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Enhancement of episodic memories by closed-loop targeted memory reactivation during
sleep

Upevnění epizodických vzpomínek pomocí zpětnovazebné cílené reaktivace paměti
během spánku

Diploma thesis

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Poděkování

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Prohlášení

Prohlašuji, že jsem tuto závěrečnou diplomovou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Podpis:

Abstract

The understanding of memory and sleep has greatly deepened in the past century and continues developing until today. The most recent advances in this field of research have allowed the invention of methods for manipulating memory consolidation by sensory stimulation during sleep. Acoustic stimulation especially gained popularity. It seems to offer not only a great opportunity for better understanding of the interplay between sleep and memory consolidation, but also a possibility for use in the therapy of neurodegenerative diseases and many more. Despite the papers already published on this topic, none has focused on the influence of closed-loop targeted memory reactivation on episodic memory as described by its three components of what-where-when. Furthermore, there remains a knowledge gap on how this intervention influences direct measures of episodic memory consolidation in sleep, such as slow oscillations and sleep spindles. Therefore, this study aimed to cover these questions. We tested episodic memory components in a 3D virtual environment where participants had to remember specific objects, where and in what order they collected them. Sleep parameters of memory consolidation were measured by polysomnography during full night sleep, with or without acoustic stimulation.

The findings obtained based on these experiments suggest that the enhancement of episodic memory and its consolidation by acoustic stimulation may be more subtle than expected. We did not see any effect of reactivation on episodic memory components. Neither did we confirm its influence on the parameters that describe memory consolidation during sleep, as there was no difference between the control and experimental groups. We reason that the effects of the targeted memory reactivation are too small to manifest on a larger scale, such as the power of slow oscillations or spindle density and are most likely hidden by the large inter-individual differences. Furthermore, we stretch the importance of good setup of the acoustic stimulation as our findings suggest that people are very sensitive to sound presentation during sleep. These findings raise the question whether these new tools are indeed capable of specifically changing the consolidation of episodic memories. That potentially this manipulation does not have such strong and long-lasting effects, which challenges its application in therapy.

Keywords: EEG, slow-wave sleep, episodic memory, targeted memory reactivation

Abstrakt

Porozumění paměti a spánku se v posledním století výrazně posunulo. Nedávné pokroky v této oblasti výzkumu umožnily vývoj nových metod pro manipulaci konsolidace paměti, a to pomocí senzorické stimulace ve spánku. Zejména akustická stimulace nabyla na popularitě a nabídla tak nové možnosti pro další pochopení vlivu spánku na upevnění vzpomínek. Navíc tato metoda nabízí možnost využití v terapii, například u neurodegenerativních onemocnění. Přestože už bylo publikováno mnoho studií na toto téma, žádný se zatím nezabýval vlivem zpětnovazebné cílené reaktivace paměti specificky na jednotlivé komponenty episodické paměti (co-kde-kdy). Kromě toho v literatuře stále zůstává relativně neprozkoumaný vliv této intervence na konsolidaci episodické paměti ve spánku a s ní spojené parametry jako jsou pomalé vlny a spánková vřeténka. Z těchto důvodů se tato studie zaměřila na výše zmíněné nedostatky. Jednotlivé složky episodické paměti jsme testovali pomocí úlohy ve 3D virtuálním prostředí, kde měli zdraví dobrovolníci za úkol si zapamtovat specifické objekty, jejich umístění a pořadí, ve kterém je sebrali. Spánkové parametry týkající se episodické paměti byly měřeny pomocí polysomnografie v rámci celonočního spánku, který probíhal buď za přítomnosti akustické stimulace nebo bez ní.

Výsledky získané z těchto experimentů naznačují, že zlepšení episodické paměti a její konsolidace pomocí akustické stimulace je pravděpodobně menší než se předpokládalo. Nepozorovali jsme žádný efekt reaktivace na jednotlivé složky episodické paměti, ani žádný vliv na spánkové parametry spojené s konsolidací episodické paměti. Z výsledků nebyl patrný žádný rozdíl mezi kontrolní a experimentální skupinou. Lze tedy usuzovat, že efekt cílené reaktivace paměti je příliš slabý na to, aby se projevil na měřítkách celkové změny neurální aktivity ve spánku jako je síla pomalých oscilací nebo denzita spánkových vřetének. Nejspíš jsou tyto efekty skryty velkými mezi-subjektovými rozdíly. Nutné je také zdůraznit důležitost správné metodologie prezentace akustických stimulací, jelikož naše výsledky poukazují na to, že lidé jsou velmi senzitivní na zvuky v průběhu spánku.

Na základě těchto výsledků se nabízí otázka, jestli jsou tyto nové nástroje akustické stimulace opravdu schopny pozměnit konsolidaci episodických vzpomínek ve spánku. Je možné, že nemají tak velký a dlouhotrvající efekt, což přináší překážky pro jejich využití v terapii.

Klíčová slova: EEG, spánek pomalých vln, episodická paměť, cílená reaktivace paměti

Seznam použitých zkratk:

<i>TMR</i>	<i>targeted memory reactivation</i>
<i>CL-TMR</i>	<i>closed loop targeted memory reactivation</i>
<i>PTSD</i>	<i>post-traumatic stress disorder</i>
<i>SWS</i>	<i>slow-wave sleep</i>
<i>LTP</i>	<i>long-term potentiation</i>
<i>NMDA-R</i>	<i>N-methyl-D-aspartate receptors</i>
<i>AMPA-R</i>	<i>alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors</i>
<i>CAMKII</i>	<i>Ca²⁺/calmodulin-dependent protein kinase</i>
<i>SWR</i>	<i>sharp wave ripples</i>
<i>PFC</i>	<i>prefrontal cortex</i>
<i>NREM</i>	<i>non-rapid eye movement</i>
<i>VR</i>	<i>virtual reality</i>
<i>REM</i>	<i>rapid eye movement</i>
<i>EEG</i>	<i>electroencephalography</i>
<i>PSG</i>	<i>polysomnography</i>
<i>EOG</i>	<i>electrooculography</i>
<i>EMG</i>	<i>electromyography</i>
<i>ECG</i>	<i>electrocardiography</i>
<i>SO</i>	<i>slow oscillation</i>
<i>PKCZ</i>	<i>protein kinase C zeta</i>
<i>PKMZ</i>	<i>protein kinase M zeta</i>
<i>AIP</i>	<i>autocamtide-2-related inhibitor peptide</i>
<i>O-LM</i>	<i>oriens-lacunosum-moleculare</i>
<i>CA</i>	<i>cornus ammonis</i>
<i>ERP</i>	<i>event-related potential</i>
<i>EMT</i>	<i>episodic memory task</i>
<i>BDI</i>	<i>Beck Depression Inventory</i>
<i>BAI</i>	<i>Beck Anxiety Inventory</i>
<i>MEQ</i>	<i>Morningness-Eveningness Questionnaire</i>
<i>PSQI</i>	<i>Pittsburgh Sleep Quality Index</i>
<i>ISI</i>	<i>Insomnia Severity Index</i>
<i>ESS</i>	<i>Epworth Sleepiness Scale</i>
<i>SSS</i>	<i>Stanford Sleepiness Scale</i>
<i>PVT</i>	<i>Psychomotor Vigilance Test</i>
<i>PEBL</i>	<i>Psychology Experiment Building Language</i>
<i>PPVT</i>	<i>PEBL Psychomotor Vigilance Test</i>
<i>RT</i>	<i>reaction time</i>
<i>RAVLT</i>	<i>Rey Auditory Verbal Learning Test</i>
<i>SIAT</i>	<i>Sound item association test</i>
<i>PSG</i>	<i>polysomnography</i>
<i>AASM</i>	<i>American Academy of Sleep Medicine</i>
<i>FFT</i>	<i>fast Fourier transform</i>

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Theoretical part

1 Introduction

Consolidation of episodic memory is an integral part of our lives, since it is a mechanism that enables us to remember our experiences and learn from them. Its importance is especially apparent in illnesses that impair memory and therefore create many obstacles in the patient's daily life (Irish *et al.*, 2011; Gagliardi and Vannini, 2022). Furthermore, sleep quality is associated with successful memory consolidation, since it has been discovered that a large proportion of consolidation occurs during restful sleep (Möller *et al.*, 2006; Ferrarelli *et al.*, 2019). Outside other evidence, this connection can also be identified in illnesses in which disorganized sleep patterns lead to memory deficiencies, for example, in depression (Baglioni *et al.*, 2016). The interconnectedness of these two is so great that it may not even be clear what comes first, whether it is memory loss or sleep deficiencies that explain the problems of remembering and learning in these patients. In addition, even in healthy individuals, memory and the capacity for learning decline with age. For these reasons, the study of memory and sleep has always been on the forefront of interests of both biologists and psychologists (Berger, 1929; Tulving, 1972). Therefore, the recent discovery that memory consolidation can be manipulated by sensory stimulation during sleep has attracted attention (Rasch *et al.*, 2007; Ngo *et al.*, 2013). Despite being a relatively new field, the discoveries already achieved suggest that the tools of targeted memory reactivation (TMR) may influence neuronal activity in a way that strengthens the consolidation of memories and, therefore, can facilitate the learning process. This could then make the new closed-loop TMR (CL-TMR) tool useful in the therapy of neurodegenerative diseases dealing with memory loss (Wolk and Dickerson, 2011; Gagliardi and Vannini, 2022) and some psychiatric diseases such as post-traumatic stress disorder (PTSD) (van der Heijden *et al.*, 2024). Furthermore, it could even be used to facilitate learning in healthy individuals (Salfi *et al.*, 2022).

However, more research is needed to better understand memory consolidation and the specific influences of CL-TMR on different types of memory. As well as the exact ways in which it affects neuronal activity during sleep. Therefore, this present study aims to test more precisely the influence of CL-TMR on episodic memory, exploring it at a deeper level by differing between its individual components. It also seeks to describe the effect of this intervention on slow-wave sleep (SWS) characteristics such as slow oscillations and sleep spindles, which have been linked to memory consolidation.

1.1 Memory

Memory is a crucial process in the brain for performing even simple everyday tasks. This can be seen in examples of episodic memory deficits such as Alzheimer's disease or lesions of brain structures associated with memory formation, namely the hippocampus (Scoville and Milner, 1957; Wolk and Dickerson, 2011). There are different types of memory, nowadays divided into sensory, short-term, and long-term memory (Figure 1). Each has distinct mechanisms, circuits, and structures involved in its formation that may or may not overlap with the other (Camina and Güell, 2017). In this work, long-term memory is the only type discussed. Therefore, all mentions of memory are related to the long-term type.

Memory is a process in which an organism gains and stores information about an experience and is later able to recall it (Josselyn, Köhler and Frankland, 2015). The basic unit of memory is the engram. This was defined as a physical representation of the information in the brain that exists even between the encoding and retrieving moments. The race to find the engram started already at the beginning of the 20th century when Semon (1921) came up with the term and its definition. Strengthening the synaptic connection between neurons activated during the experience seemed to achieve the long-term, stable storage suggested in the definition of engram. The change in synaptic transmission is described as long-term potentiation (LTP). The psychologist Donald O. Hebb described this process in his book as 'neurons that fire together, wire together' (Hebb, 1949). This was later proven to be true by many other scientists. It is the changes in density and activity of N-methyl-D-aspartate receptors (NMDA-R) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors (AMPA-R) on the neuronal membranes that are the most important for long-term storage of information (McKernan and Shinnick-Gallagher, 1997). Up-regulation of AMPA receptors, mainly through controlled exocytosis, potentiates the membrane for opening of NMDA receptors, which facilitates long-term changes in the cell. However, there are many other molecules, such as Ca²⁺/calmodulin-dependent protein kinase II (CAMKII), and complex mechanisms that precede the desired alterations in gene transcription and protein production (Sumi and Harada, 2020; Tullis *et al.*, 2023). These will be touched upon in more detail in the chapter on memory consolidation.

LTP occurs at the synapses level, allowing connected neurons to fire more efficiently when stimulated. However, memory is not safeguarded on the level of individual cells but within the synchronized activity of multiple neurons, otherwise called neuronal assemblies. Together, they store the given information through their potentiated synaptic connections (Umbach *et al.*, 2022). This coordinated activity is connected to the occurrence of sharp wave ripples (SWR) in the hippocampus. It seems to play an important role in memory retrieval, as shown in the

alternation task with rodents. There the coordinated activation of certain cell assemblies appeared before the correct choice and not before the incorrect one (Singer *et al.*, 2013).

To capture the engram, many molecular tools have been invented to tag activated neurons permanently or for long periods of time. That would also allow for easier analyses of the neuronal assemblies activated during certain behaviours. The possibility of genetic manipulation has opened the door for creating transgenic mice, and the TeTag was introduced. In the case of TeTag, the expression of Lac is bound to the activity-induced expression of c-Fos in a selected time window. In this way, neurons could be marked during a task performed in the time window and compared with neurons firing during retrieval to identify the neuronal ensemble of a specific memory (Reijmers *et al.*, 2007). These tools have been rapidly evolving and becoming more precise, as seen in the development of the FLiCRE technology. It manages to track the activity of neurons based on increases in calcium in the cell (Kim *et al.*, 2020).

With these molecular technologies for observing the engram, scientists have also started to seek out whether it is possible to manipulate memory. Multiple ways have been discovered; one example could be the electrical disruption of SWRs in the hippocampus in rodents, which prevented memory consolidation (Girardeau *et al.*, 2009). But particularly interesting are the non-invasive approaches, which can be employed in humans and therefore could potentially serve in the treatment of illnesses involving memory damage or decline. This could be transcranial magnetic stimulation in Alzheimer's disease (Koch *et al.*, 2022). Or the memory reactivation that acts through sensory stimulation during sleep, especially non-rapid eye movement (NREM) sleep (Hu *et al.*, 2020). The latter is the subject of this work. In general, long-term memory is governed by LTP at the molecular level.

At a systemic level, temporal synchronization of SWRs with thalamocortical spindles and slow oscillations is crucial to relaying memory from the hippocampus to long-term storage in the neocortex (Helfrich *et al.*, 2019).

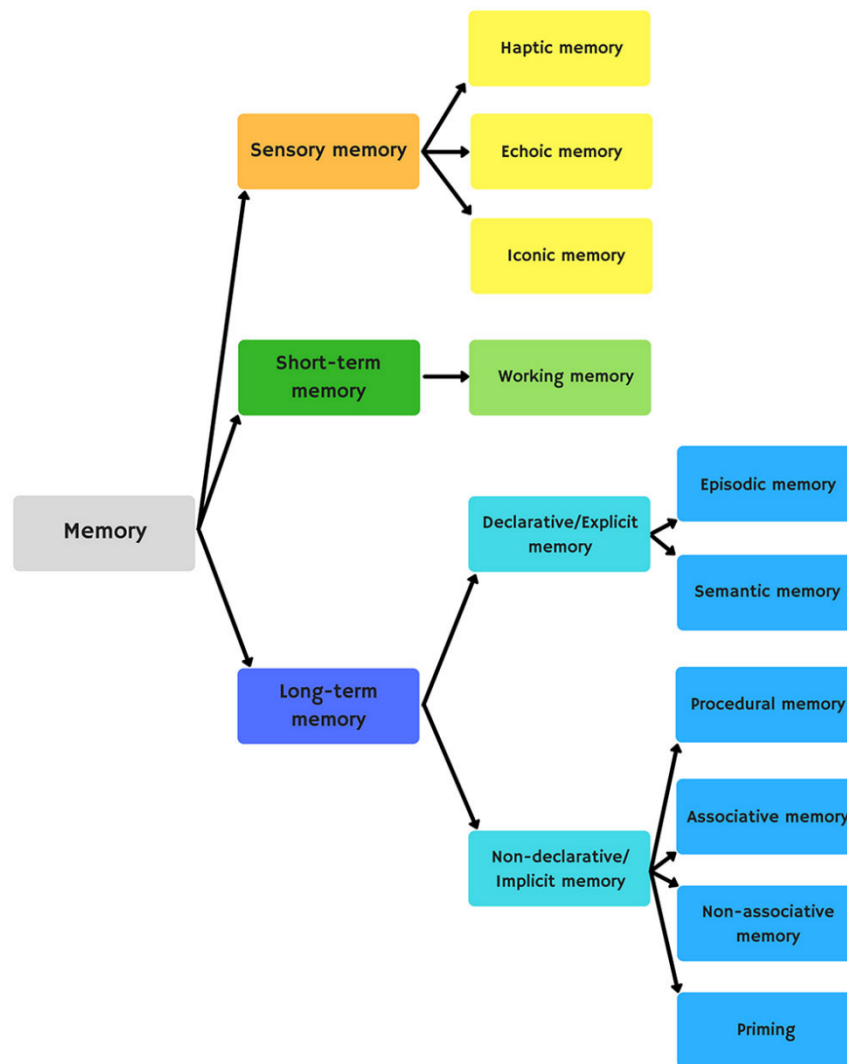


Figure 1. Schematic representation of the different types of memory (adapted from Camina and Güell, (2017)).

1.1.1 Episodic memory

There are multiple types of memory, each processing a different aspect of our lives, as shown in Figure 1. Long-term memory is usually divided into explicit (declarative) and implicit memory. Here, episodic memory belongs to declarative memory, together with semantic. Semantic memory is said to store general facts about the world, while episodic memory processes subjectively viewed events in one's life, our experiences. Or more precisely, as Tulving defined it, episodic memory stores information about specific events and their relationships in time and space, our personal ones included. Meaning that the context of the memory acquisition is crucial in episodic memories, while semantic memory is independent of context (Tulving, 1972). These two types of declarative memory seem to be separate even structurally to some extent. Semantic memory was recruited in the left inferior prefrontal cortex during tasks on semantic retrieval compared to non-semantic task (Demb *et al.*, 1995). Furthermore, stimulation of the left dorsolateral prefrontal cortex led to better control in semantic processing (Thompson-Schill *et*

al., 1997; Mitchell, Vidaki and Lavidor, 2016). On the other hand, the right prefrontal cortex has been associated with episodic memory. But the division is not that simple, and there are many areas, including the prefrontal cortex, with overlapping functions of both semantic and episodic memory (Allan *et al.*, 2000; Turriziani *et al.*, 2019).

Moreover, episodic memory falls into the hippocampus-dependent category. These findings stem mainly from research on brain lesions in epileptic patients, which, when the hippocampus was targeted, showed impaired memory of recent personal experiences. Without any improvement over time (Scoville and Milner, 1957). The regions involved in episodic memory processing and retrieval are the hippocampus, some medial temporal lobe regions and the prefrontal cortex (Svoboda, McKinnon and Levine, 2006; Das and Menon, 2022). The hippocampus is a crucial structure for forming and storing episodic memories. It achieves this by binding together various inputs that come through the parahippocampal region into the internal structures of the hippocampus (Burwell, 2000). There each neuron seems to code for a specific combination of elements characterizing a given episode (Kolibius *et al.*, 2023). Furthermore, additional information can be associated with memory formation based on the connection of the hippocampus to other structures, such as the amygdala. The amygdala provides the emotional context of the episode, which seems to strengthen the encoding. The higher the emotional arousal, the better the episode is remembered (Qasim *et al.*, 2023). Moreover, it communicates with the neocortex, specifically the prefrontal cortex (PFC), which receives information from the hippocampus for further processing and storage, as shown in Figure 2 (Das and Menon, 2022).

The hippocampus is also crucial for a specific type of episodic memory, spatial memory, which revolves around recognizing and remembering places and directions. It was discovered early on that with a damaged hippocampus, this learning and memory were impaired (Morris *et al.*, 1982). It was further described in more detail based on the research on place cells that was done mostly on rats (O'Keefe and Recce, 1993; Foster and Wilson, 2006). To better understand spatial memory, or episodic memory in general, in humans, virtual reality (VR) has recently gained popularity. It is applied not only in biology research but also in the field of psychology, as is the case for phobias and some mental illnesses (Peñate *et al.*, 2019; Park, 2022). The advantages of VR are that it can simulate the real world but still qualify as a controlled environment. Moreover, it is very versatile and reproducible. Another added value is the interactivity it can offer, which can lead to even deeper understanding of episodic memory (Horner *et al.*, 2016; Bocchi *et al.*, 2021). All in all, VR can reconstruct the complexity of real learning tasks, therefore creating better ecological validity necessary for episodic memory research (Corriveau Lecavalier *et al.*, 2020). For these reasons, VR technology was also used in this study for memory assessment.

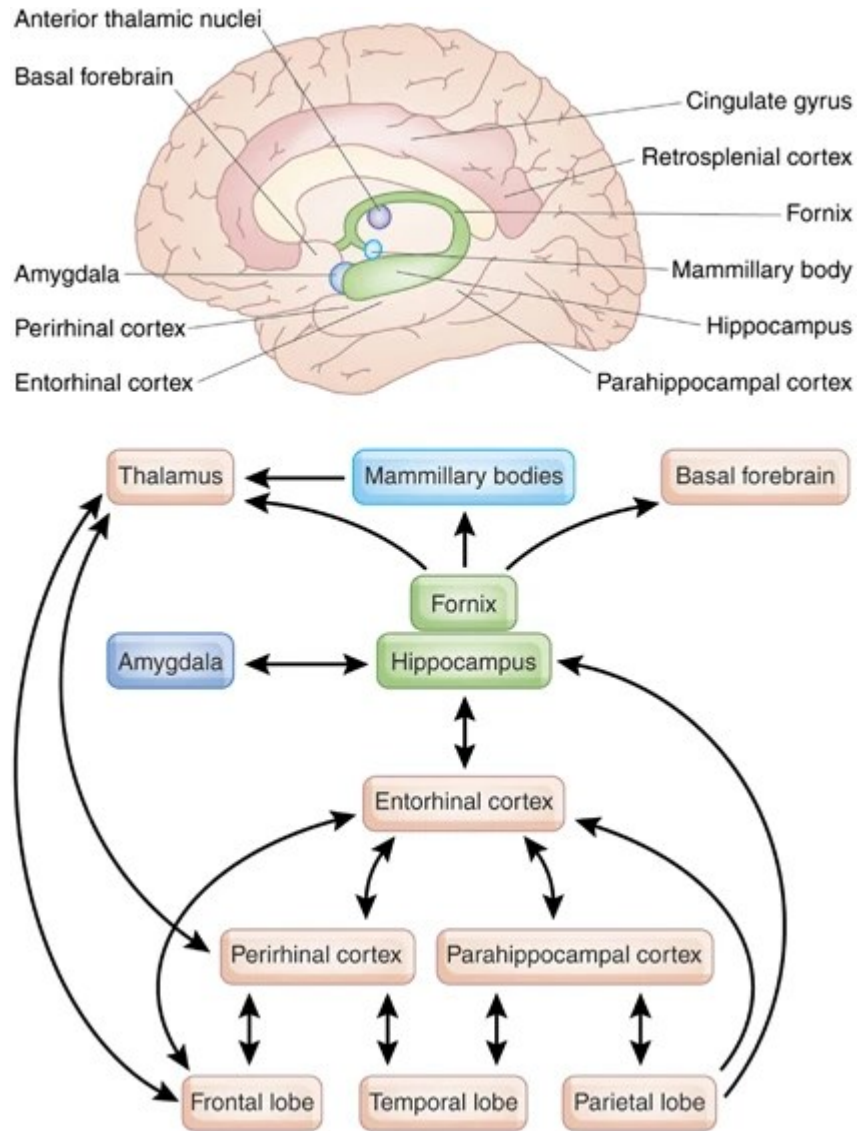


Figure 2. Schematic representation of the regions involved in episodic memory formation and their interactions within the human brain (adapted from Nadel and Hardt (2011)).

1.2 Sleep

Sleep is a state of reduced mental and physical activity. It is a state of disengagement with the environment, and historically it has been considered a passive process that serves regeneration by depriving the body of stimuli and lowering its activity. Gradually, scientific discoveries showed that the body and especially the brain are not still during sleep but are performing vital processes for survival. It can be the synthesis of various hormones, such as growth hormone, which is mainly produced during sleep in men (Jaffe *et al.*, 1998; Calvert *et al.*, 2022). Or changes in immune response to inflammation that also show circadian rhythmicity (Gibbs *et al.*, 2014). Furthermore, the crucial role of sleep is evident in memory processing,

especially supported by systemic memory consolidation theory (Heib *et al.*, 2013). All this shows that sleep is a vital mechanism to maintain homeostasis, mediating growth and learning.

1.2.1 Sleep characteristics

Sleep is accompanied by many physiological changes in the body. The most prominent is the reduced muscle tone and decreased attention to external stimuli. However, it is also associated with the drop in bodily temperature or the changes in cardiovascular (Gangwisch *et al.*, 2006) and respiratory systems (Bateman, Pavia and Clarke, 1978; Spengler, Czeisler and Shea, 2000). Sleep is divided into multiple repetitive cycles of about 90 to 120 minutes long. Each cycle comprises a Rapid Eye Movement (REM) phase and a non-REM phase (NREM). The non-REM also has three substages called NREM1, NREM2, and NREM3. Each of these phases can be characterized by specific waveforms in the electroencephalogram or other physiological events, such as movement of the eyes or activation of the skeletal muscles.

Electroencephalography (EEG) is an important tool to describe various states of neuronal activity during wakefulness and is especially useful to characterize sleep, as it is relatively temporally precise. It is often used as part of a polysomnography (PSG) procedure. That is a non-invasive method which monitors physiological parameters through EEG, electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), and other technologies such as pulse oximetry or airflow and abdominal sensors. PSG was developed as a tool for investigating sleep by adding other physiological measures to the EEG introduced in the beginning of the twentieth century by Hans Berger (Berger, 1929). EEG measures the electrical activity of simultaneous firing of pyramidal neurons of the cortex that serves to describe different states and events of brain activity (Stern, 2005). The EOG monitors eye movements, which can be captured as changes in electrical potential because the eye acts like an electrical dipole. This is useful for detecting the REM phase of sleep or for the diagnosis of some somatic illnesses. EMG captures the activation of the skeletal muscles that often produce artifacts in the EEG recording. It can also serve as an indicator of some sleep disorders such as restless legs syndrome. These electrodes are usually placed on the submental muscles and facial muscles, but also can be put on other parts of the body (e.g., on the anterior tibial muscle), depending on the objective (Homyak *et al.*, 2007). ECG is more well known, since it is routinely used in other diagnostic setups to measure heart activity by recording changes in electrical potential. Again, it may serve as another diagnostic criterion in certain sleep disorders (Sorensen *et al.*, 2012). Pulse oximetry measures the oxygen saturation of the blood, and airflow sensors follow the breathing pattern of an individual (Rofail *et al.*, 2010). Polysomnography is commonly used in the diagnosis of obstructive sleep apnea and can be used in the evaluation of other sleep disorders (Massie, Van

Pee and Bergmann, 2022; Singh *et al.*, 2022). Furthermore, it is used to assess sleep abnormalities in different psychiatric disorders, for example, schizophrenia or neurodegenerative disorders such as Alzheimer's disease (Markovic *et al.*, 2021; Zhang *et al.*, 2022). It is also used to investigate brain activity during awake time or for the detection and assessment of epilepsy seizures (Jain, Dye and Kedia, 2019).

The EEG oscillations of neuronal activity in the brain mentioned above are marked by different frequency, duration, and voltage power. Although they are linked to distinct states of brain activity, they can also be found in other stages. Therefore, the delimited categories are not entirely discrete, and the waveforms are attributed to them based on prevalence.

Starting from REM sleep, which usually occurs at the end of a sleep cycle, it is mainly characterized by the rapid movement of the eyes in various directions, low voltage EEG containing mixed frequencies, and muscle atonia. These waves resemble the EEG record of wakefulness but are mostly comprised of theta and slower alpha frequencies. Sawtooth waves are specific for the REM phase, presenting as a burst of slower activity (Stern, 2005). The REM sleep seems to play a role in procedural memory processing and learning, although not much is known about the mechanisms (Picard-Deland *et al.*, 2021).

On the borderline between sleep and wakefulness, there are the alpha waves. These indicate the state of awake rest to drowsiness. The frequency band is around 11 Hz. With eyes open or blinking, the alpha rhythm is blocked and there is greater activity of the muscles registered by the EEG. When the person moves from wakefulness to drowsiness, the myogenic activity decreases and alpha waves emerge. The eyes also start to roll slowly from left to right and some theta activity may appear. Theta waves are in the frequency range of 4 to 7 Hz (Stern, 2005; Iber *et al.*, 2007).

Following is the first stage of sleep called NREM1. There the alpha and beta activity are diminished, while new waveforms appear. A characteristic transient recognizable in NREM1 are the vertex waves (or vertex sharp transients) appearing strongest in the signal from the central electrodes. They are defined as sharp waves of duration shorter than 0.5 seconds (Stern, 2005; Iber *et al.*, 2007).

The NREM2 phase of sleep can include both previously mentioned transients but has some more prominent waveforms that distinguish it from other stages. It is mainly the K-complex and sleep spindles. The K-complex is a relatively high voltage (100 to 400 μ V) and long duration (> 0.5 s) waveform with a broad contour that can have fast activity superimposed on it. The first negative wave is usually shorter than the second positive one. The other important rhythmic activity of NREM2 is the sleep spindles taking about 0.5 to 1.5 s with a frequency between 9 and 15 Hz, sometimes defined as the sigma band. These are usually classified into two categories,

slow and fast. Slow sleep spindles have lower amplitude with frequency below 12 Hz and usually are prominent in the frontal region of the scalp. The fast spindles are best visible in the centroparietal area with a frequency from 12 to 15 Hz. Both can cooccur with the K-komplex. Sleep spindles are produced by the activity of the thalamus (Bonjean *et al.*, 2011), which is thought to block external sensory stimuli during sleep. Therefore, sleep spindles, also called thalamocortical spindles, may play an important role in sleep maintenance (Cote, Epps and Campbell, 2000; Stern, 2005). Sleep spindles were also linked to memory as their activity co-occurs with the activity of the thalamus and the temporal region containing the hippocampus (Caporro *et al.*, 2012). The connection between sleep spindles and memory consolidation has also been shown in various studies, especially focused on declarative memory. There, the number of spindles during sleep, for example, predicted the improvement in the consolidation of newly learned words (Tamminen *et al.*, 2010).

The last of NREM is the deep sleep phase called NREM3. It can be clearly identified by the diffuse low frequency and high voltage oscillations of the delta rhythm named slow waves or slow oscillations (SO). The frequency is most often around 1 Hz but can range from 0.5 to 2 Hz with amplitudes higher than 75 μ V. In NREM3 this activity is present in more than 20 % of the background (Stern, 2005). These slow oscillations reflect the organized firing of cortical neurons in synchronized hyperpolarization (on the down state of the wave) and depolarization (on the up state of the wave) (Mölle *et al.*, 2011). This stage is strongly related to cognitive performance (Lucey *et al.*, 2021), memory consolidation, and therefore to improvement in certain memory tasks (Ferrarelli *et al.*, 2019).

Both types of spindles mentioned above can also occur during NREM3, their association with slow oscillations is of great interest in memory research. The spindles are linked to the negative peak of the slow oscillations. The slow spindles occur synchronized with the downward slope and fast spindles with the depolarizing state of the slow oscillation. This different temporal coupling and localization might suggest disparate generating structure and therefore distinct functions (Mölle *et al.*, 2011; Malerba, Whitehurst and Mednick, 2022). On top of that, there seems to be a feedback regulation of spindle activity in thalamocortical neurons, which supports the theory of systemic memory consolidation (Bonjean *et al.*, 2011). This detailed understanding of sleep spindles is crucial to identify certain diseases by their abnormalities, similarly as in early detection of Parkinson's disease (Papp *et al.*, 2022).

1.2.2 Memory consolidation

Memories are created throughout the day with brain networks processing and weighing the importance of each information we encounter. There are different approaches to investigating

how memory consolidation works, from a cellular, molecular, point of view to the level of whole brain networks.

On the cellular level, long-term potentiation has been described as the main mechanism for creating memories and storing them. LTP is a process that leads to strengthening of the synaptic connection between two neurons as they fire together (Hebb, 1949). It depends on the receptors present in the postsynaptic membrane of the glutamatergic connection, namely the NMDA and AMPA receptors. NMDA receptors are ligand-dependent ion channels that let in Na^+ and Ca^{2+} when they open. But the opening of these channels depends on multiple factors; the binding of the main ligand (glutamate), glycine, and a sufficiently depolarized membrane to release blockage by Mg^{2+} ions by a ball-and-chain mechanism. When all these conditions are met, the NMDA receptors open and the influx of Na^+ and Ca^{2+} leads to depolarization of the postsynaptic membrane, further propagating the signal. On top of that, it leads to metabolic changes in the cell. Most important for LTP is the suggested introduction of new AMPA receptors into the postsynaptic membrane or their modification that potentiates the neuron for another depolarization (Benke *et al.*, 1998).

Crucial molecules involved in LTP are protein kinases, namely CaMKII and protein kinase C zeta (PKCzeta) or its transcript without regulatory domain; protein kinase M zeta (PKMzeta). CaMKII appears to be important for the induction of LTP and its early maintenance, as shown in experiments using specific inhibitors at different time points after tetanic stimulation. Application of the autocamtide-2-related inhibitor peptide (AIP) 3 h after induction did not change LTP (Yang *et al.*, 2004).

The concentration of PKMzeta has been shown to increase when long-term memory is formed and supports memory maintenance for long periods of time, from days to months (Hsieh *et al.*, 2017). When this kinase was blocked by its pseudosubstrate zeta inhibitory protein, the memory trace formed by the LTP could be disrupted when applied later and not immediately after tetanic stimulation. The authors suggest that it is not necessary for LTP induction, only for its maintenance (Franzen *et al.*, 2023).

The mechanism of stabilization of the memory trace is probably ensured by trafficking and modifications of the AMPA receptors. This could be done by phosphorylating PDZ domain containing proteins such as the 4.1N protein by CaMKII, as these appear to regulate AMPA-R trafficking by its GluR1 subunit (Hayashi *et al.*, 2000; Yang *et al.*, 2004). Or it could be mediated by the effect of PKMzeta on the NSF interaction with the GluR2 subunit of the AMPA receptor, which is involved in trafficking the receptor to the synapse (Yao *et al.*, 2008).

Nevertheless, there is still no consensus on whether PKMzeta is necessary for long-term potentiation or not. In a study with PKMzeta knockout mice for, memory and learning were not

impaired (Lee *et al.*, 2013). But molecular mechanisms are not the only factors underlying memory consolidation.

Another important phenomenon associated with synaptic plasticity, LTP, and memory functions in general is the theta rhythm. It is a rhythm of 4 to 12 Hz generated in and propagated through the hippocampus. Theta waves are believed to organize learning and memory as their occurrence increases during exploratory behaviour. This rhythm is mainly controlled and induced by the medial septum, as its inhibition prevents memory formation of a given explored object (Gonzalez *et al.*, 2022). The function of these waves appears to be the synchronization of firing and LTP in the pyramidal neurons of the hippocampus. This control is exercised through several different interneurons that are influenced by projections of the medial septum (Freund and Antal, 1988; Joshi *et al.*, 2017; Salib *et al.*, 2019). These interneurons each fire stereotypically in distinct phases of the theta wave, therefore coordinating the pyramidal activity temporally. Parvalbumin-positive basket cells project mainly to the stratum pyramidale and are active during the descending phase of the theta wave. Axo-axonic interneurons fire in sync with the peak of the theta oscillation. Lastly, the oriens-lacunosum-moleculare (O-LM) cells fire preferentially at the down state of the theta oscillations. The firing rhythm of pyramidal cells is similar to that of O-LM cells with a peak during the downstate of the theta wave and hyperpolarization during the upstate (Klausberger *et al.*, 2003). These firing patterns and the morphological organization of O-LM cells suggest that they are involved in modulating excitatory inputs from other regions that enter the hippocampus through the perforant pathway (Matt *et al.*, 2010; Lovett-Barron *et al.*, 2014).

This neuronal firing locked to distinct phases of the theta wave was described already in the twentieth century, among others, by O'Keefe and Recce (1993) during another novel discovery of phase precession in spatial encoding by place cells in the hippocampus. This phenomenon described specific neurons firing as the rat, in this case, stepped into different spots in the arena. These place cells indicated the position of the rat in the space by selectively firing each upon entrance into a different area of the environment in a distinct phase of theta oscillations. Furthermore, as the rat moved through the area, the firing of the place cells shifted to an earlier phase of the theta rhythm, marking the rat's movement through the place field. Like this, place cells form a very precise representation of the environment during exploration. Recently, it was shown that this theta phase precession applies not only to navigation in an environment, but also to encoded information of order of objects, such as pictures presented on a computer screen (Reddy *et al.*, 2021).

How this spatial information is stored was discovered later by Lee and Wilson (2002). The spatial representations were replayed during sleep as a form of memory consolidation. The pyramidal cornu ammonis 1 (CA1) cells fired in the same order as they did during the task in

the arena, repeating the sequences over and over again. Furthermore, this hippocampal replay occurred also during wakefulness, specifically in a moment of rest right after moving through the space. These sequences were mostly replayed in a forward sense, but during wakefulness the replay often also happened in the reverse order (Foster and Wilson, 2006).

As already suggested, the organized activity of pyramidal neurons and interneurons also occurred in a different state of consciousness, namely in slow-wave NREM sleep. In sleep, this synchronized activity of pyramidal neurons and interneurons was associated with sharp wave ripples in the hippocampus. Sharp waves are EEG waveforms of 5 to 15 Hz with short-duration ripples of 150 to 250 Hz superimposed on them (Oliva *et al.*, 2018). SWRs are not of rhythmic nature and their generation was attributed to the CA3 hippocampal region based on the tonic excitation of highly interconnected pyramidal cells. CA3 neurons produce organized firing bursts, which propagated towards the CA1 region where they induced fast oscillations, thus sharp wave ripples (Csicsvari *et al.*, 2000). What concerns the role of interneurons in this network, the basket cells followed the same firing pattern as the CA1 neurons, synchronized with the occurrence of sharp wave ripples. The axo-axonic cells fired the most before and in the beginning of the sharp wave ripples. The O-LM cells were completely silent during the peak of sharp wave ripples. The inactivity of the O-LM interneurons during sharp wave ripples could facilitate the LTP of inputs from the CA3 region (Klausberger *et al.*, 2003). Furthermore, the interconnectedness of CA1 pyramidal neurons with parvalbumin-positive interneurons (basket cells) points to the essential role of the latter in the pace and generation of SWR. As further proven by optogenetic manipulation of parvalbumin positive cells, as the activity of these cells was able to block or induce the generation of SWRs. The synchronized generation of SWR is thought to be a result of the reciprocal inhibitory interactions of the parvalbumin positive interneurons that contribute to the excitation of the pyramidal cells of CA3. Even possibly selecting neurons that will fire and induce generation of SWRs in the CA1 region (Ellender *et al.*, 2010; Schlingloff *et al.*, 2014).

The disruption of sharp wave ripples leads to a spatial memory impairment of the task preceding it, thus showing SWR's essential role in spatial memory consolidation (Ego-Stengel and Wilson, 2010). Moreover, it seems that the SWRs also play a role in other subtypes of long-term memory. SWRs were shown to help consolidate social memory by reactivating the hippocampal replay of neurons activated during a learning task in the sleep (Azahara *et al.*, 2020). The same was found for emotional memory where replay and consolidation of the trajectory connected to an aversive stimulus were correlated with the occurrence of SWRs in the hippocampus (Girardeau, Inema and Buzsáki, 2017). Another study showed that the firing of hippocampal neurons increased after a new learning task, spatial in this case, and was associated

with sharp wave ripples during NREM sleep. Furthermore, they showed that the replay was running for 3 to 5 hours on average, matching the duration of LTP instability, thus the formation of a memory trace (Giri *et al.*, 2019). SWRs are present not only during sleep, but even in pauses between waking behaviour. There, the information is also processed by replaying sequences of hippocampal activity corresponding to the preceding task (Karlsson and Frank, 2009). All of this suggests that sharp wave ripples play an integral role in declarative memory consolidation.

As already mentioned, sharp wave ripples are synchronized with slow neocortical waves of NREM sleep. Slow waves have been shown to play a significant role in long-term memory consolidation (Ferrarelli *et al.*, 2019), and their effectiveness is correlated with uninterrupted NREM3 sleep (Whitmore, Bassard and Paller, 2022). After a learning task, specifically of declarative but also procedural nature, both the amplitudes and densities of slow oscillations increased, marking successful memory consolidation (Heib *et al.*, 2013; Whitmore, Bassard and Paller, 2022). Memory retention also depends on the coupling of slow oscillations and thalamocortical sleep spindles. It is especially prominent in some mental illnesses with sleep abnormalities. For example, patients with schizophrenia or rat models of schizophrenia did not have slow oscillations and sleep spindles coordinated. That was correlated with the lack of improvement in motor sequence and declarative memory tasks (Bartsch *et al.*, 2019; Dehnavi *et al.*, 2021; Bastian *et al.*, 2022). It seems that the slow sleep spindles are synchronized with the up-to-down slope of SO while the fast type occurs close to or simultaneously with the peak of the slow wave. Fast spindles increased after a hippocampus-dependent learning task and improved the initiation and duration of slow oscillations (Mölle *et al.*, 2011; Dehnavi *et al.*, 2021). Sleep spindle activity was shown to predict successful learning and memory improvement overnight. And that the reprocessing of learned memories is an actively initiated process (Schönauer *et al.*, 2017).

This coupling of slow waves and thalamocortical spindles is further synchronized with the SWR in the hippocampus, together forming what is called system memory consolidation. This widely supported theory suggests that hippocampus-dependent memories gradually become more dependent on retention and retrieval in the neocortex where they are stabilized. It derives from the findings that slow waves, sleep spindles, and SWRs are activated in a synchronized manner in 1-2 s time windows (Sirota *et al.*, 2003). The firing bursts of these distinct waveforms are precisely coupled in the millisecond time frame with the slow waves. The thalamocortical spindles and hippocampal SWR both occur around or just before the peak of the slow oscillation (Siapas and Wilson, 1998; Helfrich *et al.*, 2019). This delay in the peak of the slow oscillations in the prefrontal cortex may suggest that the sharp wave ripples are the driver of systemic synchronization. On the other hand, they occur on the upward going slope of the SO, therefore

suggesting that the first to start the synchronization are the slow waves of the neocortex. As demonstrated, it is still unclear what drives the coupled bursts of neuronal activity. The strengthening and hypothetical transfer of memory traces most likely happens in the up state of the slow oscillations, as it marks the depolarized state of the cortical network, which is the state more susceptible to synaptic changes like LTP (Mölle et al., 2006; Wierzynski et al., 2009).

This synchronized activity that interconnects the neocortex, thalamus, and hippocampus during sleep reactivates the memories of newly learned information, which can then be strengthened for long-term storage (Peigneux *et al.*, 2004). Furthermore, this reactivation has been shown to be externally induced in a process called targeted memory reactivation (Rasch *et al.*, 2007; Creery *et al.*, 2015).

1.3 Targeted memory reactivation

The first experiments on the reactivation of memory traces during sleep were performed using an olfactory stimulus. During a learning session, the odour of a rose was presented as volunteers were assigned to remember the location of the cards in a 2D object location task. Later, the experimental group was again presented with the odour during slow wave sleep, which led to a significantly greater improvement in memory of card location in a recall session compared to the control group. The control group did not have the nightly reapplication of the sensory stimulus. This rather simple experiment showed that sensory stimulation during SWS can improve memory consolidation of a declarative memory task (Rasch *et al.*, 2007). Later, more research was conducted on this topic, using other sensory cues, especially auditory ones.

Targeted memory reactivation applies a stimulation synchronised with a certain recurring phenomenon, phase or waveform present during sleep. Stimuli are cues that were presented in a learning phase preceding sleep. In Bendor and Wilson (2012), it was observed that acoustic stimulation induced the activity of the rat place cells in the hippocampus that were previously active during the learning task. Furthermore, different place cells were activated depending on whether one or the other sound was replayed. It showed that it is possible to bias which memory trace will be replayed and, therefore, consolidated better by the presentation of a specific sensory stimuli during NREM sleep (Bendor and Wilson, 2012). The awareness and response to auditory stimuli during sleep is curated by sleep spindles and slow-wave oscillations. In the study by Schabus *et al.* (2012), they showed that the presentation of auditory stimuli during sleep spindles is blocked out and that the highest evoked responses occur when presented on the down-to-up slope of SOs. Supported by another study (Massimini, Rosanova and Mariotti, 2003), it seemed to be of greater effect if the sensory stimulus was targeted onto the negative-to-positive slope of SO during NREM sleep. And when NREM3 sleep was long and undisturbed by arousal

(Whitmore, Bassard and Paller, 2022). In this way, it strengthened the memory of the object or action associated with it (Batterink, Creery and Paller, 2016; Ngo and Staresina, 2022). Furthermore, it was indicated that the cues delivered during the down-to-up transition of SO increase spindle power (Göldi *et al.*, 2019). Likewise, spindle density increased during and after cueing in another study. But here it was mainly during the NREM2 stage, not during the SWS stage. Interestingly, there they also documented an increase in SO density during and after presentation of the stimuli during SWS. Event-related potentials (ERP) had a higher amplitude during SWS than NREM2, but were present at both stages (Carbone *et al.*, 2024). Furthermore, auditory stimulation induced SOs. These SOs were different from spontaneous ones only in increased amplitude, slope, and spreading (Ngo *et al.*, 2013). Furthermore, other studies indicated that fast sleep spindles could facilitate specific memory consolidation according to the presented cue (Cairney *et al.*, 2018).

An important part of the TMR applied in this and other studies is that it is a closed-loop cueing. That means that an algorithm sends the cue whenever the chosen phase of SO appears, in the case of this study, when the down-to-up state transition begins (Antony *et al.*, 2022). Mostly, these algorithms follow the real-time EEG recording and replay the cue in NREM3 when the average potential (in the frontal channels) crosses the threshold of around -80 mV (Shimizu *et al.*, 2018; Ngo and Staresina, 2022).

Previously, the positive effect on memory retention was demonstrated in simpler tasks that usually consisted of presenting images, words, or simple objects. However, there is potential for the TMR to also work on more complex memory tasks. This possibility was explored in a study by Shimizu *et al.* (2018) using CL-TMR to improve the spatial navigation task in virtual reality. This type of assignment better represents real memory tasks; therefore, moves CL-TMR closer to therapeutic application in patients with existing declarative memory problems. In that study, participants were asked to walk to a target location in a VR city while able to freely explore its different districts. These districts were marked with an appropriate sound on the border. The shortened versions of these sounds were later presented to one group of participants during a nap. The CL-TMR turned out to reduce the time of navigating to the target location during the next trial in participants with sleep stimulation compared to those without stimulation. That was measurable even after only one nap.

In recent years, the usage of VR has become more popular as it can quite reliably simulate complex real-world environments and tasks while being highly customizable. Visual fidelity and the ability to interact with virtual objects proved to improve memory in some settings. However, it seems that only some components of episodic memory are influenced by visual fidelity or active interaction (Wallet *et al.*, 2011).

1.4 Knowledge gaps

To this day, no study has tested episodic memory by its individual components, considering not only the factual component ('what') but also the temporal ('when') and spatial ('where') context associated with it. Although these components are important in the remember/know paradigm that describes episodic memory. Temporal and spatial components of episodic memories have been shown to be enhanced by overnight sleep (Abichou *et al.*, 2019). Furthermore, it was even suggested that the spatial component might be more supported by REM sleep than by the NREM stage (Rauchs *et al.*, 2004). Most studies employing manipulation of memory consolidation by TMR used it for tasks involving word lists or images, therefore, only focusing on the factual content of episodic memories (Göldi *et al.*, 2019; Whitmore, Bassard and Paller, 2022).

Furthermore, only one recent study used EEG parameters that directly assess episodic memory consolidation during sleep, such as spindle density (Guttesen *et al.*, 2024). Other studies used at most the measure of spindle power (Ngo and Staresina, 2022; Navarrete *et al.*, 2023).

Also, most studies employing acoustic stimulation during sleep for memory enhancement are using only TMR but not the more specific CL-TMR to target the stimulations. Although there is evidence that precise targeting of sounds is crucial for the reactivation effect (Göldi *et al.*, 2019; Ngo and Staresina, 2022).

Practical part

2 Aims

Due to the reasons listed in the previous chapter Knowledge gaps, we decided to utilize the latest method of CL-TMR to explore the effect of acoustic simulation on the three components of episodic memory (what-when-where). To test it in a more ecologically valid environment, the memory task was developed in VR. In addition, we assessed the EEG parameters that directly measure episodic memory such as the sleep spindle density and the power of slow oscillations in SWS, to properly examine the effect of stimulation on the individual components.

Hypotheses:

1. The number of errors for each of the components of episodic memory, measured by the episodic memory task, will decrease overnight for participants with acoustic stimulation (STIM group) compared to the SHAM group (without overnight stimulation).
2. The power of SOs in SWS will be higher in the STIM group than in the SHAM group.
 - a. The power of SOs will correlate with the number of errors in the episodic memory task.
3. The density of sleep spindles will be higher for the STIM group than for the SHAM group.
 - a. The density of sleep spindles will correlate with the number of errors in the episodic memory task.
4. The number of errors in the components of the episodic memory task will negatively correlate with the results of the Rey auditory verbal learning test (measured as the number of words recalled).
5. The results of the psychomotor vigilance test will not differ between the groups.

3 Methods and Materials

3.1 Study sample

The study sample was chosen based on multiple criteria to obtain 50 healthy participants, half for the acoustic stimulation group and half for the sham one. These criteria were assessed based on a questionnaire that each volunteer had to complete before being accepted for the study. These entry questionnaires contained multiple standardized inventories along with some demographic questions.

One of the basic criteria for acceptance was age, where only volunteers aged 18 to 35 were accepted. This is because there has been evidence for memory decline with age (Loring *et al.*, 2023; Serino *et al.*, 2023), as well as for changes in sleep architecture associated with higher age groups (Baker *et al.*, 2016). Therefore, it would produce unreliable results if participants with a larger age difference were compared. Excluded were also those whose native language was not Czech or Slovak, who worked night shifts or travelled through time zones in the last three weeks. The latter were not completely excluded, they only were asked to come at a later date due to the temporary disruption of their circadian rhythm.

There were also some anamnestic criteria for inclusion. The participants accepted had to report no sleep disorders, no mental illnesses, no serious neurological, cardiovascular or other somatic illnesses, and no recent head injuries. Additionally, they were asked about substance use, since smoking, taking drugs, or drinking alcohol could interfere with their sleep, cognition, and memory consolidation (Zhang *et al.*, 2006; Arnedt *et al.*, 2011). Lastly, participants who actively used medication for allergies, thyroid issues, mood disorders (like antidepressants), beta-blockers, or any stimulants were also not accepted into the study. In addition, multiple psychological self-reporting assessments were used to exclude volunteers with sleep deficits or symptoms of depression or anxiety. These are discussed in detail below.

In the end, sixty-one volunteers passed the criteria and were admitted to the study. Unfortunately, data only from 38 of them could be included in further analyses. The remaining 23 were excluded mainly because they did not obtain enough sound stimulations during sleep ($N = 17$), for which the threshold was a minimum of 200 per night (10 repetitions of each of the 20 sounds) ($N=15$). Other reasons included high scores on BAI ($N = 1$) or BDI ($N = 1$) re-administered on the night of the test, not finishing the episodic memory task (EMT) ($N = 1$) and not passing the sound item association test ($N = 5$).

The data set included both men and women ($N = 38$; 19 women and 19 men) and was divided between the two experimental groups, 22 participants in STIM (12 women and 10 men) and 16 participants in SHAM (7 women and 9 men). The chi-square test showed that the distribution of male and female participants was not significantly different between the two

groups ($\phi_c = 0.42$, $p = 0.517$). The mean age of the participants was 23 years ($SD = 2.83$, $Min = 19$ and $Max = 32$) and the mean number of years of education was 16 years ($SD = 2.68$, $Min = 11$ and $Max = 23$), as described in Table 1.

Table 1. Study sample descriptive statistics

	group	N	Mean	Median	Std. Deviation	T-test statistic
Age	STIM	22	22.95	22	2.820	U = 151.5
	SHAM	16	23.38	23.5	2.918	p = 0.473
Years of education	STIM	22	16.55	15.5	2.857	U = 172.5
	SHAM	16	16.31	16.5	2.496	p = 0.917

3.2 Study methods

3.2.1 Screening questionnaires

Beck Depression Inventory - II

Beck Depression Inventory (BDI) is a self-reporting assessment created to identify symptoms of depression in patients. It was created in 1961 (Beck, 1961) to discriminate between groups of differently intense depression symptoms (none, mild, moderate, or severe). It was based on 21 items, each with four responses rated from 0 to 3. The score was also shown to differ according to changes in the severity of depression in treated patients, therefore, it is a reliable assessment of depression. It was then revised multiple times by Beck and his colleagues, and some of the questions (e.g., those concerning weight loss, body image, work inhibition) were later changed to correspond more to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). It has been used and validated since then many times and in different populations (Almeida *et al.*, 2023). It was also validated for Czech translation in 2016 (Ptacek *et al.*, 2016). Only volunteers whose scores fell into the mild and lower categories were accepted.

Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) consists of 21 questions about various anxiety symptoms. Each question has answers rated from 0 to 3. These numbers are then summed and give the resulting score, which places the person in one of four categories; no, mild, moderate, or severe anxiety (Açikel, 2019).

This questionnaire was originally created based on three different anxiety assessment forms, comprising 86 items which were then reduced to 21 items through multiple analyses. It showed high internal consistency and seemed to have good test-retest reliability (Beck *et al.*, 1988). Subsequently, there were many studies aimed at confirming the validity of the BAI.

Mostly, the literature seems to validate the reliability of the test, but there is no consensus on whether it discriminates between the anxiety and depression groups well enough (Lee, Kim and Cho, 2018) or not (Oh *et al.*, 2018). Therefore, even in this study, it was used only for general categorization of volunteers, not for any diagnosis.

BAI was also used in this study to withdraw volunteers with moderate and severe anxiety symptoms because these levels were shown to interfere with sleep (Baglioni *et al.*, 2016) and spatial memory (Hørlyck *et al.*, 2022).

MEQ

The Mornigness-Evenigness questionnaire is a standard tool for discriminating between individuals with different circadian rhythms, otherwise called different chronotypes. It was created by Horne and Ostberg (1976). This questionnaire contains 19 questions, of which 5 are open type. Participants choose between different times for certain activities based on their preferences. The resulting scores range from 16 to 86 and the lower the number the more of an evening chronotype the person is (Fárková *et al.*, 2020). In this study, only volunteers with values between 30 and 70 were accepted. Due to the strict sleep window set in this study which could not accommodate for the extreme eveningness or morningness chronotypes. The existence of these chronotypes was validated multiple times, for example, by a study observing changes in body temperature and cortisol levels, which were aligned with the concept of chronotypes (Bailey and Heitkemper, 2001). It was also validated for the Czech language and showed good internal consistency (Panjeh *et al.*, 2021).

Pittsburgh Sleep Quality Index

This questionnaire (PSQI) was used to assess the sleep quality of volunteers to rule out those with potentially disordered sleep because a healthy sleep pattern is important for successful memory consolidation. Sleep quality is a clinical construct that is not well defined, and so unavoidably this questionnaire has its limitations. However, it was shown to have good test-retest reliability and to separate healthy controls from patients with poor sleep, even in multiple different languages (Buysse *et al.*, 1989; Mariman *et al.*, 2012; Scialpi *et al.*, 2022). It contains 19 items that are broken down into seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction (Buysse *et al.*, 1989). These can be judged separately but also give an overall score. In this current study, the cutoff point was set on a total score of 9 based on a previous investigation of the Czech version of the PSQI (Manková *et al.*, 2021). Therefore, participants with a score of nine or more were marked as ‘bad sleeper’ and were not admitted.

Insomnia Severity Index

This psychological test (ISI) evaluates the degree of insomnia in each patient. It is a questionnaire that assesses self-reported insomnia symptoms, during both night and during the day. But it also focuses on the dissatisfaction with sleep and the distress caused by its poor quality. The index comprises seven components that evaluate sleep onset, sleep interference, morning awakening, satisfaction, distress, noticeability by others, and interference with daily functioning (Bastien, Vallières and Morin, 2001). The questionnaire has high sensitivity and good correlation with the total score of PSQI. Greater correlations were also found with the results of the anxiety and depression indexes (BAI and BDI). The scores are classified by severity of symptoms: 0-7 without insomnia, 8-14 subthreshold insomnia, 15-21 moderate insomnia, and 22-28 for severe insomnia (Morin *et al.*, 2011). For the purposes of this study, the cutoff point was chosen at score 14. No volunteers with results that suggested moderate or severe insomnia were admitted.

Epworth Sleepiness Scale

ESS is a self-administered questionnaire that assesses general levels of sleepiness during the day. The propensity to fall asleep during daytime activities is measured and categorized into five groups. Normal levels are attributed to low (score 0-5) and high (6-10) daytime sleepiness, 11-12 suggests mild excessive daytime sleepiness, 13-15 moderate excessive, and 16-24 severe excessive. It is based on asking about the likelihood of falling asleep in eight different scenarios. It does not assess the frequency of these events as that could be tied to the frequency of engaging in a certain activity (like watching television) or daily routines rather than to the level of daytime sleepiness. The scale was significantly correlated with other tests that measure daytime sleepiness. It was able to separate patients from controls and even groups of patients with different conditions marked by daytime sleepiness. Nevertheless, it is not by itself a diagnostic tool (Johns, 1991). The questionnaire was revalidated for unidimensionality, which means that all the questions reliably measure daytime sleepiness. The revalidations presented that one of the questions was redundant and that there were no variations between participants based on age, sex, or race (Lapin *et al.*, 2018). However, another study suggested that there are differences in internal reliability by race (Beaudreau *et al.*, 2012). Furthermore, some proposed that ESS provides more information than just the overall propensity to fall asleep. It can also measure different levels of somnificity based on the different scenarios, therefore potentially uncovering people with daytime sleepiness problems which do not reach a high enough overall score (Olaithe

et al., 2013). In this study, this questionnaire was used as a tool to select only those volunteers with relatively low daytime sleepiness, therefore with scores of 12 or lower.

3.2.2 Control cognitive measures

3.2.2.1 Stanford Sleepiness Scale

At the beginning and end of each testing session (morning and evening), participants received the Stanford Sleepiness Scale (SSS). There, the volunteer chose one of the seven statements describing different states of alertness or tiredness. It was found to be sensitive to sleep loss, which is why it became a practical evaluation even in a clinical setting for people suffering from sleep disorders such as insomnia or narcolepsy. It seemed to also correspond with the performance on long, unexciting mental tasks, even though in general it did not prove sensitive to performance (Hoddes *et al.*, 1973; Herscovitch and Broughton, 1981). Despite these findings, it seems that this scale might not be internally consistent or unidimensional. It more likely measures sleepiness as two separate constructs; alertness and fatigue. Still, these constructs are interrelated, as the definition of sleepiness is multifaceted (Maclean *et al.*, 1992). For the purposes of this study, it was used as a measure of progressive changes in sleepiness throughout the testing period. As it was rather long, it could potentially have influenced performance, so the use of SSS was a way to control for this possibility.

3.2.2.2 Psychomotor vigilance test

The psychomotor vigilance test (PVT) is widely used to assess alertness, therefore indirectly measuring sleepiness or fatigue (Belenky *et al.*, 2003; Philip *et al.*, 2005). In this study, the computerized version in the Psychology Experiment Building Language (PEBL) was used. PEBL is an open-source platform for creating computerized cognitive tasks. PEBL PVT (PPVT) tests alertness and sustained attention through reaction time (RT). It is typically 10 minutes long, with visual stimuli appearing every 2 to 10 seconds at random. Participants were advised to pay attention and press the space key whenever they saw a red dot on the screen. And to withdraw from any action if nothing or any other letter appeared. The reaction time (in milliseconds) was then shown on the screen. We chose the 10-minute variant of the test, as it was suggested that shorter versions are less sensitive to sleepiness (Loh *et al.*, 2004). Multiple parameters were recorded within this test; the reaction time, the number of lapses (reaction times of 500 ms or higher) and the standard deviation. Although all serve to assess attention, reaction time has the highest test-retest reliability (Langner *et al.*, 2023). However, in another study, the number of lapses was found to be a good measure of subjective physical fatigue (Lee *et al.*, 2010).

Interestingly, there appears to be a gender difference in PPVT performance, with women showing a slower reaction time. Furthermore, an age difference in reaction time was found after short sleep deprivation. However, the age difference between the participants in this study was small, and therefore the effect of age was not relevant (Blatter *et al.*, 2006). This test was chosen to potentially uncover an effect of fatigue on performance on the episodic memory task.

3.2.2.3 Rey auditory verbal learning test

The Rey auditory verbal learning test (RAVLT), presented by André Rey in 1958, is used to measure verbal episodic memory. The validated Czech version was used in this study (Bezdicek *et al.*, 2014). In many studies, the scores of this test were found to be negatively correlated with age (Can *et al.*, 2015; Loring *et al.*, 2023).

The test consisted of list A with 15 words, which were presented to the participants 5 times. They were instructed to try to remember and then repeat as many words as they could recall. Then list B with 15 different words was presented, and the participants then tried to recall as many words as possible from list B. Subsequently, subjects were asked to recall items from list A again. Here, list B served as an interference. Then the free recall of list A was repeated after about 30 minutes and then again after night sleep in the morning together with a recognition list of 50 words. In the recognition list, there were multiple types of distractors presented along with the list A words; semantic, phonetic, and semantic and phonetic combined. The subject was asked to determine whether each word presented on the recognition list belonged to list A or not.

The RAVLT is routinely used to assess episodic memory in neuropsychology (Wolk and Dickerson, 2011). It measures verbal learning and free recall; immediate (words recalled after first presentation) and delayed. In addition, retroactive and proactive interference and recognition are also measured. Proactive interference means that list A has a negative effect on the recall of items from list B. However, retroactive interference negatively impacts the recall of list A after the presentation of list B. In some more detailed analyses, the gained access (newly recalled items) and lost access (items recalled in previous trial but forgotten in the next) was also examined (Woodard, Dunlosky and Salthouse, 1999). Most of these aspects are dependent on the hippocampus, but also the medial temporal lobes play an important role (Wolk and Dickerson, 2011).

This test was chosen for this study to recognize potential episodic memory impairments in volunteers that could interfere with the evaluation of the episodic memory test. Furthermore, the results of RAVLT were correlated with those of EMT to affirm the expected validity of the episodic memory task.

3.2.3 Episodic memory task

The layout of the episodic memory task was based on the radial arm maze used in behavioural research on rats designed by Olton, Collison and Werz (1977). This maze was and is still being used to investigate spatial learning and reference memory (Anderson *et al.*, 2015; Choi *et al.*, 2018; Kohler *et al.*, 2022). But as opposed to the original radial maze test, this one tested the episodic memory through the remembrance of what, when and where components. For the purposes of this study, the layout was recreated in a 3D virtual environment where participants could move freely by mouse and keys. It was performed on a computer with a monitor and not with a virtual reality headset. Although it could seem that the headset should be better due to higher immersion, some studies show that it does not necessarily improve memory. Therefore, it is acceptable to choose the desktop VR in some cases without compromising the objective (Dehn *et al.*, 2018). There seems to be no great difference in performance on spatial memory tasks between monitor-based tasks and headset virtual reality ones (Kim, Park and Kim, 2018). Virtual environments have increased in popularity as they correspond better to the real-world experiences and, therefore, improve performance on spatial navigation tasks. Especially when the environment is as detailed as the one used in the presented study (Wallet *et al.*, 2011). Different types of sounds and their lengths have been used in acoustic TMR research. Some studies employed short unspecific sounds of the same frequency and length (Ngo *et al.*, 2013). Other studies used words (Göldi *et al.*, 2019). And then there are some that utilized sounds naturally associated to the presented object/image to be remembered (dog barking) (Shimizu *et al.*, 2018; Ngo and Staresina, 2022). There is no unambiguous evidence to determine which type might be more effective.

Therefore, we chose the sounds corresponding to the presented objects for a better association and set the volume on 35 dB. Furthermore, an important parameter here is the length of the sounds, the most effective being of 200 – 500 ms (Rudoy *et al.*, 2009; Ngo and Staresina, 2022). That was abided in these experiments as well.

3.2.3.1 Sound item association test

Before the start of the episodic memory task there was another task, the sound item association test (SIAT), designed to help create the association between an object and a sound. Since this study was based on improving memory consolidation by acoustic stimulation, it was necessary to ensure that participants create a connection between the object in the task and the sound later that was presented during sleep.

The test was created in PsychoPy software, where participants were first presented with a sound and, in rapid succession, with a picture of a given object. There were 20 sounds and

objects in randomized order. Subsequently, each sound was replayed, and participants were supposed to choose one of four pictures that they thought corresponded to the sound presented. Generally, the objects were matched with the sounds they naturally produce so that they were relatively easy to recognize and connect. The last part of the evening version of this learning test was to write the name of the object after being presented with the corresponding sound.

This test was used again in the morning after the experimental night when they finished the recall phase of the episodic memory task. There, subjects were asked to write down the name of the object when presented with only its sound and then to attribute names to the previously presented pictures of objects (without the sound at that time).

3.2.3.2 Learning phase of EMT

After the sound item association test, participants moved onto the episodic memory task. First, the administrator explained the mechanism of the virtual environment; how and where they can walk or how to manipulate with the objects in it, in the trail phase. Then, it was explained what they were supposed to do and remember. The task was to remember what objects, where they found them, and in what order they picked them up.

The layout was created in a way that there was a central part of the island with a large object in the middle and this part was connected by bridges to five different arms with specific buildings or places. In front of those buildings or places was always placed a small object that they were supposed to pick up and remember. This setup of the island was repeated four times, each time with a different large central object, different buildings/places in the arms, and different objects for pick-up. The weather and daytime were also altered for each island.

In the learning phase, participants were instructed to follow a blue arrowhead that led them from the large object in the central part of the island to each of the five arms, one at a time (Figure 3). The path had a specific order, which was the same for all participants. Their task was to pick up the small object in each of the arms and remember what and where they picked up (generally in front of which building it was, as well as more specifically where exactly it lied on the ground). They were also supposed to remember the order of the object in relation to others already collected. With every pick-up, the object made the corresponding sound from the item sound association test. In addition, the screen was locked on the given building for five seconds to help the participant remember it. After they got back to the central part of the island, the arrowhead led them to another arm, until they visited all five of them. After which, they were automatically teleported to a different island with a new set of five arms. Like this, they explored all twenty arms of four islands and collected twenty different objects.



Figure 3. Image from the EMT virtual environment. The view from the central part of the island looking towards two different arms.

3.2.3.3 Recall phase of EMT

The participants went through the same set of four islands in the recall, only these were presented in a random order. Each setup started in the central part with the large object in place. Based on the central large object, the participants were supposed to choose five small objects that they thought belonged to the adjacent arms (illustrated in Figure 4, left). At this stage, they did not see what places or buildings were in the adjacent arms. Once they chose five of the objects, the setting changed so that the correct objects belonging to the five arms around were in the middle, instead of the large central object (Figure 4, right). That happened regardless of what had chosen beforehand. Then they were tasked to return the objects to the correct places, as precisely as possible, in the order in which they collected them in the learning phase. It was forbidden to exchange the small object for another once they picked it up. When the object was put away at a certain spot chosen by the participant as best they could remember, it was forbidden to move it anywhere else. In this way, the subjects went through all twenty places again, putting the objects back to their original positions as best as they could recall.

The recall phase was repeated in the morning, after the overnight sleep. The software counted the errors in the choice of the correct objects for the given island, the order of objects, the order of places (location error), and errors in the specific placement of the objects (in front of the corresponding building). The number of errors in each category was later assessed and evaluated in the R script designed for it. Except for the specific placement of the objects, this parameter was excluded from the analyses. This way the EMT scores could be compared between the evening and the morning and between the two groups.

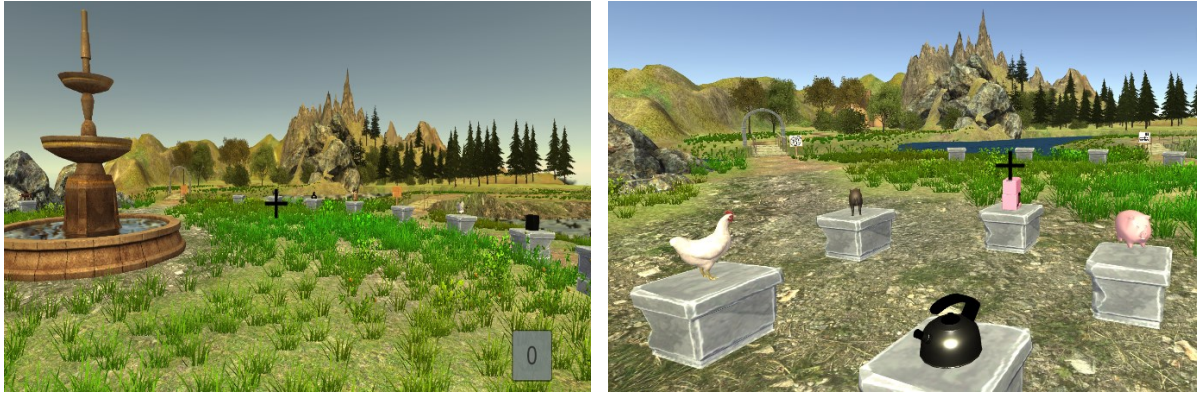


Figure 4. Images from the recall phase of the EMT. It shows the object collection phase (left) and the beginning of the subsequent phase when participants put the object back to their original position (right).

3.2.4 Polysomnography

The polysomnography (PSG) procedure was used for the purposes of this study. EEG, EOG, ECG, and EMG (with electrodes on the chin and mastoids) were used. From the different EEG montages used for the PSG measurements, we used an EEG cap with 22 electrodes placed according to the 10-20 system. The lowest number of channels for a successful full EEG recording is 4 including only the frontal and occipital regions or 8 channel montages with electrodes on the frontal, central, and occipital regions of the scalp. More advanced setups are, for example, those of 18, 21 or 128 channels. In multiple studies, montages with a reduced number of channels, less than 18, were shown to be suboptimal for the detection and localization of certain phenomena, for example, epileptic seizures (Foldvary-Schaefer *et al.*, 2006; Tacke *et al.*, 2022). Furthermore, the most common setup is 10-20, which means that the scalp surface is divided by the electrodes into 10 % or 20 % increments. For better resolution, the 10-10 system is used, for example, to localize epileptic seizures from the frontal lobe (Feyissa *et al.*, 2017). The montages can also be separated on bipolar and referential based on the primary processing of the electrical signal. The bipolar montage links adjacent electrodes in chains, each time comparing the signal from two neighbouring electrodes. There is usually a short central, parasagittal and temporal chain. These montages are better suited for catching focal and small-amplitude discharges. On the other hand, the referential montage compares the signal from each electrode to a reference electrode (often an ear/mastoid or Cz electrode) or an average of all signals (average reference). The latter was chosen for the purposes of the experiments presented here. These are more suitable for the detection of higher-amplitude and more widely distributed discharges (Stern, 2005; Acharya and Acharya, 2019).

In episodic memory research, polysomnography is widely used to monitor changes in EEG or other physiological parameters after a memory task. Here, we used it to detect the basic

sleep characteristics such as duration of different sleep stages (REM and NREM), sleep efficiency, or sleep latency. Together, they describe sleep quality that is tightly connected to memory consolidation and cognitive performance. Furthermore, there are parameters such as the density of sleep spindles or the amplitude of SWS that are important indicators of successful memory consolidation (Kim, Gulati and Ganguly, 2019; Djonlagic *et al.*, 2021; Kjaerby *et al.*, 2022). As has been shown, during sleep after a declarative memory task, an increase in spindle activity and sigma band power was observed. It appeared strongest during the NREM2 stage (Gais *et al.*, 2002; Holz *et al.*, 2012). The amplitudes of the SOs seemed to increase when there was a successful overnight memory consolidation. Moreover, the delta power band was shown to strengthen when memory consolidation was induced (Heib *et al.*, 2013; Xia *et al.*, 2023). Therefore, similar measures were also studied in this project. In research employing TMR, real-time PSG/EEG is also important for proper targeting of the stimulation. Based on it, the right sleep stage (NREM3) to launch an algorithm replaying the auditory cues can be determined. Furthermore, the algorithm can then recognize SOs and apply auditory cue precisely at the chosen phase of the SO. The stimulation had the highest positive effect during the upward slope or up-state of the SO. The length of this slope is generally around 400 ms. This means that sounds should be of the same length to prevent overlap (Göldi *et al.*, 2019). In this way, it was also applied in our experiments.

3.3 Procedure

Participants were recruited through a leaflet campaign. The leaflets were distributed in different parts of Prague, usually pinned on public or university notice boards. They were also shared in different online groups. Volunteers who were interested filled out an entry questionnaire that included inquiries regarding their contact information, sleep habits, the use of certain substances (such as nicotine, alcohol, or coffee) and anamnestic information relevant to the study. Also, several surveys were included to evaluate the mental health and sleep aspects relevant to the study: PSQI, BAI, BDI, ESS, MEQ, and ISI.

On the day of testing, the participants who passed the entry questionnaire came to the National Institute of Mental Health in the evening, around 7 pm. Then each of them was seated at a different table with a laptop, signed the informed consent, and the administrator again checked the anamnestic information. Subsequently, they received the BAI and BDI questionnaires again to check the current state of their mental health. Before administering the tests, participants were also asked to note their current level of sleepiness on the Stanford Sleepiness Scale (SSS).

The first of the tests was the PPVT, which took about ten minutes. It was followed by the RAVLT which was done individually with each participant in a separate room. Next, was the sound item association test and the episodic memory task in VR. Afterwards, they completed a questionnaire on the presence in the virtual reality task and did the RAVLT recall. This was followed by the recall phase in the EMT. Finally, they were asked to complete the SSS again.

The testing was usually completed between 8:30 pm and 9:30 pm. At 10 pm, the laboratory technicians set up the PSG with the participants. In the volunteer's room, the quality of the electrode signal was assessed. They were then asked to put on the earphones used for the presentation of stimuli. The laboratory technicians then tested whether the earphones worked by playing some white noise in them. Finally, the computer screen in the room was turned off, and the participant was left to fall asleep.

Throughout the night, the participants were monitored and recorded. When a laboratory technician recognized that the volunteer entered NREM3 phase of sleep, characterized by slow oscillations, they started the stimulation algorithm. The algorithm introduced stimulations at every detected SO, the stimulation being either sham (without any sound) or acoustic that replayed the sounds from the episodic memory task. The type of stimulation group was assigned to each volunteer randomly. The participants slept for around 8 hours, from 11 pm to 7 am.

The morning testing session started at 7:30. First, they were asked to complete the SSS again, and then they repeated the psychomotor vigilance test in the PEBL software. Subsequently, they performed the recall phase of the EMT in VR, followed by the sound association test. Then came the morning RAVLT recall and recognition. They completed another survey about the strategies used in the EMT and their experience with computer games. Finally, they marked their level of sleepiness on the SSS. When the volunteers collected their belongings and were ready to leave, they received a reward of 500 Kč.

3.4 Data Analysis

The recordings were first analysed by an experienced laboratory technician for the macrostructure characteristics of sleep according to AASM (Iber *et al.*, 2007). The data were then analysed using a pipeline from Dr. Bryce Mander, University of California, adapted by Mgr. Daniela Dudysová, in the MatLab software. The package EEGlab2019 was used. This analysis separated the recording into 30-second epochs and identified the sleep stages. Furthermore, artifacts were manually assessed by the 30 s epochs according to the AASM guidelines (Iber *et al.*, 2007). Afterwards, the density of spindles and spectral power were computed. Spindles were counted using an automatic algorithm in MatLab where the artifact-free epochs were filtered by the sigma range of 12 – 15 Hz. Subsequently, the RMS signal was calculated for each channel

using time windows of 100 ms. Spindles were detected as all signals above the threshold of 92 percentile of the artifact-free data. The final number describes the number of spindles per minute (Gais *et al.*, 2002; Porteous *et al.*, 2021). The average spindle density across all channels was chosen for further analysis. To obtain the spectral power from the EEG data, the fast Fourier transform (FFT) algorithm was employed for eight frequency bands: delta, theta, alpha, sigma, beta (1 and 2), slow oscillations, and delta oscillations. From this only the results of the relative SO power in the SWS stage were used in the analyses in this work. The relative power was calculated as the ratio between the absolute power in the SO band and the absolute power across frequencies. More precisely, the average relative SO power over the frontal channels was used for subsequent statistical analyses. Frontal channels were chosen because SOs originate predominantly in the frontal regions of the brain (Massimini, Rosanova and Mariotti, 2003; Shimizu *et al.*, 2018).

The components of episodic memory were tested in the VR test (EMT) run by the Ubisoft software (Fajnerová *et al.*, 2017). The logs for each participant were later analysed in Python to extract the number of errors for object collection, order, and location. Data for each of the four islands were aggregated to give a single number for each participant for each of the three different components and for the testing in the evening and in the morning separately.

What concerns the control cognitive measures, for the RAVLT multiple scores were calculated; the summary of immediate recall (which is the sum of scores from the first five presentations of the list of words A), the score for the second presented list, the score for the recall after interference and the score for the recall after delay in the evening. Then the score for the morning delayed recall and the recognition task were also calculated. The score of the delayed recall in the evening was used for correlations with the components of the episodic memory task. It was important to assess this relationship to determine whether the new VR task (EMT) is a good measure of episodic memory.

The EMT sound item association test was completed in PsychoPy software and analysed to check whether the participants learned to recognize the items by their assigned sounds. This was important to measure to rule out the possibility of low scores being caused simply by poor association between sound and item. That was used to exclude participants who did not form enough of these associations. The exclusion threshold was established for 2 or more mistakes.

Lastly, PPVT was assessed to rule out the possibility of fatigue and the accompanied lowered attention that caused a decrease in EMT scores and confounding the effect of the stimulation condition. The mean response time in milliseconds was calculated as it is widely used as a reliable measure of vigilant attention (Martínez-Pérez *et al.*, 2020).

3.4.1 Statistical methods

The results of testing the different components of episodic memory did not show a normal distribution. A logarithmic transformation was employed to correct it, but it did not improve the distribution enough to be considered normal. Therefore, nonparametric tests were chosen for the analysis of EMT components. The difference between the evening and morning scores was calculated and analysed using the Mann-Whitney U test for comparison between the groups. The Wilcoxon signed rank test was used for the paired data when evening and morning results were compared within a group.

Physiological data from EEG concerning the relative power of SOs and spindle density in SWS did show a normal distribution, therefore, the independent sample t-test was used for the analysis of the effect of the condition. Sleep efficiency did not report a normal distribution, as shown in Table 2. Therefore, the Mann-Whitney U test was performed.

The RAVLT results did not present a normal distribution, therefore, the same nonparametric tests as mentioned above were used. The same was true for the PPVT parameters.

Furthermore, the correlations were calculated as the bivariate Spearman ranked correlation. Because the behavioural data violated the normality assumption, regression analysis could not be employed. Furthermore, a linear regression line was fitted to all scatterplots to visually illustrate the relationship between the observed variables. The Bonferroni correction was used to adjust the significance level for multiple comparisons, moving the threshold to the p value of 0.016. All statistical analyses were performed in IBM SPSS software.

4 Results

The descriptive characteristics were computed for all parameters used later in the analyses, as presented in Table 2. Based on the results from the Shapiro-Wilk test, parametric or non-parametric tests were later used for the comparison of results between groups.

Table 2. The descriptive statistics and normality for all the parameters used for statistical analysis

Test	Parameter		Descriptive Statistics						Shapiro-Wilk test	
			N	Min	Max	Mean	Median	SD	Stat.	p value
SIAT	Free recall	Before sleep	43	16	20	18.84	19.00	1.090	0.856	<0.001
		After sleep	43	17	20	19.16	19.00	0.924	0.802	<0.001
Episodic memory task	Object errors	Evening	38	0	11	3.74	4.50	3.185	0.885	<0.001
		Morning	38	0	9	2.84	1.50	2.991	0.830	<0.001
		Difference	38	-7	4	-0.89	0	2.480	0.914	0.007
	Order errors	Evening	38	0	34	8.79	4.00	10.32	0.817	<0.001
		Morning	38	0	32	7.92	4.00	9.318	0.814	<0.001
		Difference	38	-6	12	0.87	0	3.905	0.867	<0.001
	Location errors	Evening	38	0	5	0.58	0	1.308	0.510	<0.001
		Morning	38	0	5	0.39	0	1.054	0.439	<0.001
		Difference	38	-1	5	0.18	0	0.896	0.329	<0.001
Sleep		Sleep efficiency	38	0.724	0.994	0.884	0.889	0.076	0.955	0.134
		Number of stimulations	38	229	2205	908.5	755.5	585	0.876	<0.001
		Relative power of SOs	38	0.367	0.66	0.528	0.527	0.066	0.978	0.640
		Spindle density SWS	38	0.074	1.871	0.829	0.793	0.459	0.972	0.437
RAVLT	Recalled words	Learning – all trials	38	49	74	64.08	64.00	6.024	0.964	0.257
		Evening	38	9	15	13.53	14.00	1.606	0.833	<0.001
		Morning	38	8	15	13.53	14.00	1.913	0.770	<0.001
		Difference	38	-3	2	0	0	0.919	0.861	<0.001
PPVT	Average RT	Overall	76	215.4	555.6	336.4	311.4	71.9	0.933	<0.001
		Evening	38	227.7	475.1	328.3	305.2	66.25	0.922	0.011
		Morning	38	215.4	555.6	344.5	312.5	77.17	0.935	0.030

4.1 Episodic memory task

4.1.1 Sound item association test

The sound item association test was analysed for correctly recalled names in the free recall setting. The number of correctly recalled names based on the corresponding sound presented was. The difference between the morning and evening tests in this measure is illustrated in Figure 5. For further analysis, we decided to exclude the mistakes made for the objects 'holub' and 'sova', as many participants confounded these two. There was one participant that did not fill in any names in the evening testing, therefore they had to be excluded from the data set. Furthermore, there were still four more volunteers who made two errors in the evening or in both trials, which was above the exclusion criteria. The cutoff was set on two mistakes, since that made up 36 % failure rate on the 18 objects included in total in the analysis. Therefore, these four participants were also excluded from the data set.

As presented in Figure 5, the difference between evening and morning, including all participants, yielded no significant results ($U = 773.5$, $p = 0.169$). The Figure 5 shows that the scores were already high in the evening. Lastly, the difference between the groups in the evening learning session was calculated but it did not reach significance either ($U = 227$, $p = 0.939$).

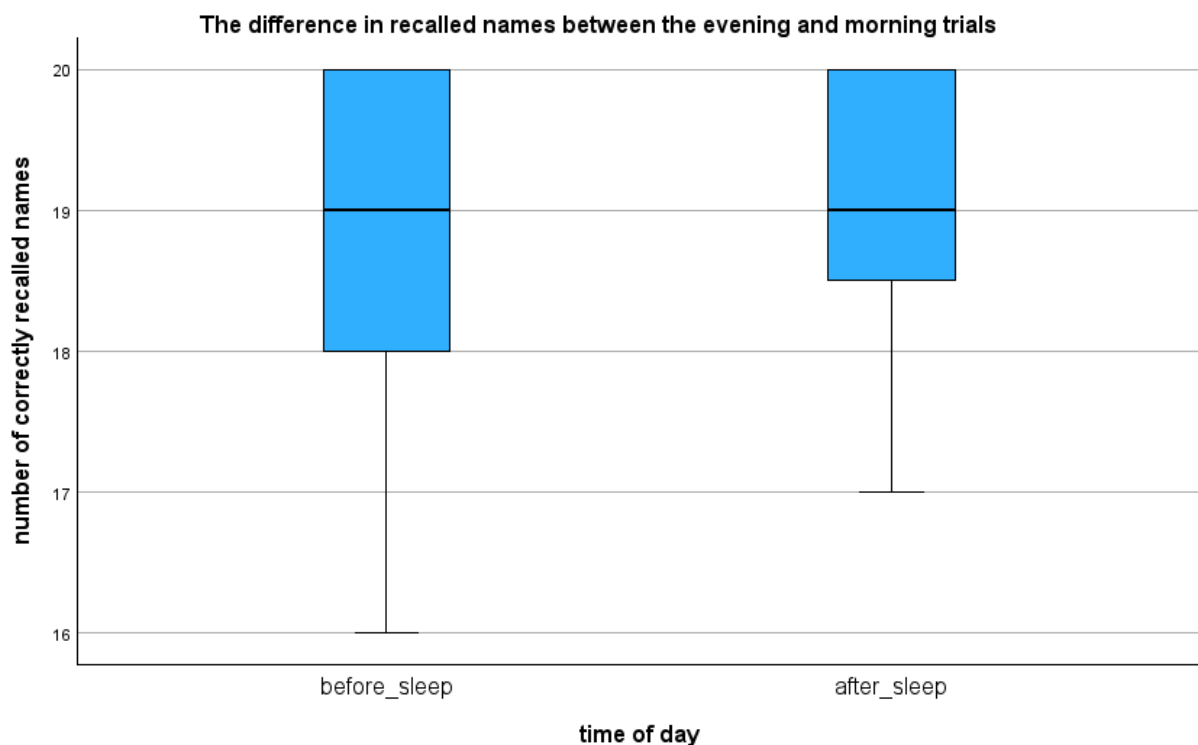


Figure 5. The box plot presents the number of correctly recalled names of objects in the testing before and after sleep.

4.1.2 Episodic memory components

The performance of the participants in the EMT recall phase was tested and three different types of errors were observed. First, the factual component 'what' was measured as errors made in items collected in the EMT pick-up phase. More precisely, it was measured as the number of items correctly recognized (and therefore collected) as belonging to the given island. These counts were then reversed to show the number of object errors for better comparison with the other two error types. There were no differences in scores between evening and morning for the STIM group ($r = 37$, $p = 0.547$), but in the SHAM group the improvement was significant ($r = 9$, $p = 0.032$), as seen in Figure 6. The difference in variance between SHAM and STIM in the evening test is also visible in Figure 6. However, this difference did not reach significance $U = 152$, $p = 0.492$, therefore it was not further accounted for.

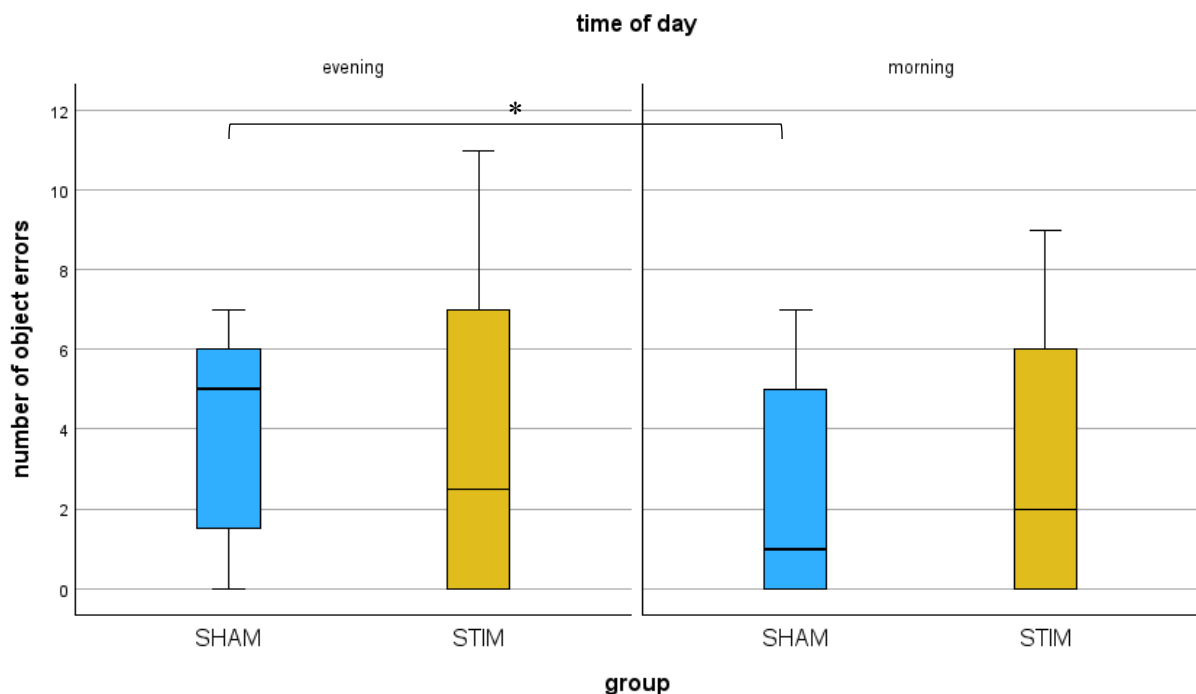


Figure 6. The box plot presenting the differences in the number of object errors between the groups in the evening and morning trials. Note the descriptives as follows: SHAM evening ($N = 16$, $Mdn = 5$, $SD = 2.67$), STIM evening ($N = 22$, $Mdn = 2.50$, $SD = 3.56$), SHAM morning ($N = 16$, $Mdn = 1$, $SD = 2.76$), STIM morning ($N = 22$, $Mdn = 2.00$, $SD = 3.19$).

Furthermore, there was no effect of the group on the difference in object errors ($U = 121$, $p = 0.097$), as illustrated in Figure 7.

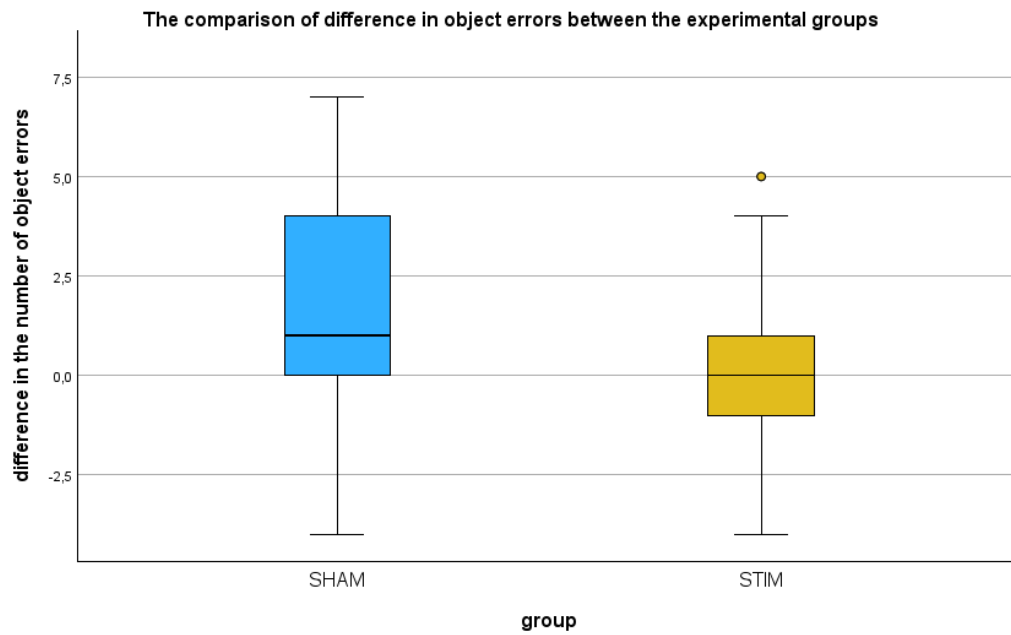


Figure 7. The box plot presenting the difference in the number of errors between morning and evening for each group. SHAM ($N=16$, $Mdn = 1.00$, $SD = 2.78$) and STIM ($N = 22$, $Mdn = 0.00$, $SD = 2.15$).

Next, the spatial or ‘where’ component of episodic memory was analysed. It was measured as the number of incidences when a given object was placed in a different arm from where it was originally. Interestingly, the participants made very few mistakes in this part of the task. The error scores were close to zero already in the evening, as shown in Figure 8.

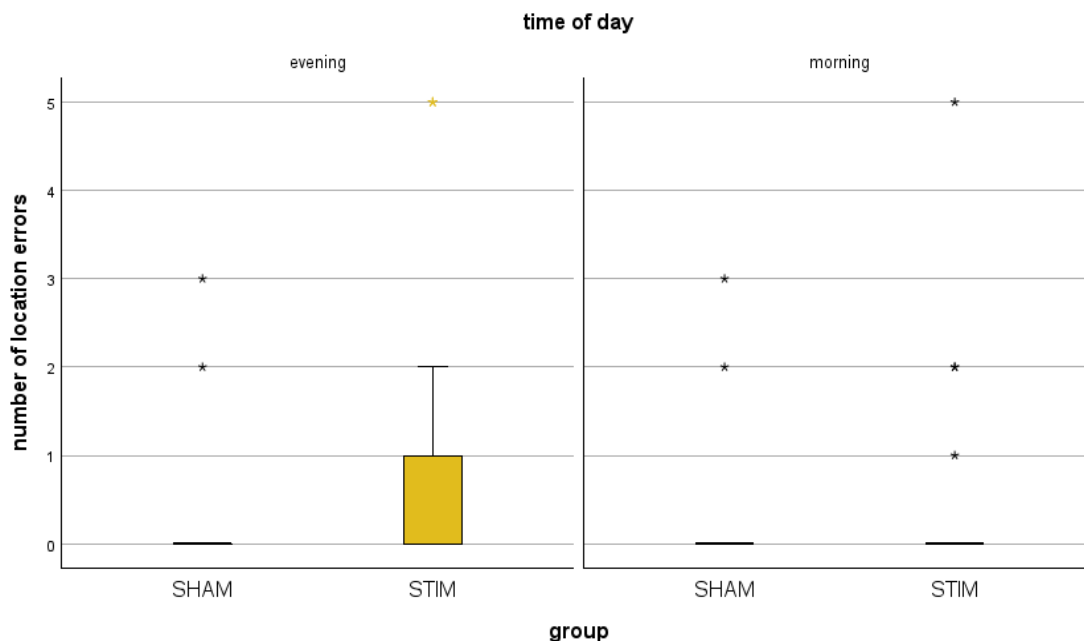


Figure 8. The box plot showing the number of errors made in the location error type in the EMT in each of the experimental groups, both in the evening and in the morning trials. Note the descriptives are as follows: SHAM evening ($Mdn = 0$, $Std. Dev. = 0.873$), STIM evening ($Mdn = 0$, $SD = 1.54$), SHAM morning ($Mdn = 0$, $SD = 0.873$), STIM morning ($Mdn = 0$, $SD = 1.184$).

Probably because the number of location errors was already very low in the evening, there was no significant difference between the evening ($Mdn = 0$) and the morning ($Mdn = 0$) results between the groups ($U = 192$, $p = 0.651$), as shown in Figure 9. Moreover, no differences in the results of morning and evening recall appeared within the SHAM group ($N = 16$, $Mdn = 0$, $r = 0$, $p = 1$) nor within the STIM group ($N = 22$, $Mdn = 0$, $r = 1.5$, $p = 0.197$), as calculated by Wilcoxon signed rank test for paired measures.

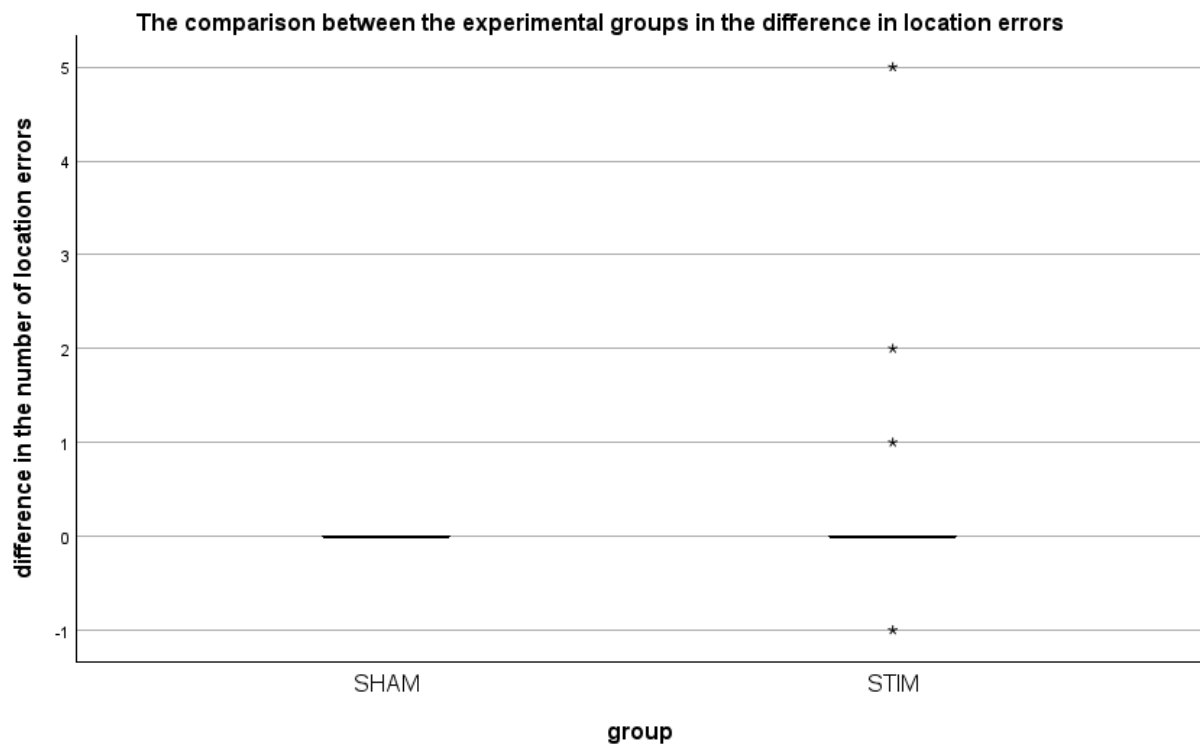


Figure 9. The box plot illustrates the number of errors of the difference between the evening and the morning recall between the two experimental groups. Note the descriptives as follows: SHAM ($Mdn = 0$, $SD = 0$), STIM ($Mdn = 0$, $SD = 1.17$)

Lastly, the temporal or more precisely the 'in what order' characteristic of episodic memory was observed. Similarly to the previous measure, it was quantified as the number of errors made in the order of objects. In the EMT, the order in which the volunteers collected the items in the learning phase was given. Therefore, in the recall, they were asked to return the objects to their respective places in the same order in which they picked them up. The method used for calculating these errors was to count as one error every skipped position in order regardless of the direction. Therefore, participants could gain more than 20 errors with the 20 items.

The distribution of order errors was not normal, showing that most of the participants had already fewer than 10 errors in the evening (Figure 10). Furthermore, there was no significant overnight change in errors within each group; SHAM ($r=19.5$, $p = 0.408$) and STIM ($r = 1.5$, $p = 0.197$), as apparent from Figure 11. Moreover, no effect of the group was observed following statistical analysis of the overnight difference in order errors ($Mdn = 0$, $U = 172.5$, $p = 0.915$).

Therefore, we must reject our first hypothesis that the number of errors for each component of episodic memory will decrease overnight for the STIM group.

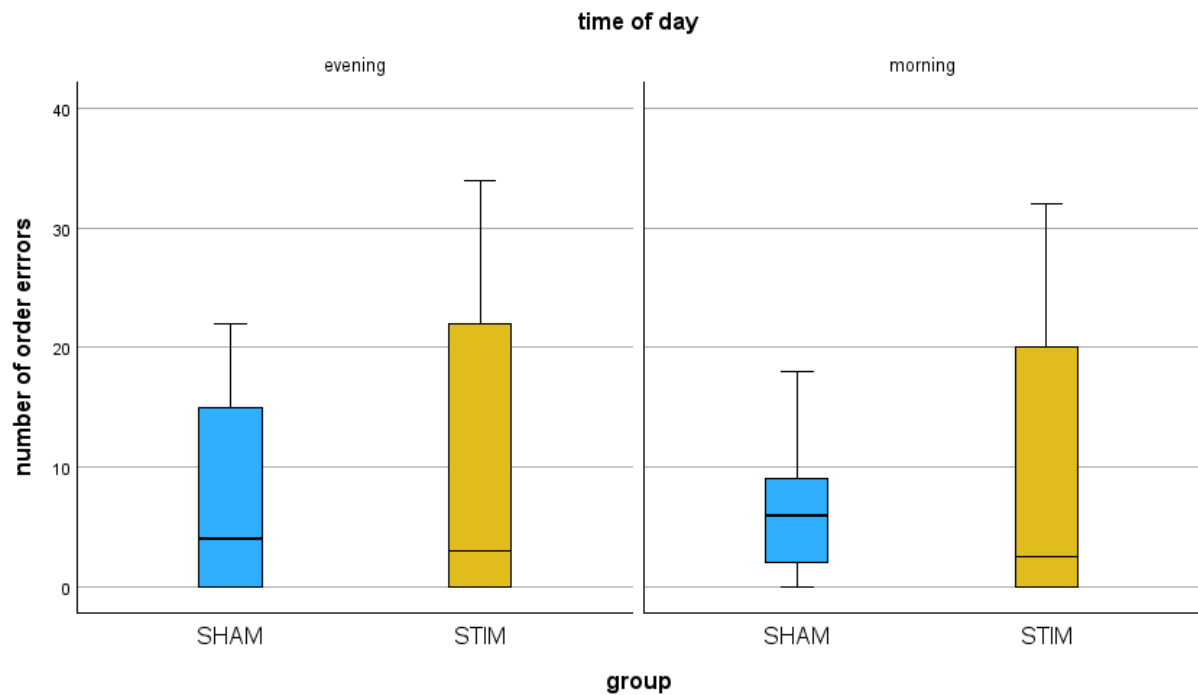


Figure 10. The combined boxplot of the number of errors in each experimental group in the evening and in the morning. Note the descriptives as follows: SHAM evening ($Mdn = 4$, $SD = 7.6$), STIM evening ($Mdn = 3$, $SD = 12.0$), SHAM morning ($Mdn = 6$, $SD = 5.62$), STIM morning ($Mdn = 2.50$, $SD = 11.28$).

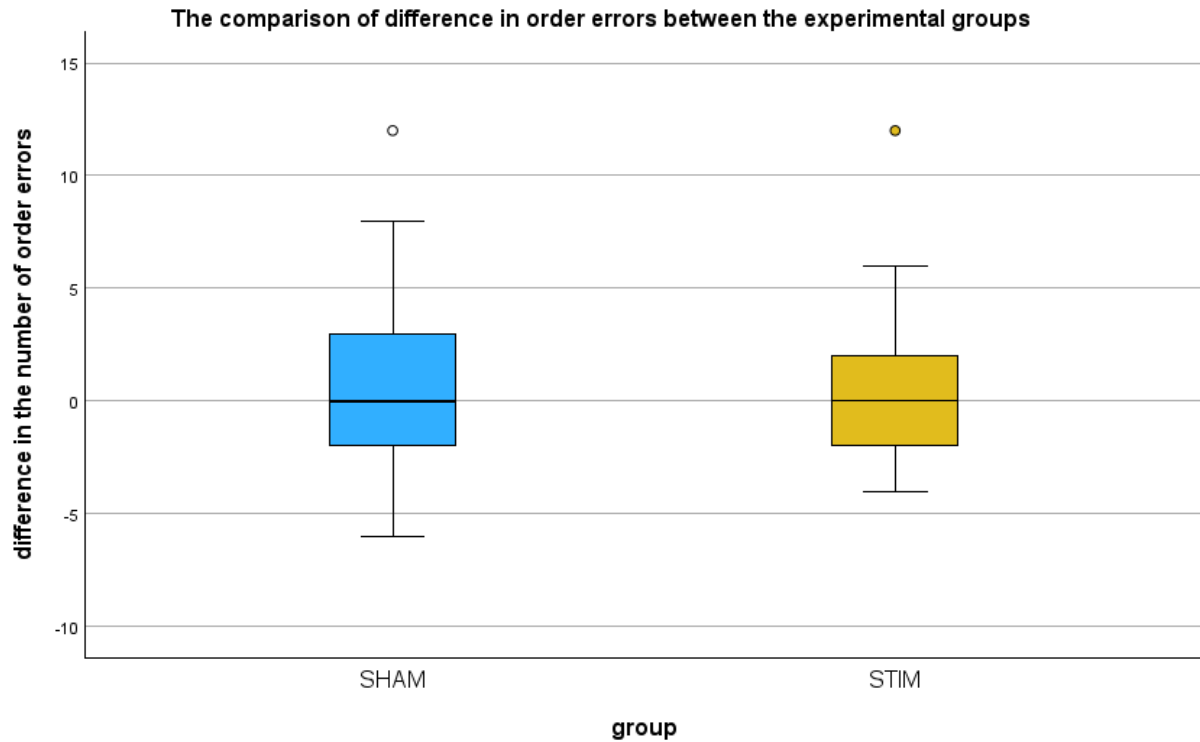


Figure 11. The box plot presents the difference in the number of errors overnight between the STIM and SHAM groups. Note that the descriptives are as follows: SHAM ($Mdn = 0$, $SD = 4.44$), STIM ($Mdn = 0$, $SD = 3.56$).

4.2 Sleep data

Changes in the chosen physiological characteristics of episodic memory consolidation were observed for overnight sleep. These were the relative power of slow oscillations in SWS and the spindle density in SWS (Tamminen *et al.*, 2010; Batterink, Creery and Paller, 2016; Ferrarelli *et al.*, 2019). But first, we evaluated the macrostructure of sleep to verify that it was not disrupted in either of the groups, as that is necessary for the effect of acoustic stimulation. These evaluations included sleep efficiency, sleep latency, total sleep duration, and time spent in individual stages of sleep (Tables 3 and 4).

Table 3. Descriptives of sleep macrostructure parameters for experimental groups STIM

Variables	Mean	Median	Std. Deviation	Shapiro-Wilk test (statistic; p value)	
Sleep latency (h)	0:33:07	0:17:59	0:53:22	0.525	<0.001
Total sleep time (h)	6:44:03	7:00:29	1:03:45	0.788	<0.001
Sleep efficiency	0.905	0.923	0.073	0.928	0.111
REM (h)	1:25:15	1:25:15	0:29:26	0.971	0.739
NREM1 (h)	0:09:52	0:08:15	0:06:17	0.924	0.091
NREM2 (h)	3:32:26	3:30:29	0:51:24	0.967	0.650
NREM3 (h)	1:36:26	1:32:59	0:28:10	0.956	0.408
Wake (h)	0:41:00	0:36:14	0:31:24	0.922	0.084

Table 4. Descriptives of sleep macrostructure parameters for experimental group SHAM

Variables	Mean	Median	Std. Deviation	Shapiro – Wilk test (statistic; p-value)	
Sleep latency (h)	0:20:23	0:15:59	0:15:18	0.863	0.021
Total sleep time (h)	6:33:42	6:47:29	0:41:03	0.992	0.179
Sleep efficiency	0.855	0.858	0.071	0.986	0.995
REM (h)	1:14:03	1:09:15	0:21:14	0.955	0.568
NREM1 (h)	0:19:05	0:13:29	0:13:20	0.865	0.023
NREM2 (h)	3:26:16	3:25:44	0:26:30	0.950	0.492
NREM3 (h)	1:34:16	1:38:59	0:28:54	0.965	0.754
Wake (h)	1:05:57	1:05:14	0:32:00	0.990	0.999

The difference in sleep efficiency between the SHAM (Mdn = 0.858) and STIM (Mdn = 0.923) groups reached significance ($U = 247$, $p = 0.036$) that suggests that the STIM group had better sleep efficiency than the SHAM group (Figure 12).

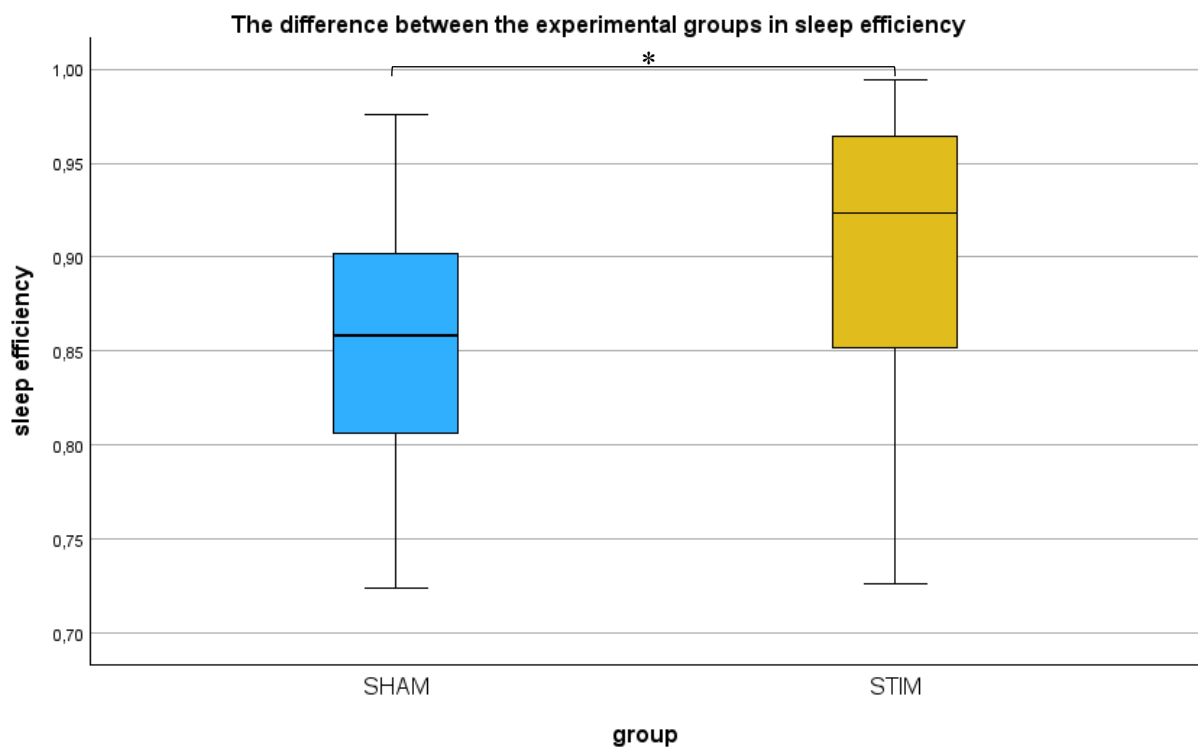


Figure 12. The box plot describes the different sleep efficiency between the two experimental groups. Note the descriptives as follows: SHAM (Mdn = 0.858, SD = 0.071), STIM (Mdn = 0.923, SD = 0.073).

We decided to investigate it further by constructing a scatterplot and computing bivariate correlations. But no correlations were found between sleep efficiency and individual EMT parameters, except for the relationship between the difference in the number of order errors and sleep efficiency in the SHAM group ($\rho = 0.502$, $p = 0.047$). The same was not true for the STIM

group ($p = 0.150$, $p = 0.505$), as illustrated in Figure 13. After the Bonferroni correction, the significance threshold changed to $p = 0.016$, so even the order errors correlated with sleep efficiency did not reach the cutoff p value in the end. This suggests that the difference in sleep efficiency between groups is independent of the EMT results. Therefore, some other parameter must be influencing it.



Figure 13. The scatterplot illustrates the relationship between sleep efficiency and the difference in the number of order errors between the recall in the evening and the morning. The linear regression line are shown for each group separately.

We also tested whether there was an effect of the group on total sleep time ($U = 213$, 0.273), sleep latency ($U = 187.5$, $p = 0.737$) or total time spent in each of the sleep stages: REM ($U = 222$, $p = 0.181$), NREM1 ($U = 90.5$, $p = 0.010$), NREM2 ($U = 199$, 0.496), NREM3 ($U = 181$, $p = 0.872$), Wake ($U = 95.5$, $p = 0.016$). The difference between the groups in total sleep time and sleep latency did not reach significance. In terms of sleep stages, the only notable difference was between the groups in the total time spent in the N1 phase and in Wake, which were not of our interest. Overall, participants in the SHAM group spent more time in the N1 sleep stage and Wake than those in the STIM group.

4.2.1 Number of stimulations

First, the number of stimulations during sleep was compared between the two groups. The discrepancy in the number of stimulations between them was very pronounced ($U = 72$, $p = 0.002$). The STIM group received significantly less stimulations than the SHAM group (Figure 14).

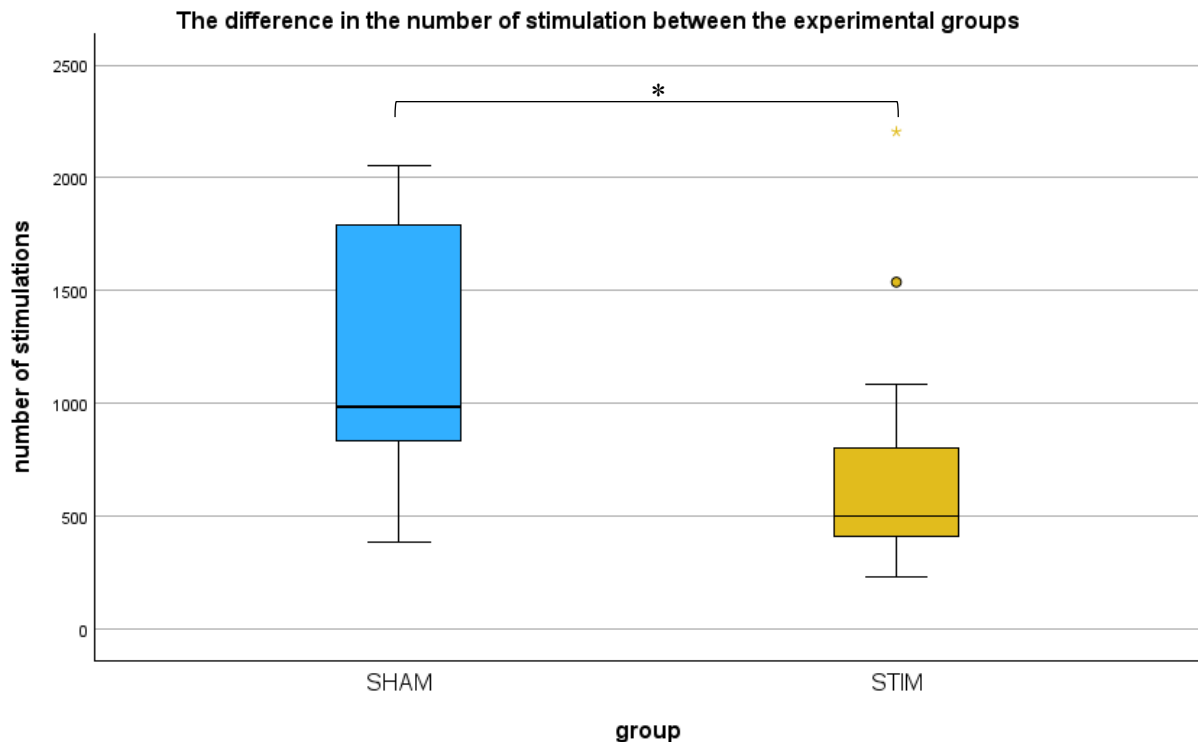


Figure 14. The box plot shows the difference in the number of stimulations during sleep between the SHAM and STIM groups. The descriptives for the number of stimulations are as follows: SHAM ($Mdn = 987$, $SD = 576$), STIM ($Mdn = 579$, $SD = 349$).

Then, the number of stimulations was correlated to sleep efficiency, as it could have potentially influenced the reported difference between the SHAM and STIM groups. The acoustic stimulations could have disrupted sleep and therefore change the sleep efficiency of one of the groups. The overall correlation was not significant ($\rho = -0.026$, $p = 0.879$), but upon closer look it was moderate with the SHAM group ($\rho = 0.553$, $p = 0.026$) and none with the STIM group ($\rho = -0.280$, $p = 0.208$), as illustrated in Figure 15.

Lastly, we explored whether there are any correlations between the number of stimulations and the overnight difference in the EMT error scores. As any correlation between these two measures could mean that the number of stimulations influenced the performance on EMT, or rather the effect of CL-TMR on memory consolidation. But there was no relationship between the number of stimulations and the difference in either of the three error types in EMT, as described in Table 5.

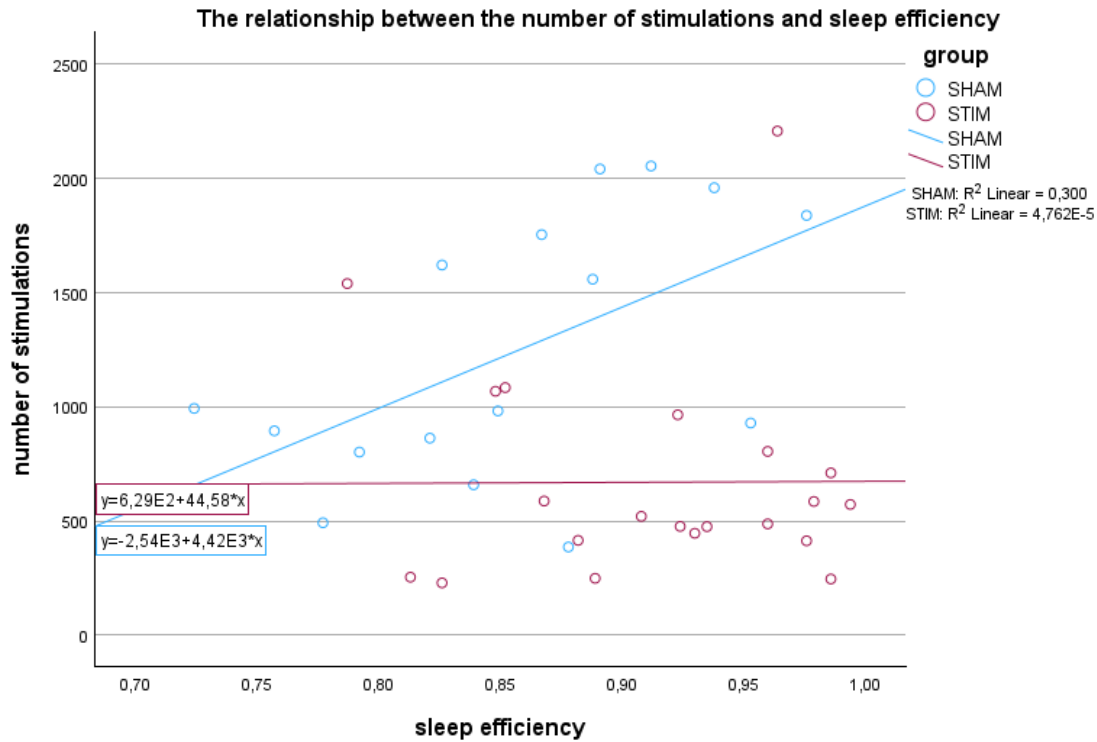


Figure 15. Scatterplot presents the correlation between sleep efficiency and the number of stimulations overnight in both experimental groups separately and illustrates the difference between them.

Table 5. The results from correlation analysis between the number of stimulations and the EMT error types in the evening testing

Type of error	Group	Spearman's ρ	p value
Object error difference	SHAM	0.049	0.856
	STIM	-0.199	0.375
Order error	SHAM	0.406	0.118
	STIM	-0.250	0.262
Location error	SHAM	None	None
	STIM	-0.342	0.120

4.2.2 Relative power of slow oscillations in SWS

To characterise the influence of TMR on power of SO was one of our main aims. Therefore, independent sample t-test was performed to assess the difference between the groups in the relative SO power. The average of all frontal electrodes was used for this analysis. It did not show any significant difference between the SHAM and STIM groups ($t = -1.870$, $p = 0.070$), as illustrated in Figure 16. Therefore, we must reject the second hypothesis that the power of SOs will be higher in the STIM group.

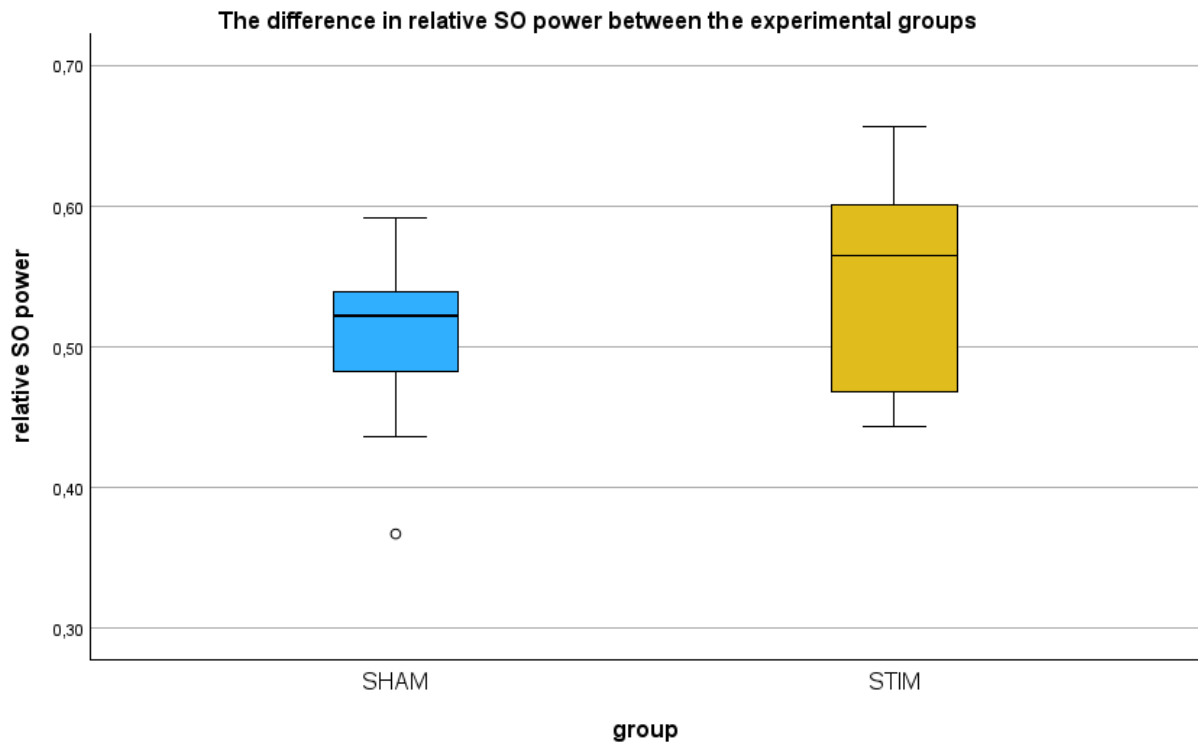


Figure 16. The box plot graph of the difference between experimental groups in relative SO power averaged over frontal channels. The descriptives are as follows: SHAM ($Mdn = 0.522$, $SD = 0.055$), STIM ($Mdn = 0.565$, $SD = 0.07$).

Correlations with individual EMT measures were performed to investigate the relationship between episodic memory and the physiological measure of relative SO power in SWS. The correlation analysis did not report a significant relationship for the overnight difference in object errors and relative SO power in either group (SHAM $\rho = 0.356$, $p = 0.176$, STIM $\rho = 0.086$, $p = 0.705$). The difference in the number of errors in location (SHAM $\rho = 0$, STIM $\rho = 0.034$, $p = 0.879$) and order (SHAM $\rho = 0.288$, $p = 0.280$, STIM $\rho = -0.084$, $p = 0.711$) did not correlate with the relative power of SOs either. However, it seems from the scatterplot in Figure 17. that the positive correlation between the SHAM difference in object errors and relative SO power is approaching significance. Similar tendencies for both groups can also be seen in the case of the overnight difference in order errors in Figure 18.

Nonetheless, we must reject the hypothesis that the power of SOs will correlate with the number of errors from EMT.

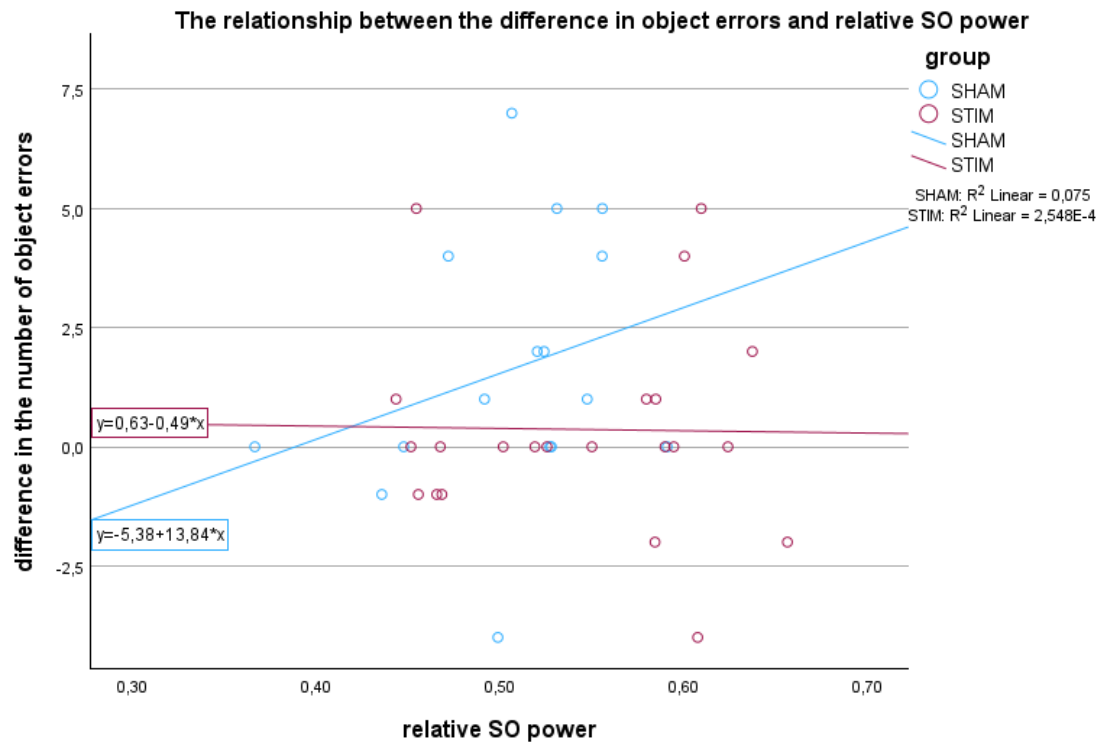


Figure 17. Correlations between the difference in the number of object errors overnight and the relative SO power. The linear regression line is fitted for each group separately.

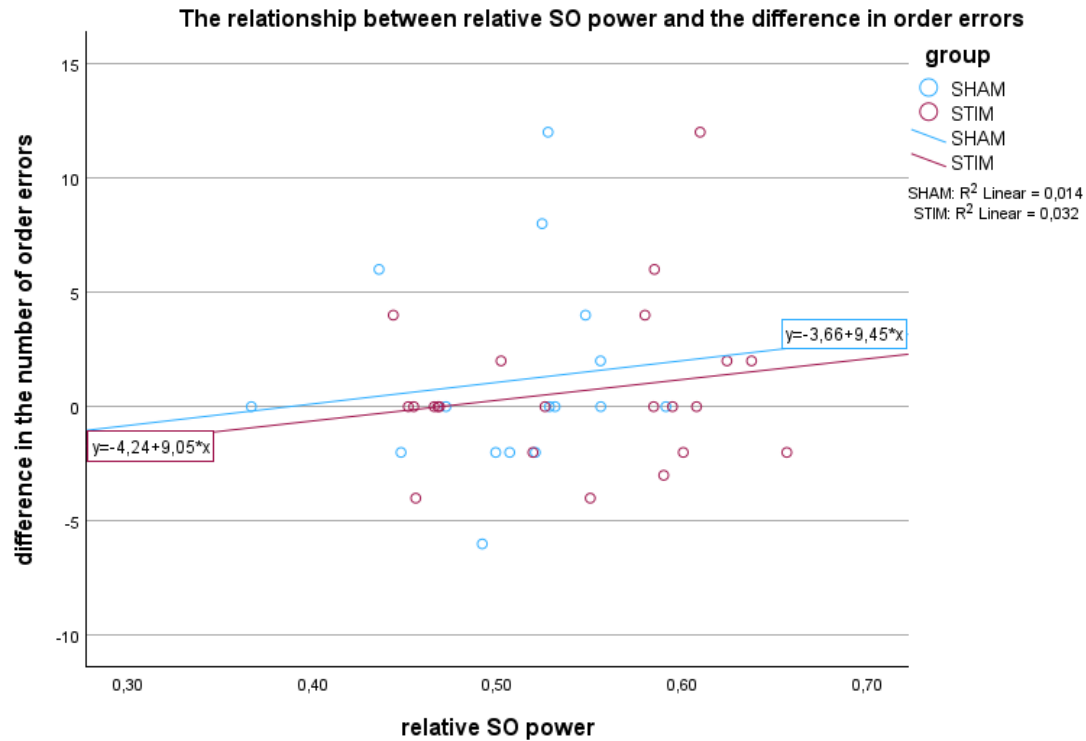


Figure 18. Correlation between the difference in the number of order errors overnight and the relative SO power. Linear regression lines are fitted to the scatterplot for each group separately.

4.2.3 Spindle density

Spindle density did not show any significant differences between groups when a t-test was performed ($t = -289$, $p = 0.775$) as visually confirmed by the box plot presented below (Figure 19).

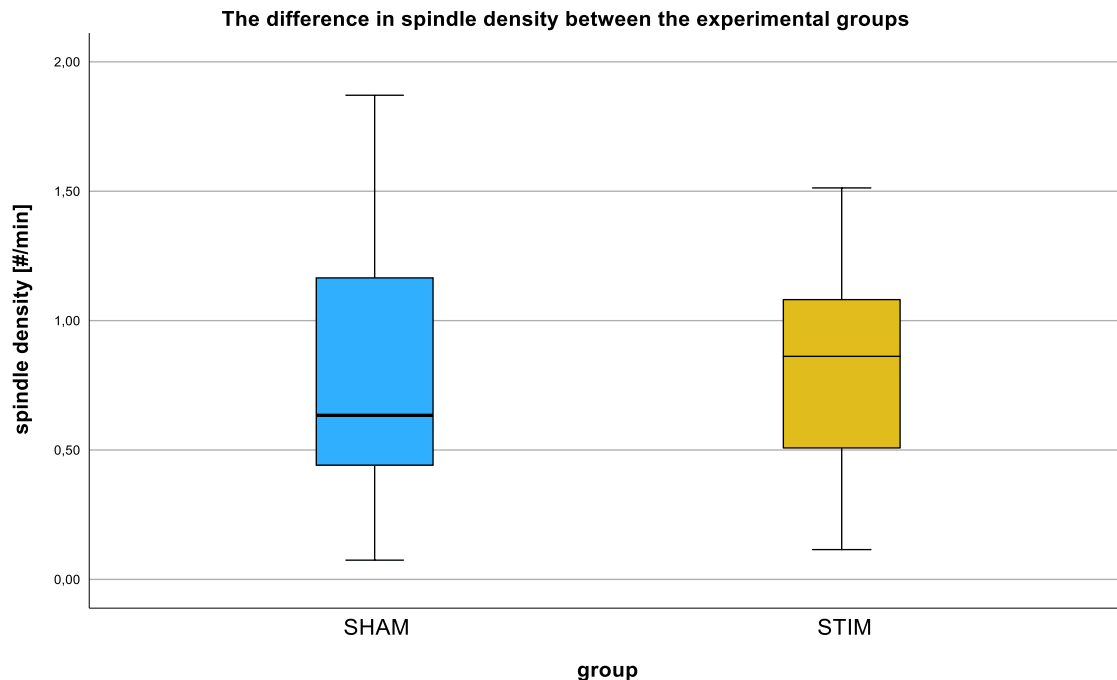


Figure 19. The box plot presents the difference in spindle density between the experimental groups SHAM ($Mdn = 0.635$, $SD = 0.557$) and STIM ($Mdn = 0.862$, $SD = 0.385$).

In the same way as with the relative power of SOs, correlations were made between each measure of the behavioural test EMT and the spindle density. The scatterplot below (Figure 20) illustrates the distribution of the correlated data. It does not show a linear relationship between the average spindle density over all channels and the individual measures of EMT. This was further confirmed by the bivariate correlation results for the difference in object errors (SHAM $\rho = -0.010$, $p = 0.969$; STIM $\rho = -0.103$, $p = 0.649$), location errors (SHAM $\rho = 0$; STIM $\rho = -0.261$, $p = 0.241$) and the difference in order errors (SHAM $\rho = -0.310$, $p = 0.242$; STIM $\rho = 0.141$, $p = 0.532$). In Figure 20, it is visible that there are some differences between the groups in the correlation, for example, with the difference in order errors. However, they are mainly driven by outliers and do not reach the level of significance after Bonferroni correction for multiple comparisons.

Based on the presented results, the hypothesis that the spindle density will be higher in the STIM group and that it will correlate with the number of errors from EMT must be rejected.

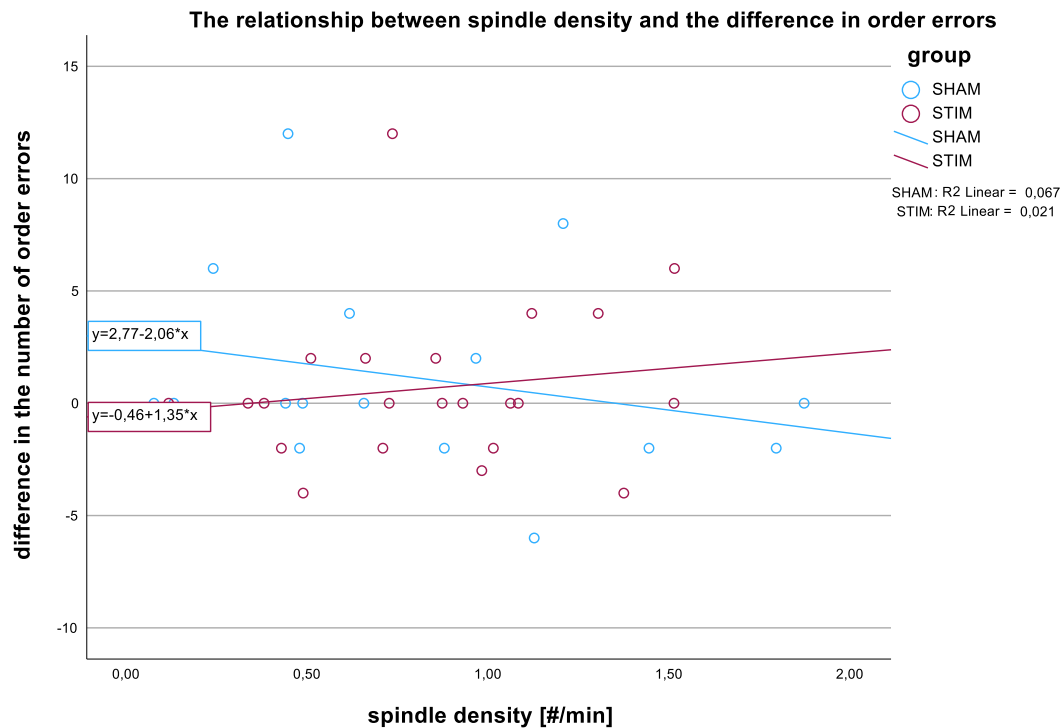


Figure 20. The scatterplot of the correlation between spindle density averaged over all channels and the difference in the number of order errors between the evening and morning recall. The linear regression line is plotted for each group separately.

4.3 Control cognitive measures

4.3.1 RAVLT

Four variables from the RAVLT were chosen for statistical analyses. The scores in each category were compared across groups. Neither of these four parameters of episodic memory measured by RAVLT differed between the SHAM and STIM groups. These are the individual results for the total number of words recalled during the learning part of list A ($U = 301$, $p = 0.164$), the words recalled in the evening after a delay of 30 minutes ($U = 283$, $p = 0.313$), the words recalled in the morning ($U = 281$, $p = 0.333$) and for the difference between the words recalled in the evening and morning ($U = 287$, $p = 0.240$).

The correlations between the RAVLT and EMT measures were calculated. It was done to verify that the EMT is a good test of episodic memory. The correlation between the evening scores from RAVLT and EMT would suggest that EMT indeed assesses episodic memory just as well as this standard episodic memory test. There was a moderate negative correlation detected between the RAVLT evening scores and the evening number of object errors in EMT, as is apparent from the scatterplot below (Figure 21) and the results of bivariate Spearman ranked correlation $\rho = 0.536$, $p = <0.001$. Moreover, the same is visible for the correlation between the number of order errors and the correctly recalled words in RAVLT in the evening ($\rho = -0.436$, p

= 0.006, Figure 22). In case of location error, the relationship with the words recalled in RAVLT in the evening did not reach significance ($\rho = -0.275$, $p = 0.094$, Figure 23).

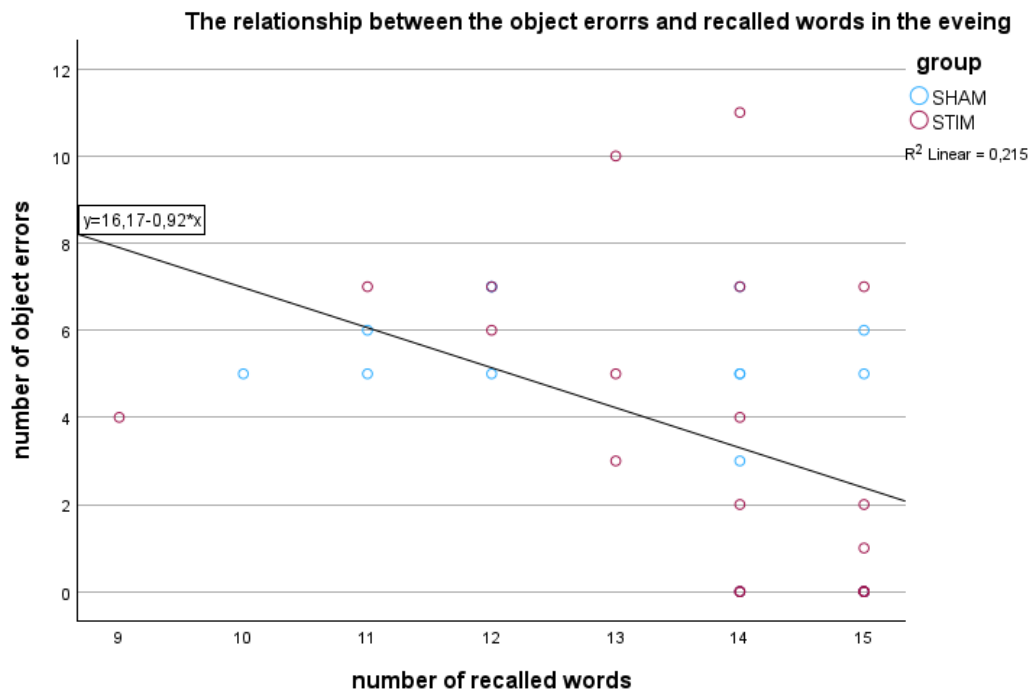


Figure 21. The scatterplot presents the correlation between the words recalled in the evening in RAVLT and the number of object errors in the evening recall phase of EMT.

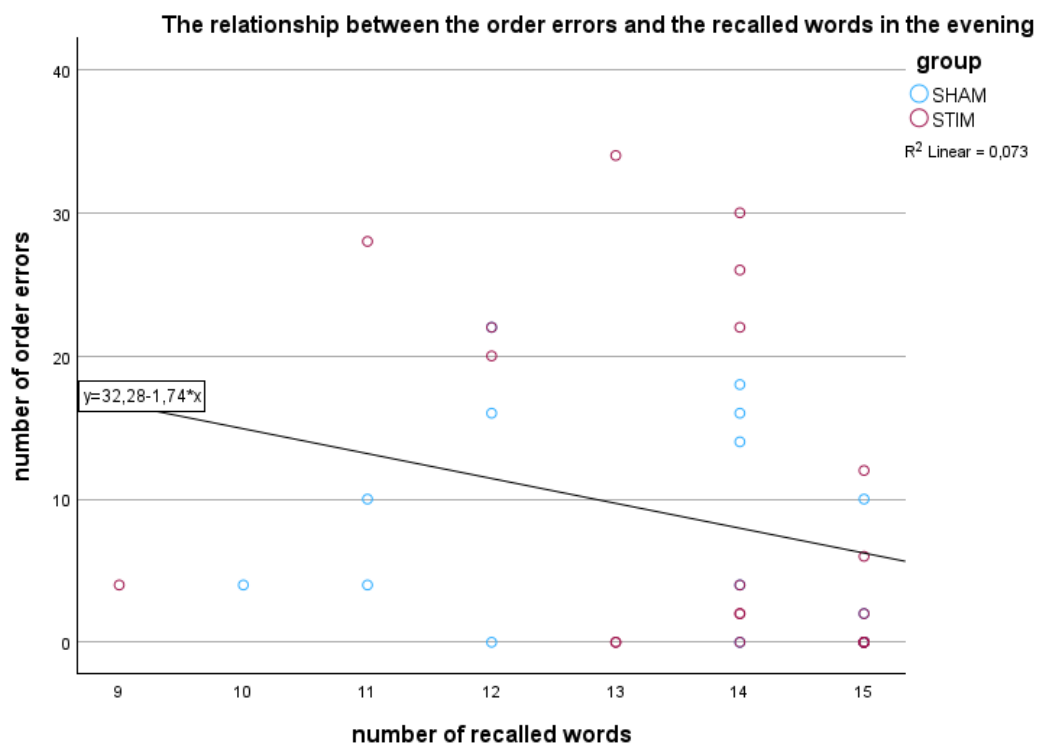


Figure 22. The scatterplot reveals the correlation between the number of words recalled in RAVLT and errors in order, in the evening.

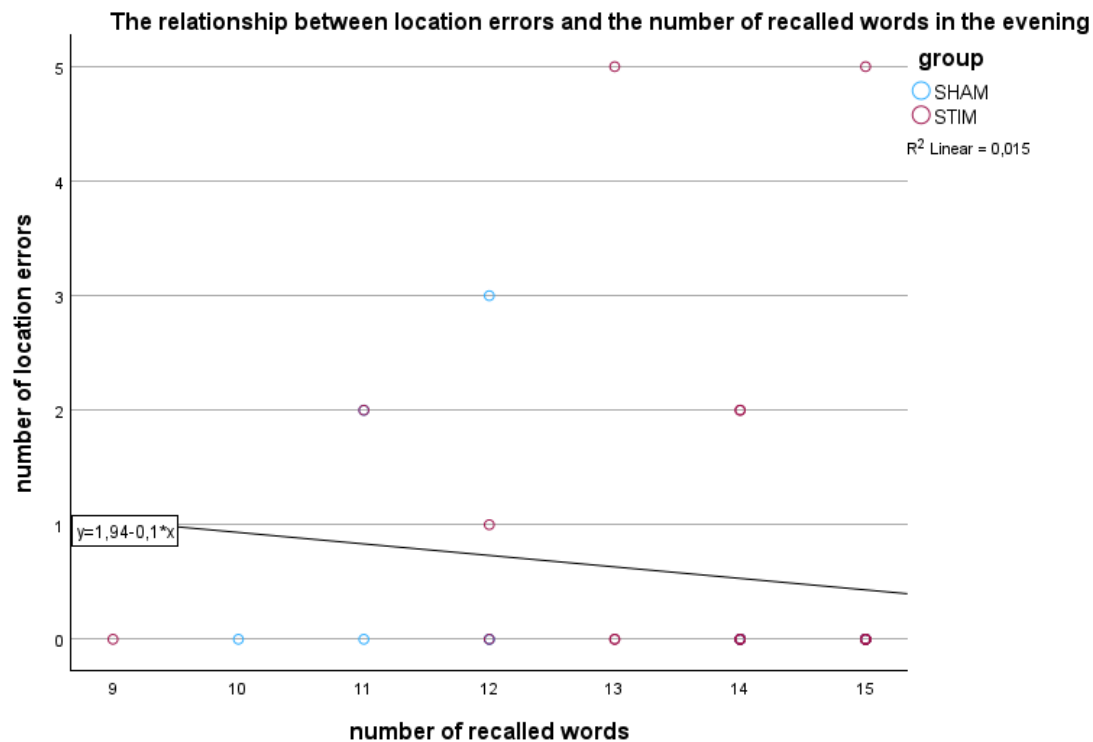


Figure 23. The scatterplot demonstrates the relationship between the words recalled in the evening in RAVLT and the number of location errors.

Surprisingly, when evening RAVLT scores were correlated separately with the SHAM (Mdn = 14, SD = 1.702) and STIM (Mdn = 12, SD = 1.55) EMT evening errors, none of them reached the set level of significance. These results are shown in Table 6.

Nonetheless, based on the above presented results we confirmed our fourth hypothesis.

Table 6. The results of the correlation between the EMT error types and the RAVLT words recalled in the evening delayed recall

Type of error	Group	Spearman's ρ	p value
Object error	SHAM	-0.564	0.023
	STIM	-0.095	0.676
Order error	SHAM	-0.136	0.617
	STIM	-0.236	0.290
Location error	SHAM	-0.218	0.417
	STIM	-0.154	0.493

Note. Bonferroni correction set the significance level at $p = 0.016$, for the evening testing the SHAM and STIM correlations were computed separately, while the difference encompasses the overall correlation (difference between evening and morning for the error type correlated with the difference in recalled words).

4.3.2 PEBL Psychomotor vigilance test

The PPVT served as a control measure considering the influence of attention on EMT. No differences in mean reaction time have been detected between the evening and morning tests ($U = 816$, $p = 0.329$), illustrated by Figure 24. We also analysed the difference in mean reaction times between the groups for each testing session. There was a rather strong difference between the groups in the evening test ($U = 258$, $p = 0.015$). But no such difference appeared in the morning test ($U = 215$, $p = 0.249$), as can be seen in Figure 25.

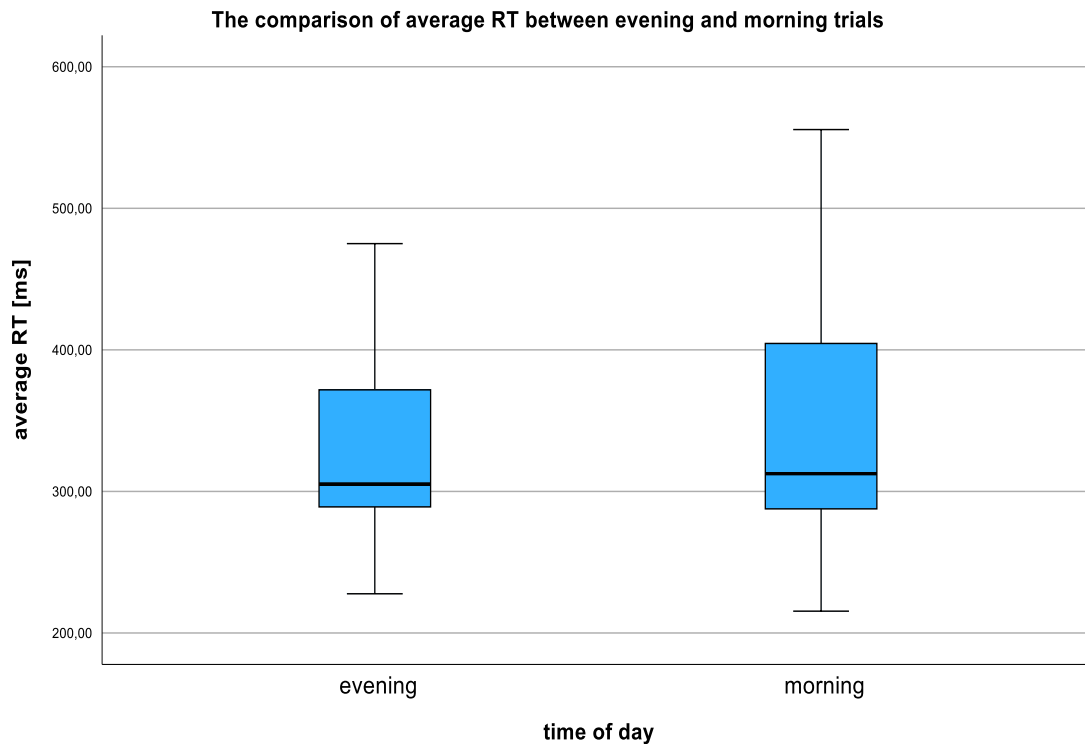


Figure 24. The box plot comparing the difference in average reaction time between the evening and morning tests.

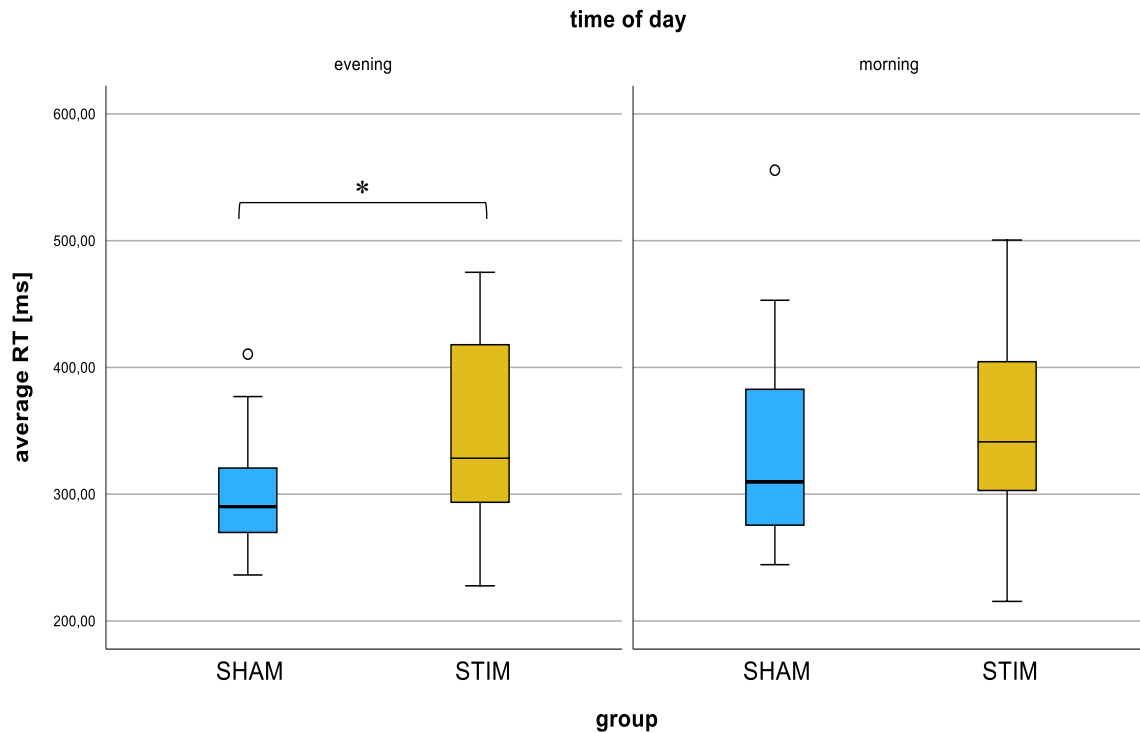


Figure 25. The box plot shows the difference in average reaction times between the groups in the evening and morning testing sessions, measured in milliseconds. Note the descriptives are as follows: SHAM evening ($Mdn = 290.2$, $SD = 46.87$), STIM evening ($Mdn = 328$, $SD = 71.08$), SHAM morning ($Mdn = 309.75$, $SD = 86.7$), STIM morning ($Mdn = 341.3$, $SD = 70.67$).

Due to the difference in the average reaction time between the groups in the evening, we explored the possibility of the influence of impaired attention on the EMT scores in the evening testing session. But no correlations were found, as shown in Table 7. However, we must reject our hypothesis that there will be no difference in the PPVT results between the groups.

Table 7. The results of the correlation analysis between the average reaction time and the EMT error types in the evening testing

Type of error	Group	Spearman's ρ	p-value
Object error	SHAM	- 0.020	0.942
	STIM	0.224	0.317
Order error	SHAM	0.366	0.163
	STIM	0.153	0.495
Location error	SHAM	0.233	0.386
	STIM	0.317	0.150

Note. The descriptive measures of the average RT for each group in the evening are as follows: SHAM ($Mdn = 290.184$, $SD = 46.865$) and STIM ($Mdn = 328.368$, $SD = 71.08$)

5 Discussion

Previous studies have shown that acoustic stimulation has the potential to manipulate memory consolidation during sleep. This topic has drawn attention for its memory enhancing effects that could be used to improve learning and memory both in various illnesses as well as in healthy individuals (Salfi *et al.*, 2022; van der Heijden *et al.*, 2024). Some studies even claimed that the influence can be very specific (Schechtman *et al.*, 2021). However, so far, no studies have focused on the precise functionality of CL-TMR on individual components of episodic memory. Therefore, this study aimed to investigate more up-close the effect of the newest memory enhancing tool of acoustic closed-loop TMR by focusing on the three components of episodic memory individually. This effort did not confirm the enhancing effect of CL-TMR on episodic memory components and, therefore, cannot support the claims of previous studies suggesting precise manipulation of episodic memories.

Furthermore, this study also set out to explore the connection between the episodic memory components and physiological measures of sleep, such as SO power and sleep spindle density in SWS. The aim was to establish the link between the effect of CL-TMR on neuronal activity and episodic memory consolidation during sleep. Despite promising results from other studies (Göldi *et al.*, 2019; Xia *et al.*, 2023), there was no tangible connection between these general measures of brain activity during sleep and the components of episodic memory, as tested in our experiments. It could mean that the effect of sensory stimulation may not be as robust as previously suggested. On the other hand, despite the lack of any disruptive effect on sleep quality parameters, we found some discrepancies in our stimulation method. This could have greatly influenced CL-TMR impact on the physiological measures of episodic memory consolidation.

Nonetheless, the moderate correlation with RAVLT, as a standard measure of episodic memory, confirmed that the EMT did test episodic memory. This means that the negative results were not due to a dysfunctional episodic memory test. Furthermore, the differences in fatigue, as measured by PPVT, had no effect on the performance on EMT.

In terms of EMT specifically, no effect of acoustic stimulation was found on any of the three components. The STIM group did not differ from the control SHAM group in scores on the episodic memory task. The only marked difference was between the object errors within the SHAM group, where a significant improvement was observed. But that could have been due to the indirect feedback built into the EMT. The correct items appeared in the central part of the island, regardless of what the participant chose in the previous collection phase of recall. This setup was necessary to prevent the transition of object errors to location and order errors that

were directly linked to object's identity. Therefore, participants could use this feedback in the morning EMT recall and improve their score significantly.

Potentially, the improvement in episodic memory might only be visible when an overall measure is observed and not at the level of individual components, such as the length of the trajectory in a spatial navigation task (Shimizu *et al.*, 2018). The EMT test did not include such overall measure to confirm this. The trajectory could not be used here, since participants always had to return to the central part of the island to proceed to another location. Therefore, they had little freedom in choosing the path. Furthermore, the time spent on the task could have been largely influenced by the ability to move in the virtual environment, which differed between participants, preventing us from utilising such measure.

The missing effect of CL-TMR on episodic memory components could also be caused by an overly simple test. For example, in the location error (the 'where' component), most of the participants made no mistakes already in the evening. Suggesting that it was too easy to remember the correct positions of individual object. In the pilot phase of this experiment, a version with only three islands was tested, but it was deemed too easy and therefore the number of islands was raised to four. That seemed to be difficult enough for the group tested in the pilot study to make mistakes. However, four sets of islands (that is, 20 items) could still have been too easy for the participants in this study. Ultimately, this means that the participants had little room for improvement; therefore, the effect of acoustic stimulation could not appear. We might find support for this explanation in the studies where substantially more objects were investigated (Schechtman *et al.*, 2021; Schechtman, Heilberg and Paller, 2023). When taken from a different angle, the perceived simplicity of the test could have been caused by a too uniform group of participants. They mostly came from a university background (either still studying or recently finished) and therefore could have had more practice with exercising their memory compared to the group tested in the pilot study.

The sleep architecture analyses showed that there was no difference between the groups in the length of the different stages of sleep or in the total duration of sleep. Sleep efficiency was even significantly better for the STIM group compared to the SHAM group. This could have been influenced by the higher variability in the SHAM group. The STIM group could have had lower variability because there were many participants excluded from this group due to not achieving a minimum of 200 stimulations per night. This threshold may have been even set too high, as other studies showed improvement in declarative memory tasks with fewer incidences of overnight stimulation (Whitmore *et al.*, 2022).

Due to these differences in sleep efficiency, stimulations were analysed. The number of stimulations differed greatly between the groups and the SHAM group received substantially more of them. However, there was no correlation of the number of stimulations with sleep efficiency for the STIM group and, surprisingly, there was a positive correlation with the SHAM group. Therefore, it seems that it was not the number of stimulations that led to the better sleep efficiency of the STIM group. It might also be slightly complicated to compare these stimulations, since there was no sound presented in the SHAM group condition. The stimulations basically corresponded to how many times the algorithm detected a SO in NREM3. In the STIM group, a sound paired with the objects in EMT was replayed every time the algorithm detected a SO in NREM3. EEG technicians reported that these stimuli sometimes lead to visible arousals and disruption of the NREM3 sleep stage. Although the duration of the NREM3 phase did not differ between the groups, a higher fragmentation of sleep caused by these arousals could have been the reason for the lower number of stimulations in the STIM group. Furthermore, this could have had an influence on the CL-TMR effect, as undisturbed sleep was shown to be necessary for its positive influence on memory (Whitmore, Bassard and Paller, 2022). The cause of these disturbances could have been an incorrect intensity of the replayed sounds. Because in a similar study they found that the TMR did not work effectively with high-intensity sounds, only with those of low intensity (Whitmore *et al.*, 2022). But in our study we used rather quiet sounds of 35 dB, which is even lower than what was used in other studies (Wang *et al.*, 2019; Guttesen *et al.*, 2024). Potentially, a less disruptive presentation could be achieved by presenting the cues within a white noise background (Rudoy *et al.*, 2009; Guttesen *et al.*, 2024). Nevertheless, in other studies, they used similar types of sounds and did not report any problems with it. However, they did adjust them to achieve uniform intensity (Shimizu *et al.*, 2018).

There were no significant differences in the relative SO power in SWS recorded between the groups. Additionally, no correlations were found with the EMT error types, suggesting that any changes in the relative SO power were not related to the changes in the EMT scores. However, this could have been affected by the absence of detectable primary changes in any of the EMT scores. In most studies, changes in individual slow oscillations or induction of new ones following acoustic stimulation were explored, but not the power of SOs throughout the night. There, they showed that the difference in SOs amplitude increased when the stimulations were applied, considering the time window immediately after the sound presentation. Therefore, it was generally focused more on the qualitative changes connected to the event-related potentials and not on the spectral power modulations (Ngo and Staresina, 2022; Navarrete *et al.*, 2023). Nevertheless, some studies did analyse the spectral power of different bands, including the delta band, which encompasses the SO band. These studies did show an increase in these parameters

in the stimulation condition (Navarrete *et al.*, 2023). But the relationship with memory improvement could be more complicated than originally assumed since in some studies the correlation between SW power and memory improvement or cognition was negative (Bar *et al.*, 2020; Djonlagic *et al.*, 2021). This means that a higher power of SWs was correlated with a lower performance on cognitive or memory tasks. Therefore, this raises the question whether the relative SO power is indeed a good measure of the CL-TMR effect on memory consolidation. Lastly, the between-subjects design has the downside of greater variability between the control and stimulation conditions. Therefore, this noise could have hidden the differences in SO power if they were more subtle. Even though, the meta-analysis by Hu *et al.* (2020) showed that TMR has a significant effect on SWS and on memory consolidation in multiple different learning paradigms.

The analyses also did not show any difference in spindle density in SWS between the experimental groups. There were also no significant correlations with the EMT results. No studies have focused on spindle density in this context of episodic memory so far, but there were some suggesting that the effect of cueing in the up-state of SO could be mediated by spindles, as they showed an increase in spindle power when stimulations were targeted in such way (Göldi *et al.*, 2019; Ngo and Staresina, 2022; Guttesen *et al.*, 2024). We did not replicate these results, despite the cues being targeted to the up slope of SOs. In a different study, a refractory period was found between the sleep spindles. The cues presented in the refractory period were not associated with memory improvement compared to the cues delivered after this period (Antony *et al.*, 2018). Therefore, incorrect targeting could lead to the suppressed effect of the TMR as observed in our study. There could also be the influence of the type of sound used. Because a recent study described that spindle power showed a stronger response to verbal cues compared to nonverbal ones (Guttesen *et al.*, 2024). Finally, the spindle density change might not be detectable in the SWS stage but could be more prominent, for example, in the NREM2 stage (Gais *et al.*, 2002). This could also be influenced by the higher variability between people in the experimental between-subjects design, which could hide the effect of stimulation on the sleep spindles.

Regarding the validation of the EMT task, the correlations between the number of words remembered in the RAVLT evening recall and the number of object and order errors in EMT in the evening were moderately strong. No correlation was observed for location error, which was most likely caused by the low variability of this parameter, as illustrated by the low number of errors already in the evening recall. However, the results for object and order errors suggest that EMT does measure episodic memory just as well as RAVLT. That is in agreement with the results of the validation of a similar task in VR (Fajnerová *et al.*, 2017). The correlations were

not substantial when done for the SHAM and STIM groups separately. This could be the result of our groups being too small for this level of correlation, since there were only 16 participants in the SHAM group. The difference between morning and evening RAVLT scores was not significant. This shows that the results of the EMT could not have been influenced by insufficient consolidation, as it was sufficient for the RAVLT.

The PPVT results suggest a significant difference between the groups in the average reaction time in the evening testing session. The STIM group had longer reaction times on average, suggesting that the participants were more tired and therefore had trouble with maintaining attention. However, there were no correlations between PPVT scores and the EMT evening results. Therefore, it seems that even though the groups differed in vigilance, it had no effect on the scores acquired in EMT. It might be that there were more people who did not sleep enough prior to testing in the STIM group compared to the SHAM group, since the PPVT is a good measure of fatigue caused by sleep deprivation (Basner, Mollicone and Dinges, 2011). Nonetheless, there was not any difference in the average reaction time between the groups in the morning session. This suggests that neither group suffered significant sleep deprivation from the testing night.

5.1 Limitations

The main limitations of this study concern the stimulation method. As suggested above, the intensity and type of sound could have influenced the efficiency of CL-TMR. Furthermore, the sounds could have induced arousals that disrupted sleep without influencing the parameters of the sleep architecture analysed. And therefore, it might have impaired the other physiological measures of relative SO power and spindle density.

Furthermore, the group of participants could have been too small to show the expected effects. That was partially accounted for in the analyses by using nonparametric tests. In our case, it could have been not only the small group size, but also its characteristic. This being the fact that most of the participants were university students. Therefore, they could have been better trained in memorising, which could have made the EMT too easy for them to show any significant changes. Possibly, the pilot study suggesting the application of four sets of islands in the EMT as sufficient was carried out on a wider spectrum of volunteers. Therefore, it did not work later for the more uniform group of participants included in the experiments. Besides, the STIM group had lower variability as many participants were excluded from this group because they did not reach the 200 stimulations per night threshold.

Lastly, the between-subjects design of this experiment brings the obstacle of high initial variability between the experimental and control groups in both memory and sleep measures. We

chose this design to prevent the effect of practice on the EMT results. Because in the within-subjects setting, the participants would perform the task twice as many times and the effect of already knowing the task could confound the results. Most studies done on this topic to this day have employed the within-subjects experimental design (Rudoy *et al.*, 2009; Ngo and Staresina, 2022; Whitmore *et al.*, 2022). It is possible that the effects of TMR on consolidation of episodic memory component may be too subtle to be detected in the between-subjects condition.

The limitations listed above should be addressed in future studies.

6 Conclusion

This study explored the effect of CL-TMR on episodic memory, more precisely, on the three components of episodic memory: factual content (the object), spatial context, and temporal context. Additionally, it also focused on the influence of CL-TMR on neuronal activity during sleep as a measure of memory consolidation. The findings suggest that the effect on episodic memory consolidation by targeted memory reactivation may be less robust and less selective than previously proposed. No effect of acoustic stimulation was found for either of the episodic memory components. This could suggest that the reactivation might be less specific and that it only influences episodic memory in general but cannot differ between different contextual information selectively. Furthermore, we also showed that there is no change in the overall physiological parameters of episodic memory consolidation during sleep when memory reactivation is used. The changes reported by other studies may manifest only in changes in ERPs and not in the parameters focusing on variations in general neuronal activity, when mapping full-night sleep (Carbone *et al.*, 2024).

Furthermore, the setup of stimulation may be another crucial element to ensure positive results of this intervention. As it seems from our results, the acoustic stimulations may be too disruptive during sleep, even when quiet sounds are used. Therefore, the sound presentation must be carefully prepared to prevent any confounding effects.

Moreover, we propose that the inter-individual differences in sensory stimulation processing and memory consolidation may be too large to clearly show the enhancing effect of CL-TMR. Our sleep data support this notion, as we did not observe any clear overall effect of stimulation on episodic memory consolidation at the level of slow oscillations and sleep spindles in the between-subjects study design applied. Despite the possible changes in ERPs as reported in other studies, these did not seem to manifest themselves in the broader physiological measures followed in this study. It suggests that these individual changes may not have the far-reaching effect as proposed. To verify this, the analyses concerning ERPs should be also carried out on the data from experiments presented here. Overall, it raises the question of whether CL-TMR significantly helps to consolidate all components of episodic memories during sleep, as we did not confirm such claims.

Further research should focus on the gating of sensory stimuli during sleep and the mechanism of translation of changes at the level of event-related potentials into the general physiological measures of episodic memory consolidation.

7 References

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