF). [Theoretical analysis of a multidimensional mood questionnaire (MDBF).]. *Diagnostica*, 40(4), 320-328.

Stickgold, R. & Walker, M. P. (2013) Sleep-dependent memory triage: evolving generalization through selective processing. *Nat Neurosci*, 16(2), 139-45.

Suzuki, A., Josselyn, S. A., Frankland, P. W., Masushige, S., Silva, A. J. & Kida, S. (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *Journal of Neuroscience*, 24(20), 4787-4795.

Tamminen, J., Ralph, M. A. L. & Lewis, P. A. (2017) Targeted memory reactivation of newly learned words during sleep triggers REM-mediated integration of new memories and existing knowledge. *Neurobiology of learning and memory*, 137, 77-82.

Tononi, G. & Cirelli, C. (2006) Sleep function and synaptic homeostasis. *Sleep Med Rev*, 10(1), 49-62.

Tononi, G. & Cirelli, C. (2014) Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*, 81(1), 12-34.

Tse, D., Langston, R. F., Kakeyama, M., Bethus, I., Spooner, P. A., Wood, E. R., Witter, M. P. & Morris, R. G. (2007) Schemas and memory consolidation. *Science*, 316(5821), 76-82.

Tse, D., Takeuchi, T., Kakeyama, M., Kajii, Y., Okuno, H., Tohyama, C., Bito, H. & Morris, R. G. (2011) Schema-dependent gene activation and memory encoding in neocortex. *Science*, 333(6044), 891-895.

Tulving, E. & Thomson, D. M. (1973) Encoding specificity and retrieval processes in episodic memory. *Psychological review*, 80(5), 352.

Van Der Werf, Y. D., Altena, E., Schoonheim, M. M., Sanz-Arigita, E. J., Vis, J. C., De Rijke, W. & Van Someren, E. J. (2009) Sleep benefits subsequent hippocampal functioning. *Nature neuroscience*, 12(2), 122.

van Kesteren, M. T., Ruiter, D. J., Fernández, G. & Henson, R. N. (2012) How schema and novelty augment memory formation. *Trends in neurosciences*, 35(4), 211-219.

Wagner, U., Gais, S., Haider, H., Verleger, R. & Born, J. (2004) Sleep inspires insight. *Nature*, 427(6972), 352.

Wamsley, E. J., Tucker, M., Payne, J. D., Benavides, J. A. & Stickgold, R. (2010) Dreaming of a learning task is associated with enhanced sleep-dependent memory consolidation. *Current Biology*, 20(9), 850-855.

Wilhelm, I., Diekelmann, S., Molzow, I., Ayoub, A., Mölle, M. & Born, J. (2011) Sleep selectively enhances memory expected to be of future relevance. *Journal of Neuroscience*, 31(5), 1563-1569.

Wylie, G. R., Foxe, J. J. & Taylor, T. L. (2007) Forgetting as an active process: An fMRI investigation of item-method–directed forgetting. *Cerebral Cortex*, 18(3), 670-682.

Yordanova, J., Kolev, V., Verleger, R., Bataghva, Z., Born, J. & Wagner, U. (2008) Shifting from implicit to explicit knowledge: different roles of early-and late-night sleep. *Learning & Memory*, 15(7), 508-515.

Zelano, C. & Sobel, N. (2005) Humans as an animal model for systems-level organization of olfaction. *Neuron*, 48(3), 431-454.

Index of Figures

Index of Tables

Affidavit

The thesis I have submitted entitled “Testing the Effects of Targeted Memory Reactivation during Rapid Eye Movement Sleep and Wakefulness on Problem-Solving” is my own work. The experiments and thesis were conducted under PD Dr. Susanne Diekelmann as supervisor. My work was part of a study titled “Increasing Problem-Solving Skills using Targeted Memory Reactivation during Sleep”, which was conceptualized by Dr. Felipe Beijamini, PD Dr. Susanne Diekelmann and Prof. Dr. Jan Born of the Department of Medical Psychology and Behavioral Neurobiology of Tübingen.

Subject recruitment, experiments, figures, tables and statistical analyses included in this thesis were conducted by me after preparatory training by Dr. Felipe Beijamini and PD Dr. Susanne Diekelmann. Live sleep scoring and primary sleep scoring was performed independently by me. Dr. Felipe Beijamini performed the secondary sleep scoring and an agreement of at least 80 % was reached.
I have only used the sources indicated and have not made unauthorized use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given. I have not yet presented this thesis or parts thereof to a university as part of an examination or degree. I confirm that the declarations made above are correct.

Tübingen,

Acknowledgments

I would like to express my deepest gratitude to PD Dr. Susanne Diekelmann and Dr. Felipe Beijamini who supervised my work and provided invaluable feedback and support.

The selection of this thesis’ topic was done by Dr. Felipe Beijamini, whom I would like to thank for this opportunity. Furthermore, I am grateful for the training he provided, without which I would not have been able to conduct this work. I want to extend my thanks to the Department of Medical Psychology and Behavioral Neurobiology of Tübingen, which graciously provided the tools and materials needed to conduct the experiments. Moreover, I would like to thank the laboratory personnel and fellow students with whom it was easy to organize experiment scheduling and maintenance of laboratory equipment. Special thanks go to the developers of Speedy Eggbert Mania®, without whom this specific problem-solving test would not have been possible.

Furthermore, I want to express my appreciation to the study participants that cooperated with the study protocols.

I want to thank my fiancée, my family and loved ones for their support during my studies, which enabled me to dedicate the time and work necessary to complete them and to do my research.

Appendices

Table 13: Descriptive statistics of Game Experience Questionnaire variables

Competence								
Run 1[1]								
REM Stim			Wake Stim			Both		
Non-Solvers[2]	Solvers[3]	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.3 (1.3)[4]	1.1 (0.6)	1.23 (1.07)	0.34 (0.43)	1.98 (0.7)	1.26 (1.02)	0.91 (1.12)	1.63 (0.78)	1.24 (1.03)
Run 2[5]								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.04 (1.22)	1.67 (0.77)	1.28 (1.09)	0.29 (0.43)	2.29 (0.61)	1.41 (1.15)	0.73 (1.02)	2.04 (0.72)	1.34 (1.1)
Sensory and Imaginative Immersion								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.62 (0.85)	1.42 (0.43)	1.54 (0.71)	1.05 (0.79)	1.72 (0.62)	1.43 (0.76)	1.38 (0.85)	1.6 (0.56)	1.48 (0.73)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.43 (0.86)	1.17 (0.55)	1.33 (0.75)	0.98 (0.77)	1.74 (0.72)	1.41 (0.81)	1.25 (0.83)	1.51 (0.7)	1.37 (0.77)
Flow								
Run 1								
REM Stim			Wake Stim			Both		

Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
2.5 (0.61)	2.5 (0.72)	2.5 (0.63)	1.86 (0.66)	2.24 (0.62)	2.08 (0.65)	2.24 (0.69)	2.35 (0.65)	2.29 (0.67)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
2.06 (0.88)	2.23 (0.77)	2.13 (0.82)	1.97 (0.99)	2.02 (0.76)	2 (0.84)	2.02 (0.9)	2.11 (0.75)	2.06 (0.82)
Tension/ Annoyance								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.37 (1.12)	1.39 (1.39)	1.38 (1.18)	1.9 (1.37)	0.89 (0.83)	1.33 (1.18)	1.59 (1.22)	1.09 (1.07)	1.35 (1.16)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
2.33 (1.54)	1.56 (1.07)	2.04 (1.4)	3.14 (0.66)	1 (1.35)	1.94 (1.54)	2.67 (1.29)	1.22 (1.24)	1.99 (1.45)
Challenge								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.84 (0.82)	2.2 (0.7)	1.98 (0.77)	2.03 (1.3)	1.64 (0.9)	1.81 (1.07)	1.92 (1.01)	1.87 (0.85)	1.89 (0.92)
Run 2								
REM Stim			Wake Stim			Both		

Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
2 (1.09)	2.2 (0.68)	2.08 (0.93)	2.26 (0.95)	1.38 (0.64)	1.76 (0.89)	2.11 (1.01)	1.71 (0.76)	1.92 (0.91)
Negative Affect								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.15 (1.02)	1 (0.55)	1.09 (0.86)	1.18 (0.81)	0.89 (0.47)	1.02 (0.64)	1.16 (0.91)	0.93 (0.49)	1.05 (0.74)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.8 (0.99)	0.88 (0.52)	1.45 (0.95)	1.68 (0.66)	0.89 (0.83)	1.23 (0.84)	1.75 (0.85)	0.88 (0.7)	1.34 (0.89)
Positive Affect								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
2.1 (1.16)	1.93 (0.73)	2.04 (0.99)	1.09 (1.04)	2.69 (0.63)	1.99 (1.15)	1.68 (1.19)	2.39 (0.75)	2.01 (1.06)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.52 (1.24)	2.27 (0.86)	1.8 (1.14)	0.54 (0.49)	3 (0.67)	1.93 (1.39)	1.12 (1.09)	2.71 (0.81)	1.86 (1.25)
Positive Experience								

Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.28 (0.81)	1.06 (0.25)	1.2 (0.66)	0.86 (0.67)	1.69 (0.61)	1.32 (0.75)	1.11 (0.77)	1.43 (0.58)	1.26 (0.69)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.43 (1.24)	1.89 (1.45)	1.6 (1.29)	0.38 (0.23)	2.3 (0.77)	1.46 (1.14)	1 (1.08)	2.13 (1.06)	1.53 (1.2)
Negative Experience								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
0.88 (0.91)	0.83 (0.73)	0.86 (0.82)	0.98 (1.06)	0.5 (0.33)	0.71 (0.75)	0.92 (0.94)	0.63 (0.53)	0.79 (0.78)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.35 (1.21)	0.69 (0.71)	1.1 (1.07)	1.4 (0.85)	0.44 (0.61)	0.86 (0.86)	1.37 (1.05)	0.54 (0.64)	0.98 (0.96)
Tired								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.3 (1.09)	1 (0.89)	1.19 (1)	0.64 (0.56)	0.5 (0.35)	0.56 (0.44)	1.03 (0.94)	0.7 (0.65)	0.88 (0.82)

Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
1.1 (1.13)	0.17 (0.26)	0.75 (1)	1.93 (1.21)	0.56 (0.63)	1.16 (1.14)	1.44 (1.2)	0.4 (0.54)	0.95 (1.07)
Returning to Reality								
Run 1								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
0.4 (0.44)	0.39 (0.53)	0.4 (0.46)	0.1 (0.16)	0.22 (0.24)	0.17 (0.21)	0.27 (0.38)	0.29 (0.38)	0.28 (0.37)
Run 2								
REM Stim			Wake Stim			Both		
Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total	Non-Solvers	Solvers	Total
0.5 (0.53)	0.17 (0.28)	0.38 (0.47)	0.24 (0.37)	0.44 (0.62)	0.35 (0.52)	0.39 (0.47)	0.33 (0.52)	0.36 (0.49)

[1] Run 1 being training session.

[2] Non-Solvers being subjects who did not solve the Problem-Solving Test (PST).

[3] Solvers being subjects who solved the PST.

[4] All values representing mean (SD).

[5] Run 2 being testing session.

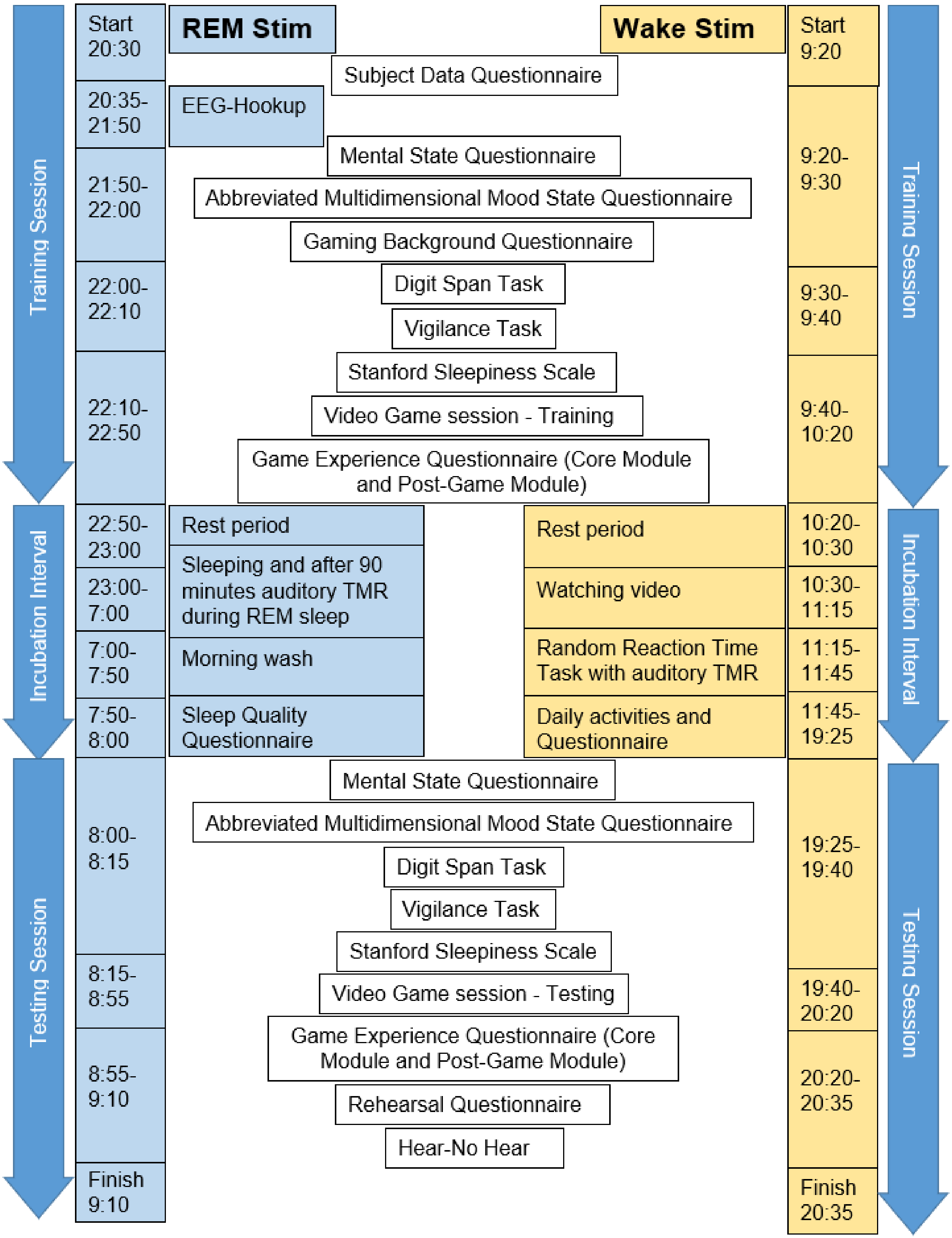

Figure 4: Detailed experimental schedule

Light blue: REM Stim procedure

Yellow: Wake Stim procedure

White: Procedure of both conditions

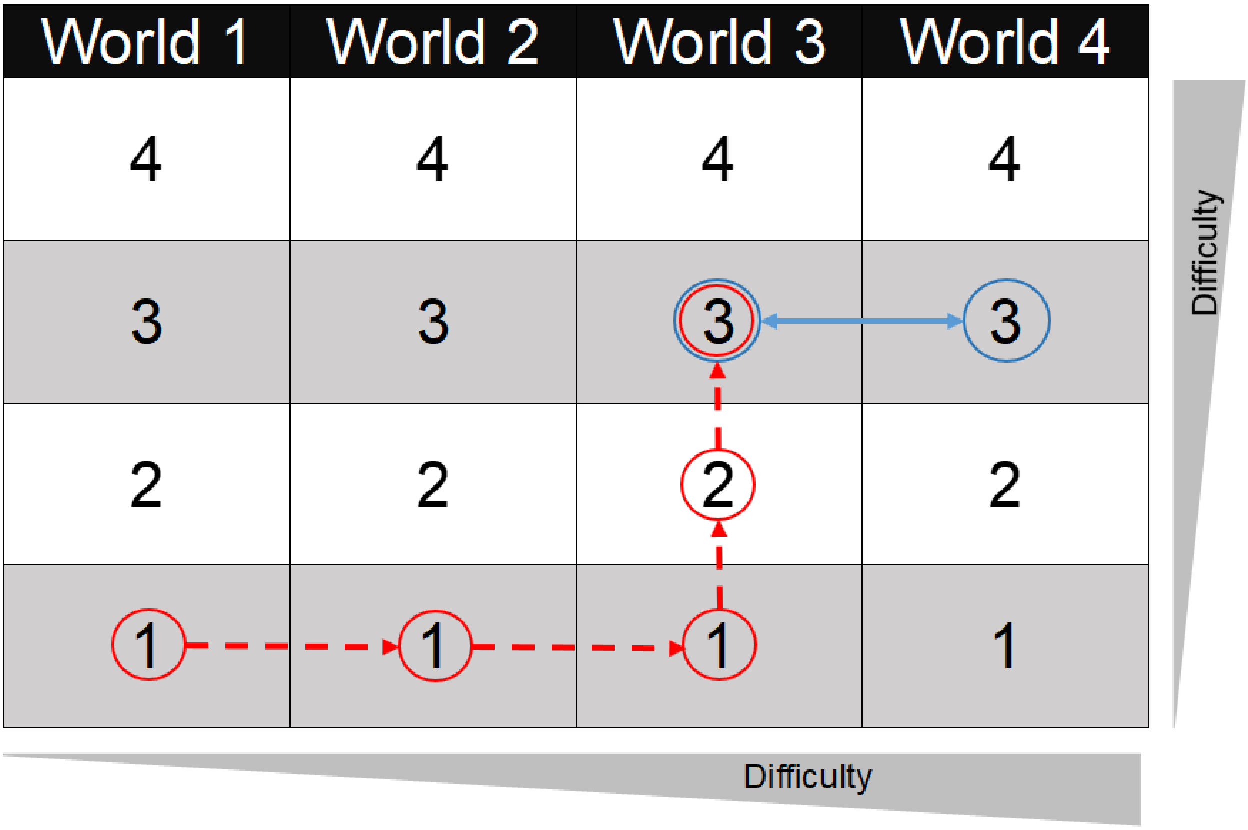

Figure 5: Schematic overview of levels

World 3 Level 3: Problem-Solving Test (PST)

World 4 Level 3: Analogical Problem-Solving Test (APST)

Red: Levels played during the training session.

Blue: Levels played during the testing session. REM Stim and Wake Stim were split in to subgroups. Subgroups started the testing session with either PST or APST.

Lebenslauf

Anthony St. Clair Valentin

Persönliche Angaben

Geburtsdatum	03. Oktober 1993
Geburtsort	Worms (Rheinland-Pfalz)
Staatsangehörigkeit	Deutsch

Promotion

Juli 2018	Übernahme der Betreuung durch PD Dr. Susanne Diekelmann
März 2016	Annahme als Doktorand an der medizinischen Fakultät im Institut für Medizinische Psychologie und Verhaltensneurobiologie bei Prof. Dr. Jan Born

Studium

November 2018	Drittes Staatsexamen (M3) Humanmedizin mit der Note „Sehr Gut“, Gesamtnote Ärztliche Prüfung mit „Sehr Gut“ (1,5)
Oktober 2017	Schriftliches Examen (M2) Humanmedizin mit der Note „Gut“
Juli-Sept 2014	Physikum Humanmedizin mit der Note „Sehr Gut“
SoSe 2013	Beginn des Humanmedizinstudiums parallel zur Zahnmedizin an der Universität Tübingen
Sept 2012	Vorphysikum Zahnmedizin mit der Note „Sehr Gut“
WS 2011/12	Beginn des Zahnmedizinstudiums an der Universität Tübingen

Schulbildung

2003-2011	Heinrich-Heine-Gymnasium in Kaiserslautern (Rheinland-Pfalz), Allgemeine Hochschulreife (Abitur) mit der Note 1,4
1999-2003	Grundschule am Atzenberg in Carlsberg (Rheinland-Pfalz)